10

COPPER-MEDIATED ARYL–ARYL BOND FORMATION LEADING TO BIARYLS: A CENTURY AFTER THE ULLMANN BREAKTHROUGH

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10.1 INTRODUCTION

The synthesis of functionalized biaryls has been an important research objective in organic synthesis, biaryl motifs being found in a wide range of functional molecules such as biologically active natural products,[1] optoelectronic molecules,[2] and asymmetric catalysts.[3] Naturally, transition-metal-mediated aryl–aryl bond formation reactions have been extensively investigated; and, in particular, palladium-catalyzed cross-coupling reactions have been devised and have been continuously sharpened as most efficient tools to construct functionalized biaryls.[4] The successful progress in this area of research culminated in the Nobel Prize in Chemistry 2010, which was awarded to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki for the development of palladium-catalyzed cross-coupling reactions.

In striking contrast to the tremendous success of the palladium-catalyzed cross-coupling reactions, the development of copper analogues lagged behind despite the fact that more than a century has passed since the first report of transition-metal-mediated aryl–aryl bond formation, namely, the Ullmann coupling of haloarenes with copper bronze.[5] This underdevelopment is partly associated to the difficulty in predicting and understanding the reaction

Copper-Mediated Cross-Coupling Reactions, First Edition. Edited by Gwilherm Evano and Nicolas Blanchard.

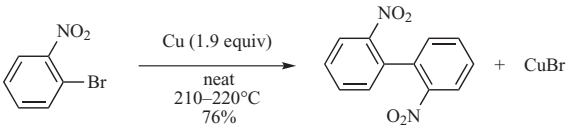
mechanisms of copper-mediated coupling, which strongly hampered the design of new catalytic systems with increased efficiencies. For instance, copper occurs in a variety of oxidation states (0–IV) and tends to be present at more than one oxidation state under certain reaction conditions and single-electron transfer processes as well as disproportionation complicates mechanistic investigations. Nevertheless, renewed interest in first-row transition metals, due to their cost-effectiveness and environmentally benign characteristics, has spurred a resurgence of Ullmann chemistry, and this has led to the recent significant progress in copper-catalyzed coupling processes.[6] Among them, C–O, C–N and C–S bond-forming reactions (described in Chapters 1 and 2) have been extensively studied,[7] while less attention has been devoted to copper-mediated aryl–aryl bond formation. Thus, a survey of the development of copper-catalyzed biaryl syntheses is expected to contribute to increased researcher interest and further advances in this area.

This chapter outlines developments in the copper-mediated aryl–aryl coupling methods. These can be classified into several major categories depending on the types of reactions and precursors involved: (i) coupling of aryl halides and diazonium salts; (ii) coupling of aryltin, arylboron, or arylsilicon reagents; (iii) coupling via arylation involving C–H or C–C bond fission; and (iv) oxidative coupling of 2-naphthols. The third category can be further divided into direct C–H arylations using prefunctionalized or nonfunctionalized arylating agents and decarboxylative coupling of benzoic acid derivatives. In addition to cross-coupling reactions, each category includes homocoupling reactions, useful tools for the construction of symmetrical biaryl frameworks from a single precursor. The conventional Ullmann reaction is still practical for large-scale production of less-functionalized biaryls as it is easily scalable due to the simple procedure and the lack of requirement for special ligands and additional promoters, although excess copper is required. The first part of this chapter is devoted to a brief survey of Ullmann coupling and related aryl–aryl bond formation reactions. The later sections survey the modern copper-mediated coupling reactions beyond the classical Ullmann biaryl synthesis.

10.2 BIARYL SYNTHESIS BY COUPLING OF ARYL HALIDES AND DIAZONIUM SALTS

10.2.1 Ullmann Couplings of Aryl Halides

The history of copper-promoted aryl–aryl bond formations can be traced back to the seminal report by Fritz Ullmann and Jean Bielecki in 1901 (see the Preface for a presentation of these early discoveries from a historical perspective).[5] They discovered that mixing *o*-iodonitrobenzene with 1.9 equiv of copper powder at 210–220°C under neat conditions formed the homocoupling product (i.e., 2,2′-dinitrobiphenyl) in 76% yield with concomitant production of CuBr (Scheme 10.1). Since then, the Ullmann coupling has been studied



Scheme 10.1 Copper(0)-mediated homocoupling of *o*-bromonitrobenzene: the historical discovery of Fritz Ullmann (1901).

extensively, and its scope and applications have been thoroughly reviewed.[6,8] Thus, only a brief overview is given here for the classical Ullmann coupling to demonstrate the essence of this process; and then, newer Ullmann-type couplings will be overviewed.

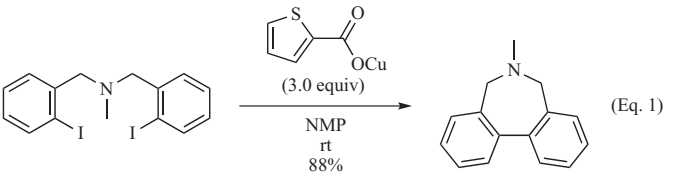
The order of reactivity of the halogens, that is, I > Br > Cl, is common to most transition-metal-mediated cross-coupling reactions and the most challenging Ullmann coupling via the C–F bond cleavage of fluorobenzenes has not been reported to date. The activating effect of electron-withdrawing substituents such as nitro and carbomethoxy groups at the *ortho*-position was observed and elegantly used in some cases to promote the reaction under milder conditions than those initially reported by Ullmann; this effect is dramatically affected by the position of the activating group and decreases in the following order: *ortho* ≫ *para* > *meta*. Chloro, methyl, and methoxy substituents also favorably affect the reaction regardless of their positions, although no explanation has been provided. In contrast, functional groups with labile proton(s) inhibit the coupling; typical inactive substrates include phenol, aniline, and benzoic acid derivatives, which may preferentially undergo Ullmann–Goldberg condensation[6,7] or decarboxylation.[9] Polar aprotic solvents such as dimethylformamide (DMF) and *N*-methylpyrrolidinone (NMP) can be used for milder protocols, although the original synthesis was conducted without solvent, and nitroarenes as well as aromatic solvents have also been used. However, the former undergoes reductive arylation at high temperatures, and it has been reported that the Ullmann coupling of iodobenzene in nitrobenzene resulted in a triphenylamine by-product. Reductive dehalogenation also occurs as a side reaction in the presence of proton sources. For the copper source, commercially available, mechanically pulverized copper has been used with or without activation by successive washing with acetone solutions of iodine and hydrochloric acid. It has been reported that milder reaction conditions improve the yields of biaryl products. For example, the homocoupling of *o*-bromonitrobenzene over 60 hours at 60°C using a 10-fold excess of activated copper bronze improved the yield of 2,2′-dinitrobiphenyl from 76% under the original Ullmann conditions to 99.6%.[10a] The copper loading could be further reduced to 4 equiv, and the reaction rate was enhanced by presonication of the copper bronze with ultrasound in air,[10b] and copper powder that was freshly prepared by the reduction of aqueous copper sulfate with zinc powder was reported to be superior to commercial copper bronze.[11] In

addition, it was also found that γ-alumina-supported copper is superior to copper powder for Ullmann coupling of *p*-chlorotoluene.[12]

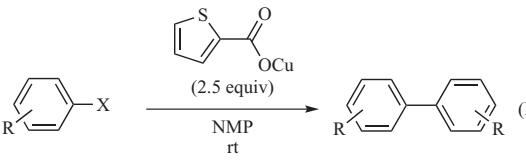
In place of metallic copper(0), copper(I) ions have been employed for milder Ullmann-type coupling reactions. *o*-Iodonitrobenzene was, for example, treated with freshly prepared copper(I) triflate and 20% aqueous ammonia in acetone at ambient temperature for less than 5 minutes to produce the corresponding 2,2′-biphenyl in 92% yield.[13] A tetrakis(acetonitrile)copper(I) perchlorate catalyst was reported to be similarly effective.[13] It was also discovered that 2.5–3.0 equiv of copper(I) thiophene-2-carboxylate (CuTC) promoted inter- and intramolecular Ullmann-type couplings of iodoarenes in moderate-to-high yields, even at ambient temperature, which represents one of the most efficient coupling reactions,[14a] a typical example being 2,2′-dinitrobiphenyl, which was obtained in 92% yield from *o*-iodonitrobenzene with this procedure (Scheme 10.2). This method was also applied to the synthesis of fluorinated oligo(*para*-phenylenes) and to the enantioselective synthesis of *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene.[14b,c]

In all examples of Ullmann coupling described up to this point, a large excess of copper was generally imperative. In contrast, when copper nanoparticles are used as the copper source, Ullman coupling of iodobenzene was executed at 150–200°C with a copper : iodobenzene ratio in the 1.6:1–1:1 range to obtain the corresponding biphenyl in good yields.[15] Moreover, a catalytic version of the Ullmann coupling was achieved using supported copper(II) diamine compound **1** (Scheme 10.3),[16] the immobilized copper(II) catalyst being easily removed and reused. Notably, various bromoarenes bearing electron-withdrawing and electron-donating substituents underwent homocoupling to give biaryls in good yields.

Besides the development of activated systems for the Ullmann biaryl synthesis, the atroposelective aryl–aryl coupling has also attracted much interest due to the wide occurrence of axially chiral biaryls in natural products and asymmetric catalysts (see Chapter 18 for an overview of copper-catalyzed aryl–aryl coupling reactions in total synthesis of natural products).[1,3,17] Accordingly, enantiomerically pure chiral biaryls, which form the axially chiral backbone of asymmetric catalysts, were synthesized by the Ullmann coupling of 2,6-disubstituted haloarenes and subsequent optical resolution of the racemic products.[18] Since optical resolution gives a maximum yield of 50% of the desired enantioenriched product and requires tedious procedures, notably for the separation of the diastereoisomers formed in the course of the reactions, the diastereoselective coupling of substrates substituted with appropriate chiral auxiliaries is more desirable and has been quite extensively studied. Toward this goal, Ullmann coupling of several haloarenes in the presence of a chiral inducer was examined; however, the observed diastereoselectivity was not sufficient and further optical resolution was required.[19] To synthesize more efficiently C_2-chiral biaryls, Meyers and coworkers introduced a chiral oxazoline as an auxiliary.[20] As shown in Scheme 10.4, valinol-derived *o*-bromooxazolinylbenzene **2** was treated with copper powder in refluxing

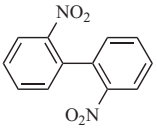


(Eq. 1)

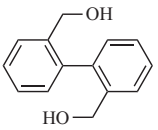


(Eq. 2)

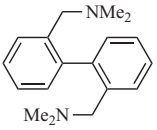
Representative examples



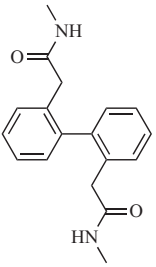
X = I: 92%
X = Br: 86%



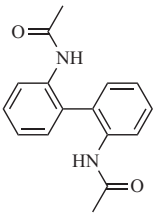
X = I: 48% (at 70°C)



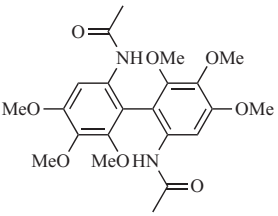
X = I: 97%



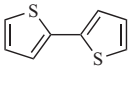
X = I: 51%



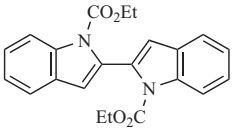
X = I: 90%



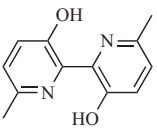
X = I: 86%



X = I: 77%

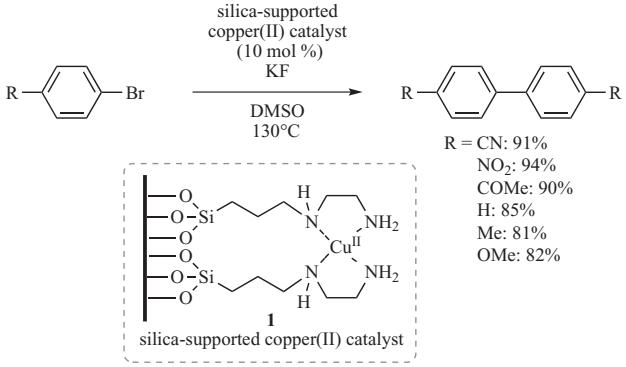


X = I: 60% (at 0°C)

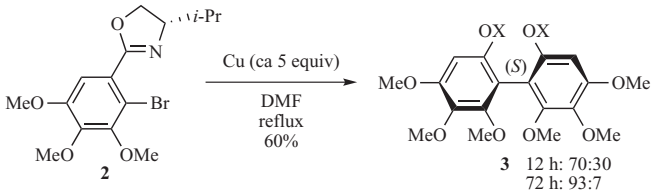


X = I: 69%

Scheme 10.2 Homocoupling of iodobenzenes mediated by copper(I) thiophene-2-carboxylate.



Scheme 10.3 Homocoupling of bromoarenes catalyzed by a silica-supported copper(II) diamine complex.

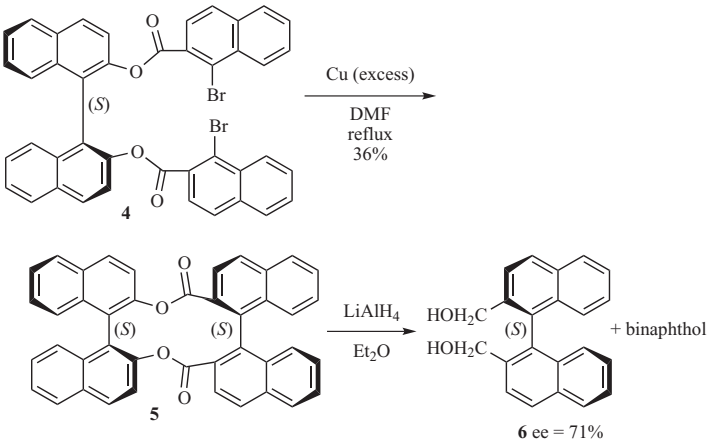


Scheme 10.4 Diastereoselective homocoupling of *o*-bromooxazolinylbenzene.

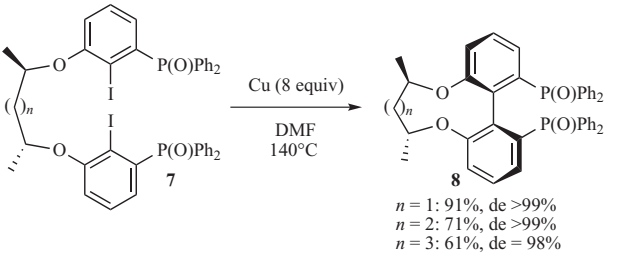
DMF to furnish the corresponding biaryl bis(oxazoline) **3**, and the diastereomeric ratio was 70:30 after 12 hours and was remarkably improved to 93:7 after 72 hours, which implies that the Ullmann coupling of oxazoline **2** first affords a copper complex of bis(oxazoline) **3** with modest diastereoselectivity followed by atropisomerization to the thermodynamically favorable (*S*)-enantiomer. The enantiopure product **3** was ultimately isolated in 60% yield and the oxazoline approach was next extended to the synthesis of binaphthyls and various natural products.[20]

An alternative promising approach is the intramolecular Ullmann coupling that involves a temporary chiral tether developed by Miyano and coworkers, who obtained (*S*)-2,2′-di(hydroxymethyl)-1,1′-binaphthyl (**6**) albeit in a moderate optical purity from the intramolecular coupling of binaphthol tethered bis(1-bromo-2-naphthoate) **4** followed by the reduction of the resulting coupling product **5** with lithium aluminum hydride (Scheme 10.5).[21] The same group also reported intramolecular cross couplings using a similar strategy.[21a] In these examples, the axial chirality of the tether was transferred to that of the newly formed binaphthyl moiety.

Tethers bearing central chirality were also extensively studied.[21c,22] For example, (*o*-iodophenyl)diphenylphosphine oxides linked by chiral diol tethers **7** underwent intramolecular coupling to furnish biaryl bis(phosphine oxides)



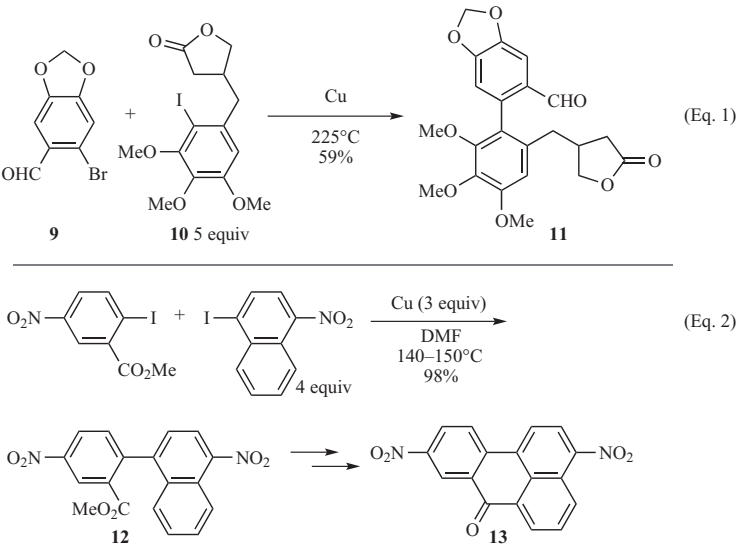
Scheme 10.5 Diastereoselective intramolecular homocoupling of BINOL-derived bis(1-bromo-2-naphthoate).



Scheme 10.6 Synthesis of chiral biaryl bis(phosphine oxides) via intramolecular diastereoselective homocoupling of (iodophenyl)diphenylphosphine oxides.

8 with an excellent diastereoselectivity of over 98% in 61–91% yields, and the smaller the tether, the higher the yield (Scheme 10.6).[22a,b] Intramolecular Ullmann coupling of 2-iodo-3,4,5-trimethoxybenzoate connected by sugar moieties was examined for the biomimetic synthesis of ellagitannins and the coupling products were generally obtained as single atropisomers, albeit in low-to-moderate yields.[23]

In terms of synthetic utility, one of the serious disadvantages of the Ullmann coupling is its little efficiency for the cross coupling of two different haloarenes to obtain unsymmetrical biaryls. Indeed, the cross Ullmann coupling is only successful if one of the coupling components is more reactive than the other, and in addition, the most reactive haloarene component must have an activating group at the position *ortho* to the halogen substituent, and an excess of the less-active component is often required. Moreover, the reaction should be carried out at temperatures below that at which the less-reactive component

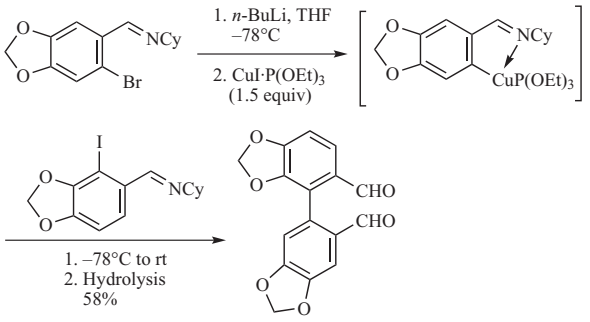


Scheme 10.7 Examples of cross Ullmann coupling of halobenzenes.

reacts with copper. One of the early examples involves the Ullmann cross coupling of 2,4-dibromonitrobenzene and iodobenzene, which gave the desired product in a moderate yield of 52% together with small amounts of 2,4-dibromonitrobenzene.[24] As another example, intermediate **11** was obtained in the total synthesis of steganone in a moderate yield from the cross coupling of 6-bromopiperonal **9** and highly congested iodoarene **10** (Scheme 10.7, Eq. 1).[25] A high-yielding procedure was later established using iodonaphthalenes as the less-reactive components.[26] This synthesis involves the dropwise addition of a DMF solution of 2-iodo-5-nitrobenzoate over 4 hours to a mixture of 1-iodo-4-nitronaphthalene and copper bronze at 140–150°C to afford the corresponding cross-coupling product **12** in a remarkable 98% yield (Scheme 10.7, Eq. 2). This product was further converted to benzanthrone derivative **13**.

10.2.2 Coupling of Organocopper Reagents Generated from Aryl Halides

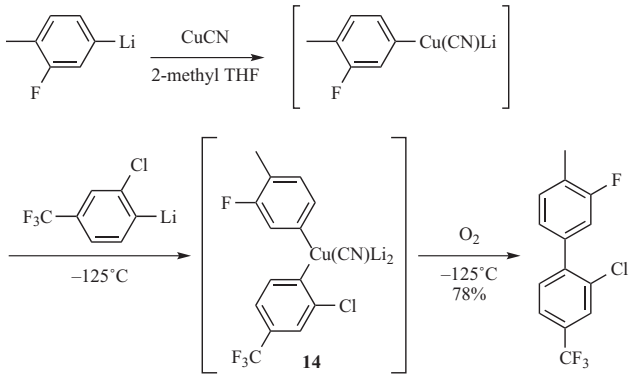
An alternative approach to achieve this kind of cross coupling is the reaction of preformed arylcopper reagents with iodoarenes. Even if these reactions are outside the scope of this book, these procedures are clearly among the most efficient ones for the syntheses of biaryls to date and will undoubtedly be at the origin of developments in copper-mediated biaryl syntheses without preformed organocopper reagents for the years to come. Due to the utmost importance of these underdeveloped reactions, they should appear in this chapter and they will be overviewed in the next pages.



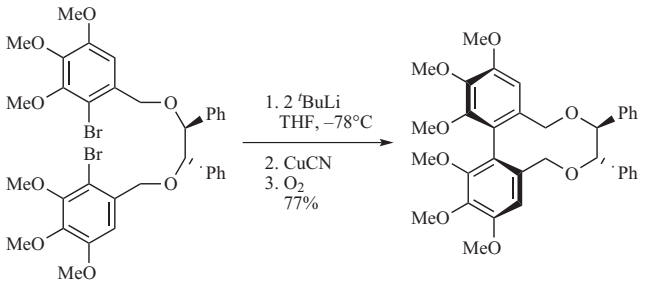
Scheme 10.8 Cross-coupling reaction using *in situ* generated organocopper(I) reagent.

Phenyl-, 2-thienyl-, 2-pyridyl-, and polyhaloarylcopper reagents successfully react with iodoarenes to furnish the corresponding cross-coupling products.[27] However, homocoupling side products were also formed from phenylcopper via a copper–halogen exchange. In response to this limitation, Ziegler and coworkers developed a selective cross-coupling protocol under mild conditions,[28] which involves the *in situ* generation of an arylcopper reagent stabilized by a phosphite ligand and an internal coordinating group such as imine or oxazoline at the *ortho*-position. The arylcopper reagent was then allowed to react at ambient temperature with an iodoarene also bearing an *ortho* imine substituent to produce the corresponding unsymmetrical biaryl in a good yield. A typical example is given in Scheme 10.8. This strategy was successfully applied to the synthesis of steganacin[28] and other natural products,[29] and in addition, the synthesis of (*S*)-(–)-*N*-acetylcolchinol was accomplished by a similar method employing an acetal as the internal coordinating group.[29d]

The oxidation of organocuprates has been known to induce C–C bond formation between the ligands on copper.[30] However, this phenomenon is in general rather useless for organic synthesis when two different ligands are involved as all combinations of the two ligands lead to three coupling products in statistical ratios except in peculiar cases. Nevertheless, Lipshutz and coworkers discovered that the aerobic oxidation of higher-order cyanocuprates (e.g., **14** in Scheme 10.9), which were prepared from sequential addition of aryllithium reagents to copper(I) cyanide in 2-methyltetrahydrofuran at –125°C, predominantly yielded cross-coupling products.[31] The success of this method is based on the formation of "kinetic" higher-order cuprates at –125°C; at higher temperatures, ligand scrambling occurs, which results in a loss of selectivity. This method is applicable to heteroaromatic systems as well as intramolecular coupling reactions, and notably, intramolecular cross-coupling reactions in tetrahydrofuran (THF) can be carried out at a higher temperature of –78°C because ligand scrambling is not as significant as it is for intermolecular couplings. Enantioselective syntheses of biaryls were also achieved by implementing a chiral tether method (Scheme 10.10).[32]

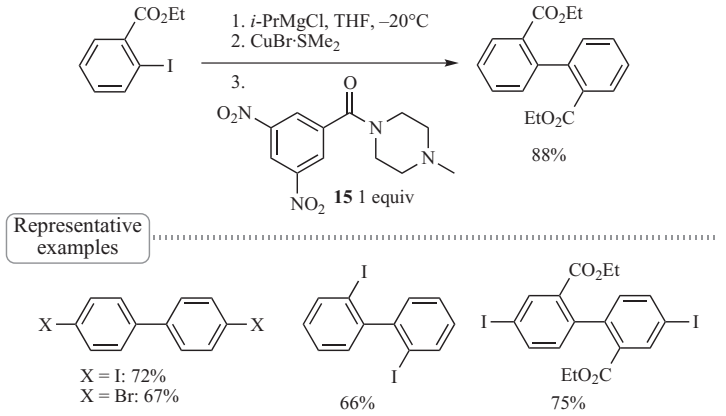


Scheme 10.9 Cross-coupling reaction of aryllithium reagents via higher-order cyanocuprate.

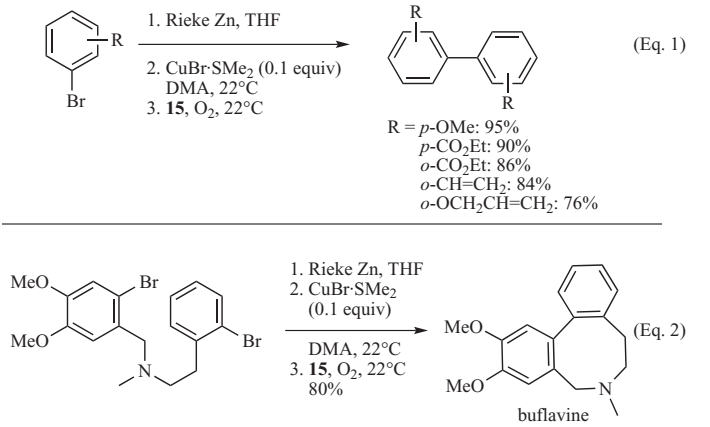


Scheme 10.10 Diastereoselective intramolecular homocoupling of arylbromide via higher-order cyanocuprate.

Recently, several significant modifications have been made to expand the scope of Lipshutz's method. Iyoda and coworkers contended with diminished yields of the homocoupling product obtained from the oxidation of $(p\text{-}ClC_6H_4)_2Cu(CN)Li_2$ with conventional oxidants such as molecular oxygen and 1,3-dinitrobenzene.[33] As a result, they screened various electron acceptors and determined that tetramethyl-*p*-benzoquinone was optimal. In addition, they achieved cyclocoupling via dimetallacyclic cuprates to obtain 10-membered cyclophanes. Spring and coworkers investigated the synthesis of more challenging compounds such as iodinated biaryls.[34] Toward this aim, they examined the oxidation of cuprates produced from Grignard reagents since they are obtained under mild conditions via iodide–magnesium exchange.[34a] Their optimization revealed that the reaction using $CuBr{\cdot}SMe_2$ and 3,5-dinitrobenzoic amide **15** successfully furnished the homocoupling products in moderate-to-high yields (Scheme 10.11). Notably, dihaloarenes were able to undergo homocoupling and retain one of the halogen atoms. Furthermore,

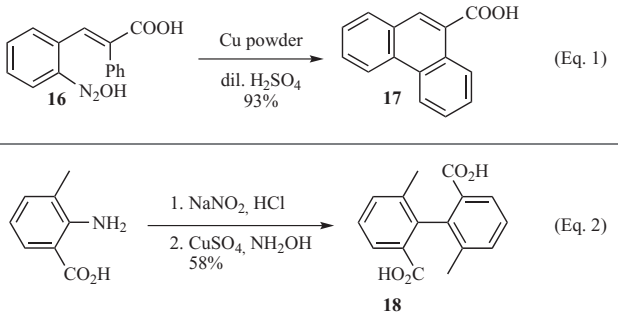


Scheme 10.11 Homocoupling of aryl Grignard reagents via cuprates.



Scheme 10.12 Homocoupling and intramolecular cross coupling of arylzinc reagents via cuprates.

organozinc reagents, which are more tolerant to a wide range of functional groups than organolithium or Grignard reagents, proved to be applicable in the cuprate oxidation strategy. Spring and coworkers demonstrated that cuprates derived from the reaction of arylzinc reagents and $CuBr{\cdot}SMe_2$ were oxidized by amide **15** to give symmetrical biaryls in good yields.[35] In addition, performing the reaction under an atmosphere of oxygen enables copper loading to be reduced to 0.1 equiv, which represents the first example of the catalytic use of copper for biaryl synthesis via cuprate oxidation (Scheme 10.12, Eq. 1 and Eq. 2). Magnesium and zinc cuprate oxidation methods were also successfully applied to the synthesis of ellagitannin natural products.[36]



Scheme 10.13 Copper-mediated coupling of aryl diazonium compounds.

10.2.3 Coupling of Aryl Diazonium Compounds

The last part of this section briefly outlines the copper-mediated coupling of aryl diazonium compounds to obtain biaryls. In 1896, Robert Pschorr reported that the treatment of diazonium salt **16** with copper powder affords phenantherene-9-carboxylic acid **17** in 93% yield (Scheme 10.13, Eq. 1).[37] The intermolecular coupling of aryl diazonium salts with aromatic compounds is also known as the Gomberg–Bachmann reaction[38] and the intermolecular copper-mediated homocoupling of aryl diazonium salts has been applied to the synthesis of highly congested biaryls (e.g., **18** in Scheme 10.13, Eq. 2), which are difficult to access via other methods.[39]

After extensive research, it was revealed that the coupling of aryl diazonium salts proceeds using a variety of mediators such as iodide anions, iron(II) and titanium(III) ions, tetrathiafulvalene, and cobaltocene. This shows that copper is not essential for these reactions, and there are evidences that support the involvement of aryl radicals in the aryl–aryl bond formations.[38,40] However, it has also been suggested that arylcopper species, which are generated via the reaction of aryl radicals and copper ions, are involved in the aryl–aryl coupling process.[41] Cohen and coworkers observed decreased yields of biaryls and azoarenes when the copper(I)-mediated decomposition of *p*-nitrobenzenediazonium tetrafluoroborate was performed in the presence of a radical trapping agent such as iodomethane or THF.[41a] In addition, the yields of these bimolecular products rose with increases in the concentration of the copper(I) salt, and the addition of copper(II) ions increased the biaryl : azoarene ratio. From these data, biaryl formation was determined to occur via both radical and arylcopper species. The decomposition of *p*-methoxybenzenediazonium in the presence of tetrakis(acetonitrile)copper(I) in aqueous acetonitrile phosphate buffers under a variety of conditions yielded symmetrical 4,4′-dimethoxybiphenyl as the major aryl–aryl coupling product. Computational analysis of the obtained product distributions gave kinetic data corresponding to elementary processes, which indicates that the arylcopper species is involved in the aryl–aryl bond formation.[41b]

As seen in the above-mentioned examples, copper-mediated coupling reactions of aryl halides and diazonium salts to the corresponding biaryls are efficient tools for the rapid elaboration of these important motifs. The next section will focus on copper-mediated and copper-catalyzed coupling reactions of aryltin, boron, and silane derivatives that have been extensively studied in the past decade.

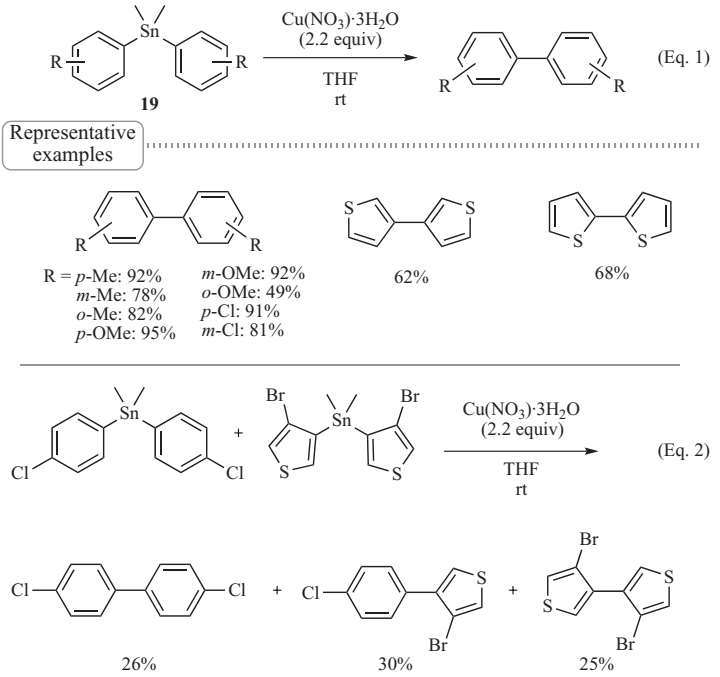
10.3 BIARYL SYNTHESIS BY COUPLING OF ARYLTIN, BORON, AND SILANES

10.3.1 Coupling of Organostannanes

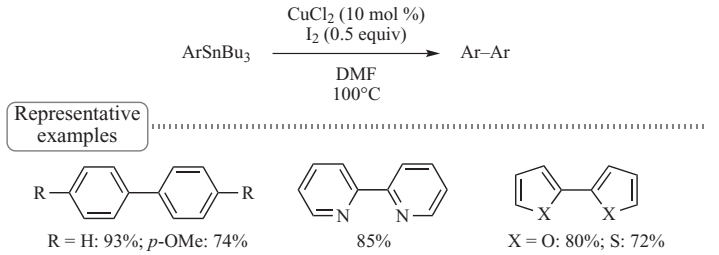
The palladium-catalyzed cross coupling of organostannanes and organic halides, which is known as Migita–Kosugi–Stille cross coupling, has found numerous applications in organic synthesis.[4c,42] The closely related homocoupling of arylstannanes was achieved using copper(II) nitrate as a stoichiometric promoter and *p*-tolyl-, *o*-tolyl-, or *p*-anisyl-stannanes were individually treated with $Cu(NO_3)_2{\cdot}3H_2O$ (1 equiv) in THF at 23°C to obtain symmetrical biaryls in 45–67% yields.[43] In contrast, application of this method to a more hindered 2,6-dimethoxyphenyl analogue resulted in a low yield of 14%. It was also reported that benzofuran-2-ylstannane and its sulfone analogue underwent homocoupling in moderate yields,[43b] and this method was also applied to the synthesis of cyclic oligophenylenes.[44] Later, the yield and scope of copper(II)-mediated homocoupling reactions were improved using diaryldimethyltin reagents **19** as outlined in Scheme 10.14, Equation 1.[45] In the presence of 2.2 equiv of $Cu(NO_3)_2{\cdot}3H_2O$, a variety of biaryls were obtained within 30 minutes, the only exception being the reaction of an *o*-methoxyphenyl derivative, which required 4 hours. It is assumed that the coupling proceeds via monoarylcopper(II) species, that is, Ar–Cu–ONO_2, rather than diarylcopper(II), which was confirmed by a crossover experiment between two different diarylstannanes that resulted in both homo- and cross-coupling products (Scheme 10.14, Eq. 2).

Kang and coworkers established a catalytic protocol for homocoupling that employs molecular iodine as an oxidant (Scheme 10.15).[46] In the presence of 10 mol % of copper(II) chloride and half an equivalent of iodine, (hetero) arylstannanes were heated in DMF at 100°C for 4 hours to obtain symmetrical biaryl products in good yields.

Related intramolecular homocoupling of **20** is a powerful method for the synthesis of seven-membered ring compounds **21**, which are otherwise difficult to obtain (Scheme 10.16),[47] and this strategy was applied to the synthesis of tubulin-binding agents.[47] Since 2 equiv of copper(0) are produced for each carbon–carbon bond formation,[43] the researchers proposed a route comprising reversible transmetallation to form dicopper(I) intermediates **22**, which undergo disproportionation to yield copper(II) metallacycle species **23**.



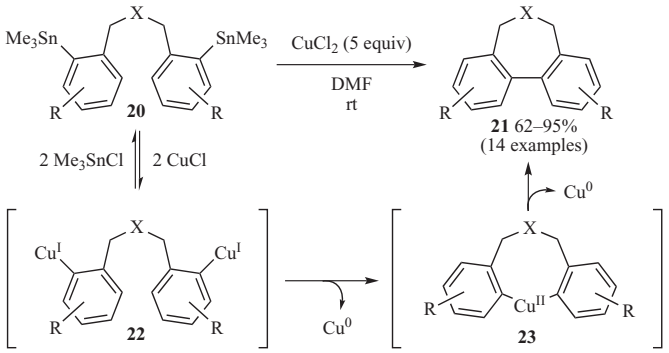
Scheme 10.14 Copper(I)-mediated biaryl synthesis using diaryltin reagents.



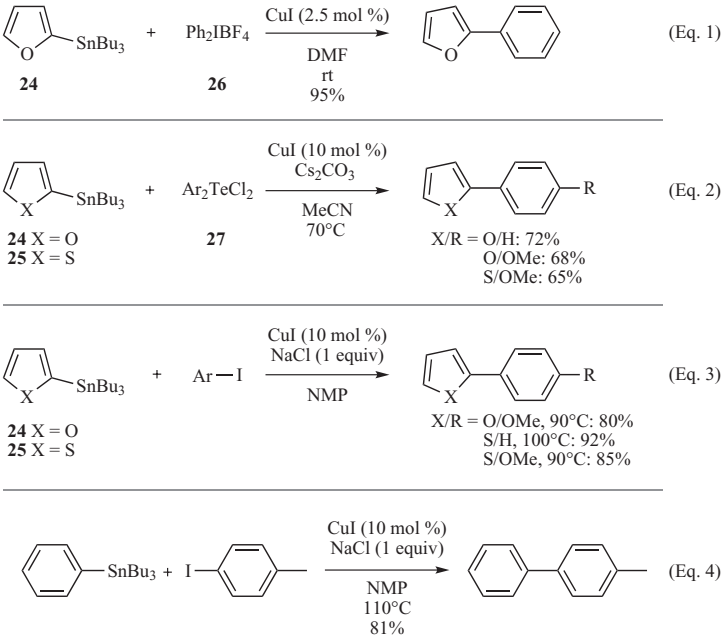
Scheme 10.15 Copper(II)-catalyzed homocoupling of arylstannanes.

Subsequent reductive elimination furnishes the desired cyclic biaryls **21**. Alternatively, the biaryls could be directly produced via binuclear reductive elimination from the dicopper(I) intermediates.[48]

Copper(I)-mediated Migita–Kosugi–Stille-type cross couplings of alkenyl- and alkyl-stannanes have been extensively developed,[49,50] and in particular, the copper(I) thiophenecarboxylate-mediated cross coupling of alkenylstannanes, which was developed by the Liebeskind group, has practical advantages including mild and simple procedure, wide substrate scope and high yields. Thus, this method was soon employed for numerous applications including the



Scheme 10.16 Copper(II)-mediated intramolecular homocoupling of arylstannanes.

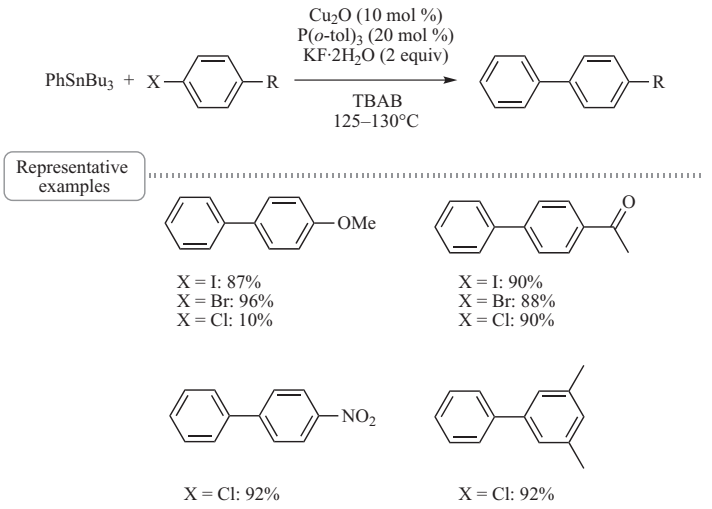


Scheme 10.17 Copper(I)-catalyzed cross-coupling reactions of arylstannanes.

total synthesis of complex natural products (see Chapter 18).[50] With respect to biaryl synthesis using this strategy, several catalytic methods have been developed,[51] and the first copper(I)-catalyzed Migita–Kosugi–Stille-type aryl–aryl coupling was achieved by Kang and coworkers using hypervalent reagents as electrophiles (Scheme 10.17, Eq. 1).[51a] The reaction involves the treatment of 2-stannylfuran **24** and diphenyliodonium tetrafluoroborate (**26**) with copper(I) iodide (2.5 mol %) in DMF at an ambient temperature for 10

minutes to obtain 2-phenylfuran in 95% yield. In this report, the scope was not expanded further, although the cross coupling of arylboronic acids was also accomplished (see next section). Similarly, the coupling of 2-furyl- or 2-thienylstannanes **24** and **25** with diaryltellurium dichlorides **27** in the presence of 2 equiv of cesium carbonate was shown to proceed at 70°C to give cross-coupling products, albeit in lower yields (Scheme 10.17, Eq. 2).[51c] The Kang group also achieved copper(I)-catalyzed Migita–Kosugi–Stille-type couplings using iodoarenes as the coupling partners;[51b] these reactions required elevated temperatures and sodium chloride as an additive to suppress the reversible transmetallation by converting tributyltin iodide to tributyltin chloride and the slow addition of the arylstannanes with a syringe pump to avoid homocoupling (Scheme 10.17, Eq. 3 and Eq. 4).

This cross coupling was later extended to the use of recyclable catalysts using copper oxide nanoparticles, tri(*o*-tolyl)phosphine, potassium fluoride, and tetrabutylammonium bromide (TBAB) (see Chapter 20 for an overview of reusable copper catalysts).[52] In this report, phenylstannane underwent cross coupling with aryl iodides and bromides that contained both electron-withdrawing and electron-donating substituents to furnish the corresponding biaryls in high yields (Scheme 10.18). Remarkably, this method also successfully converted *p*-acetyl-, *p*-nitro-, and 3,5-dimethyl-phenyl chloride to their corresponding biaryls in high yields; however, the reaction resulted in a low yield (10%) when electron-rich *p*-methoxyphenyl chloride was used. A significant advantage of the Cu_2O/P(*o*-tolyl)$_3$/TBAB system is its recyclability; the coupling of *p*-iodoanisole and tributylphenylstannane was repeated for up to five cycles without loss of catalytic activity (average yield of 94%).

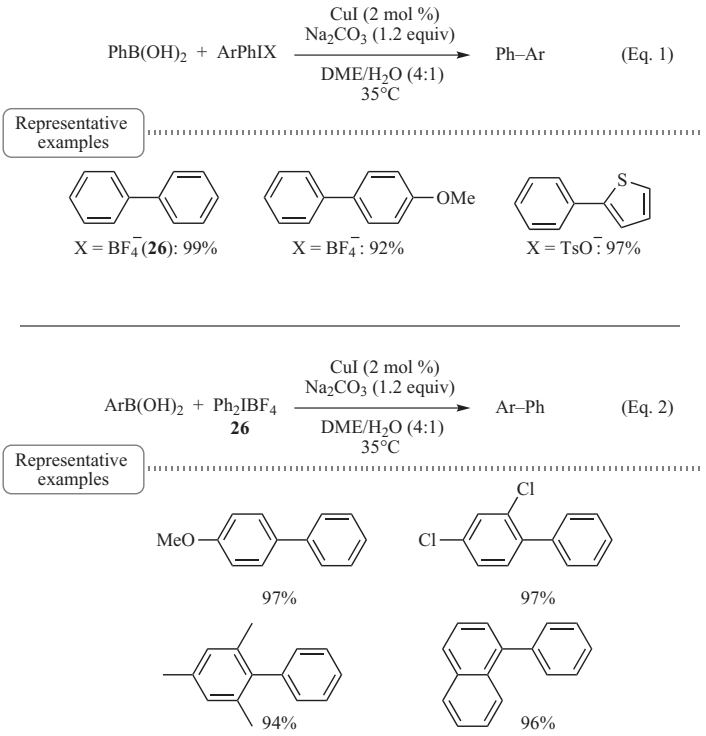


Scheme 10.18 Cross coupling of arylstannanes with aryl halides catalyzed by copper nanoparticles.

Besides these efficient copper-catalyzed Migita–Kosugi–Stille-type couplings of arylstannanes, numerous studies have been devoted to the homo- and cross-coupling reactions of arylboron derivatives. The most representative examples of this strategy are overviewed in the next section.

10.3.2 Coupling of Organoboranes

The palladium-catalyzed cross coupling of organoboronic acids and organic halides, which is known as Suzuki–Miyaura cross coupling, is one of the most powerful tools for the formation of carbon–carbon bonds, organoboron reagents being readily accessible and less harmful than the corresponding organostannanes.[53] A copper-catalyzed version of this cross coupling was realized for the first time in 1996 using hypervalent iodonium reagents. Arylboronic acids were allowed to react with diaryliodonium reagents in a mixture of dimethoxyethane (DME) and water at 35°C in the presence of copper(I) iodide (2 mol %) and sodium carbonate (1.2 equiv) to give the desired biaryls in high yields (Scheme 10.19).[51a] In each case, a selective transfer of the more

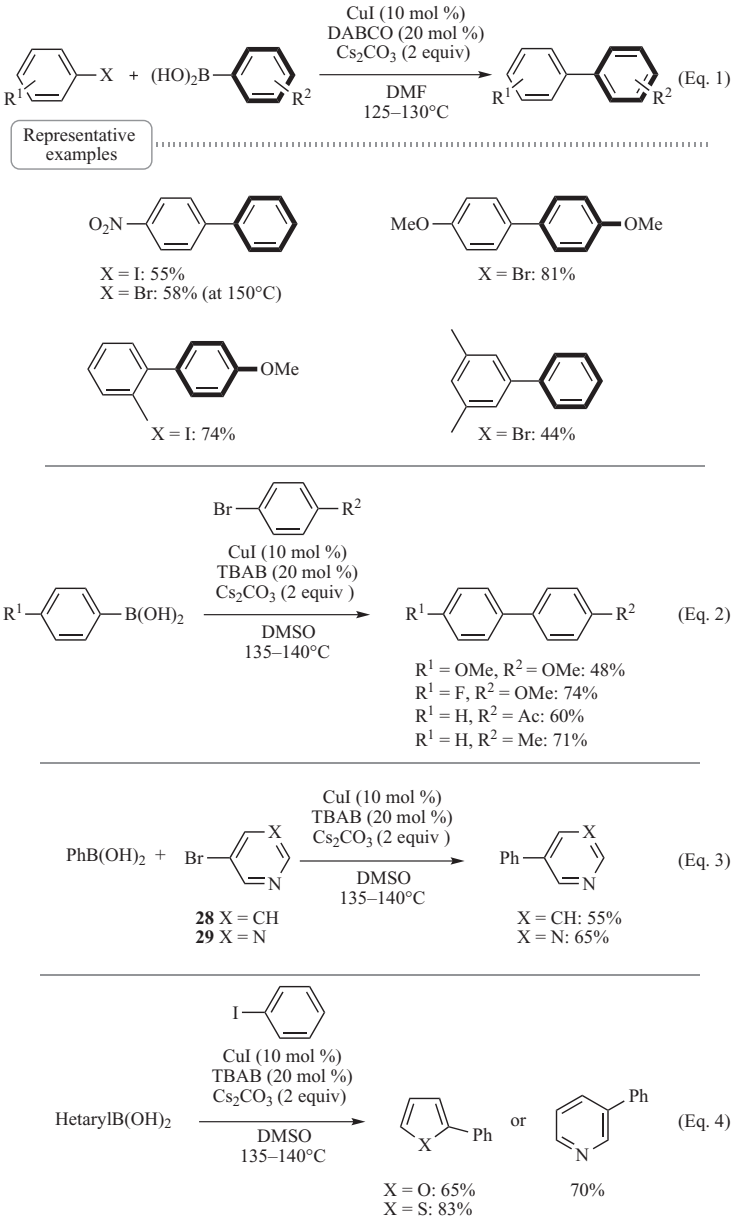


Scheme 10.19 Copper(I)-catalyzed cross coupling of arylboronic acids with diaryliodonium salts.

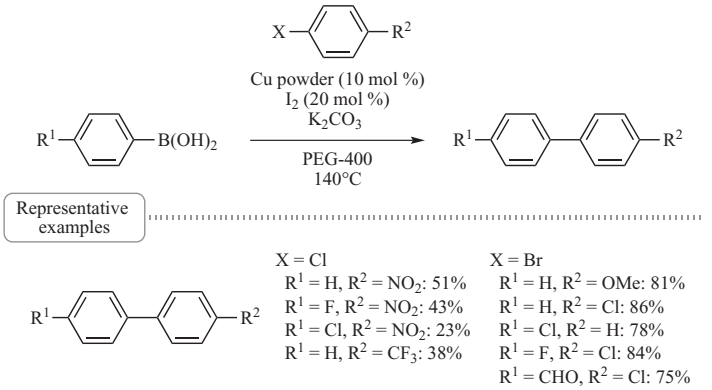
electron-rich (hetero)aryl group of the iodonium was observed. Interestingly, the same reaction produced diaryl ketones when executed under an atmosphere of carbon monoxide.

The Suzuki–Miyaura cross coupling of phenylboronic acid and haloarenes was also investigated using copper-based mixed nanoclusters (see Chapter 20 for more details).[54] The metal clusters, with sizes in the range of 1.6–2.1 nm, were prepared from copper, palladium, and ruthenium as well as various combinations of copper with palladium, platinum, and ruthenium. Their catalytic activities toward the Suzuki–Miyaura coupling of phenylboronic acid and iodobenzene, which was performed with a 2 mol % catalyst loading in DMF at 110°C, were evaluated. Among the nanoclusters investigated, the Cu/Pd bimetallic cluster showed a high activity that was similar to that of a palladium cluster and the copper cluster also catalyzed the cross coupling at a reasonable reaction rate, the coupling of *p*-iodotoluene being complete after 8 and 2 hours using the Cu and Cu/Pd clusters, respectively. The use of a simple copper salt for the cross coupling of haloarenes was reported by Li and coworkers, who demonstrated that the choice of an appropriate ligand was imperative for the success of the reaction.[55] In the absence of any ligand, the coupling of *p*-iodoanisole with phenylboronic acid using copper(I) iodide (10 mol %) and cesium carbonate as a base in DMF at 125–130°C for 20 hours gave the corresponding 4-methoxybiphenyl in 78% yield, while the yield improved to 98% when 1,4-diazabicyclo[2.2.2]octane (DABCO) was employed as a ligand (Scheme 10.20, Eq. 1).[55a] Triethylamine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), or *N*,*N*'-dimethylethylenediamine (DMEDA) were also investigated as ligands but resulted in decreased yields of 66%, 6%, and 31%, respectively, and although phosphines are known as effective ligands for the palladium-catalyzed Suzuki–Miyaura cross coupling, the addition of neither triphenylphosphine nor tricyclohexylphosphine led to increased yields (20% and 6%, respectively). This method proved to be effective for the coupling of arylboronic acids with substituents at the *para*- and *ortho*-positions, but the use of substrates with electron-withdrawing substituents resulted in diminished yields. When bromoarenes were used as coupling partners, stoichiometric amounts of copper(I) iodide and the addition of TBAB were usually required to obtain satisfactory yields. Modified ligand-free conditions with TBAB as an additive and DMSO as the solvent enabled the catalytic cross coupling of bromoarenes and arylboronic acids albeit with limited scope (Scheme 10.20, Eq. 2).[55c] This new protocol was also effective for the coupling of heteroaromatic precursors as exemplified with the phenylation of 3-bromopyridine **28** and 5-bromopyrimidine **29** with phenylboronic acid or 2-furyl-, 2-thienyl-, or 4-pyridyl-boronic acids with iodobenzene, which were achieved in 55–83% yields (Scheme 10.20, Eq. 3 and Eq. 4).

Due to the recent focus on environmental concerns, the development of recyclable catalysts has garnered enormous interest with respect to sustainable chemistry and the immobilization of transition metals is a viable solution for the development of readily recyclable catalysts. While such methods, however,



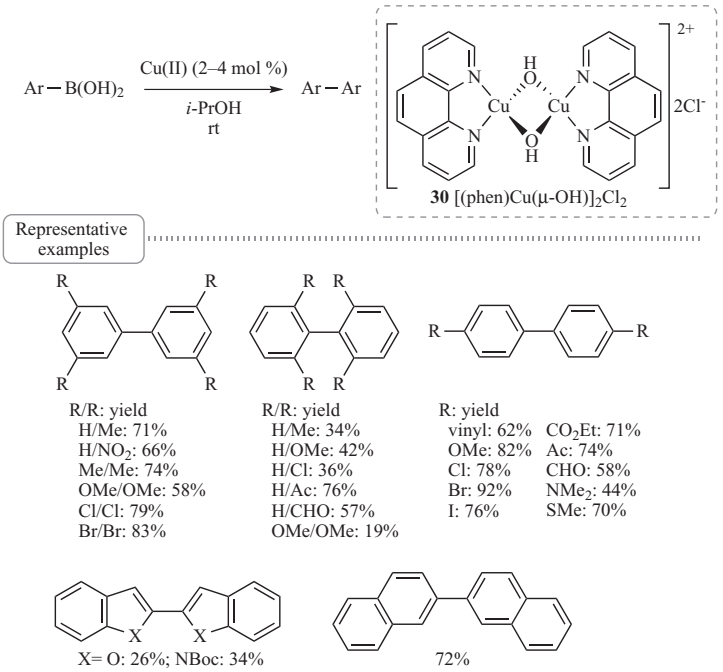
Scheme 10.20 Copper(I)-catalyzed cross coupling of arylboronic acids with aryl halides.



Scheme 10.21 Cross-coupling reaction of arylboronic acids with aryl halides using recyclable copper catalyst.

often decrease the catalytic activity and/or selectivity (see Chapter 20 for details), the Mao and Ji group successfully demonstrated that the use of poly(ethylene)glycol (PEG) as a solvent enables the immobilization of copper catalysts with concurrent improvement of the catalytic efficiency (Scheme 10.21).[56] The Suzuki–Miyaura cross coupling of various arylboronic acids and iodoarenes indeed occurred in good to excellent yields when the reaction was carried out in the presence of copper powder (10 mol %) and potassium carbonate (2 equiv) in PEG-400, which is considered to act as a ligand, at 110°C for 12 hours. Notably, the new catalytic system was effective for the coupling of bromoarenes and electron-deficient chloroarenes, although the yields for the latter were relatively low. For the reaction of these less-reactive haloarenes, catalytic amounts of iodine (20 mol %) were added and the reactions were performed at elevated temperatures. Recycling experiments on the coupling of phenylboronic acid with *p*-nitroiodobenzene revealed that the activity of the catalyst was maintained for at least three cycles without significant lowering of the yields (average 94%). However, the yield dropped to 66% after six cycles. Recently, a new catalytic system comprising copper oxide and 2,2′-diamino-6,6′-dimethylbiphenyl ligand was reported to be also effective for the Suzuki–Miyaura cross coupling involving aryl iodides and bromides, the advantages of this type of axially chiral ligand being its potential for future developments in asymmetric cross-coupling reactions.[57]

Besides the use of arylboronic acids in copper-catalyzed cross-coupling reactions involving various aryl halides or synthetic equivalents, they have also been used for the preparation of symmetrical biaryls by homodimerization. Indeed, the homocoupling of arylboronic acids was first accomplished with half an equivalent of copper(II) acetate in DMF at 100°C with various efficiencies (30–95%) depending on the steric bulk and orientation of the substituents, the presence of *ortho*-substituents resulting in low yields.[58a] Some arylboronic acids also underwent homocoupling when the copper(II) loading was reduced to 0.1 equiv under an atmosphere of oxygen, albeit in slightly lower yields. As



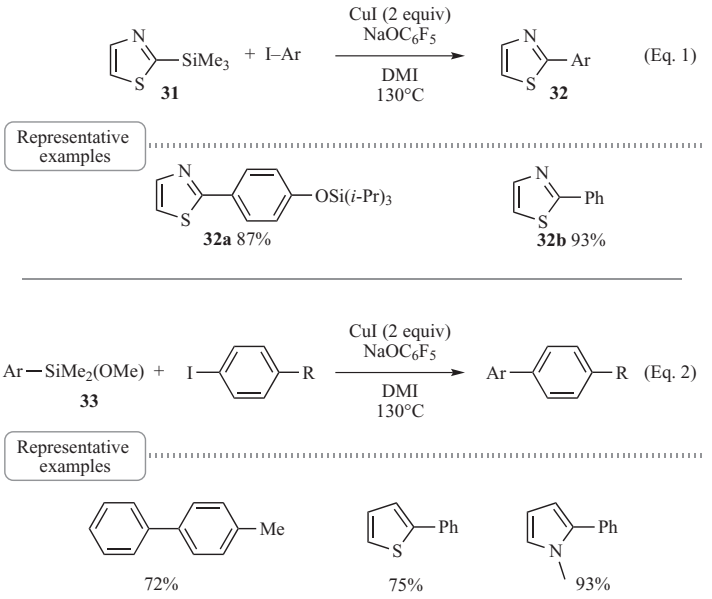
Scheme 10.22 Copper(II)-catalyzed homocoupling of arylboronic acids.

for the copper source, copper(II) sulfate can also be used for the stoichiometric homocoupling of arylboronic acids under base- and ligand-free conditions.[58b] Catalytic homocoupling with lower amounts of copper was achieved using 1,10-phenanthroline as a ligand. In the presence of copper(II) acetate (5 mol %) and 1,10-phenanthroline (6 mol %), *p*-tolylboronic acid was stirred in isopropyl alcohol at ambient temperature for 4 hours to furnish 4,4′-dimethylbiphenyl in 83% yield (Scheme 10.22).[59] Isopropyl alcohol was found to be a superior solvent to ethanol or methanol, and it was also revealed that the isolated hydroxo-bridged dinuclear Cu(II) complex [(phen)Cu(μ-OH)]$_2$Cl$_2$·3H$_2$O (**30**·3H$_2$O) showed the highest catalytic ability, the use of 2–4 mol % of this catalyst enabling the transformation of various arylboronic acids into the corresponding biaryls in moderate-to-good yields, presumably via a bimolecular reductive elimination. Nevertheless, this catalytic system was found to be less effective with *ortho*-substituted arylboronic acids and heteroaryl boronic acids as well. Later on, Cheng and Luo modified this protocol to eliminate the need for the 1,10-phenanthroline ligand and reported that the use of copper(I) chloride in methanol at room temperature was especially efficient and also improved the substrate scope.[60a] Finally, Kaboudin and coworkers next reported on the use of dinuclear (μ-hydroxo)copper(II) β-cyclodextrin complex for the homocoupling of arylboronic acids.[60b] They also proposed a binuclear reductive elimination mechanism.

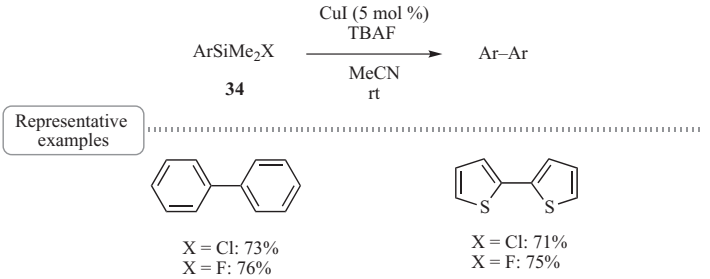
10.3.3 Coupling of Organosilanes

The palladium-catalyzed cross coupling of organosilicon compounds with organic halides, which is known as Hiyama cross coupling, has received significantly less attention than those involving organotin and boron compounds (i.e., Migita–Kosugi–Stille coupling and Suzuki–Miyaura coupling), despite the low toxicity and easy handling of organosilicon compounds.[61] This is mainly due to the transmetallation from silicon to palladium that is less efficient than those from the corresponding tin or boron reagents and usually requires fluoride anion to activate the silicon–carbon bond and facilitates the transmetallation. The coupling efficiency, however, has been significantly improved by the use of silanols[62] or 2-(hydroxymethyl)phenylsilanes,[63] which enabled the application of Hiyama-type coupling to the synthesis of complex natural products.[62c]

In striking contrast to such dramatic advances in palladium-catalyzed methods, the progress in organosilicon-based coupling using copper promoters has been relatively stagnant. To date, only one example of copper-mediated Hiyama-type cross coupling has been reported by Ito and coworkers, who disclosed that copper(I) pentafluorophenoxide, prepared *in situ* from copper(I) iodide and sodium pentafluorophenoxide, is an effective promoter for this reaction (Scheme 10.23).[64] In the presence of this promoter, the reaction of trimethylsilylthiazole (**31**) with iodobenzene was performed in dimethylimidazolidinone (DMI) at 130°C for 12 hours to give the coupling product **32** in 93% yield. It should be noted that triisopropylsilyl ether was retained in coupling product **32a** since fluoride ion sources, which generally remove this



Scheme 10.23 Copper(I)-mediated cross coupling of arylsilanes with aryl iodides.



Scheme 10.24 Copper(I)-catalyzed homocoupling of arylsilanes.

protecting group, are unnecessary for the transmetallation in this case. In contrast, the coupling of phenyltrimethylsilane with *p*-iodotoluene under the optimal conditions failed and the cross coupling with these less-reactive substrates was enabled by the use of methoxydimethylsilyl analogues **33** which undergo transmetallation under the same conditions (Scheme 10.23, Eq. 2).

Meanwhile, the copper-catalyzed homocoupling of arylsilanes was being developed by Kang and coworkers, who employed aryldimethylhalosilanes **34** as substrates and tetrabutylammonium fluoride (TBAF) as an additive to promote a rapid homocoupling, even at ambient temperature (Scheme 10.24).[65] Fluoride is a slightly superior halide ligand on silicon to chloride in terms of yields, and this method was found to be also applicable to the corresponding alkenyl- and alkynyl-silanes. As a note, a stoichiometric copper(I) chloride-mediated homocoupling of arylethyldifluorosilane was also reported.[66]

As developed in the previous paragraphs, biaryls could be efficiently synthesized via copper-mediated and copper-catalyzed homocoupling and cross-coupling reactions of arylstannane, borane, and silane derivatives with different electrophiles such as aryl halides or iodonium salts. More recently, the construction of biaryls has witnessed a significant shift of paradigm with the development of direct and more practical methods relying on arene carbon–hydrogen or carbon–carbon bond fission. The most relevant copper-catalyzed strategies for biaryl elaboration are discussed in the next section.

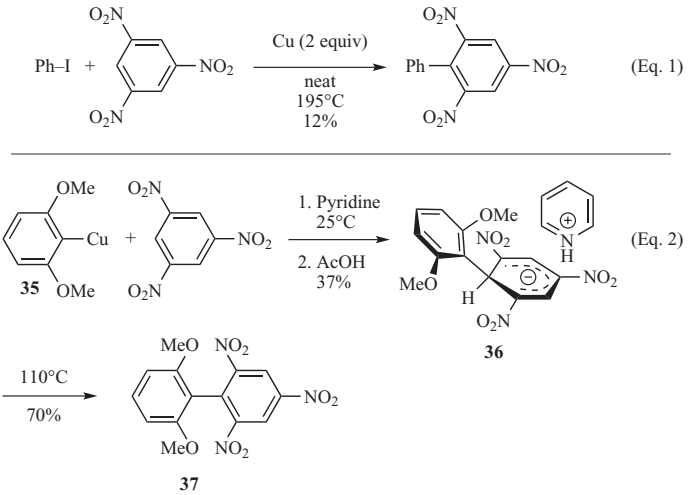
10.4 BIARYL SYNTHESIS BY ARYLATION INVOLVING ARENE C–H OR C–C BOND FISSION

10.4.1 Direct C–H Arylation of Arenes with Prefunctionalized Arylating Reagents

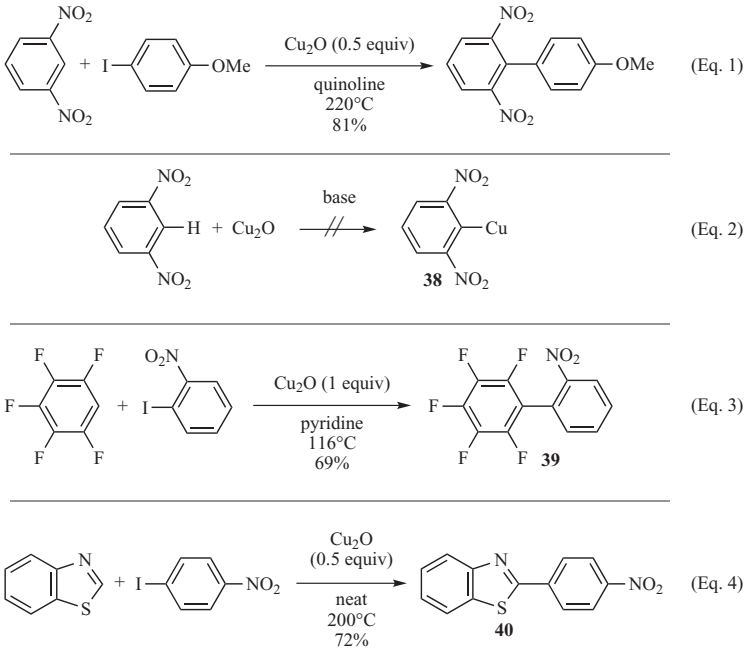
Direct functionalization of C–H bonds is an ideal process that enables omission of synthetic steps such as halogenation or metallation (which can also require additional protection step) and also reduces harmful waste. The development of transition-metal-catalyzed C–H functionalization reactions entails

a dramatic paradigm shift from conventional synthetic tactics based on functional-group manipulation to modern, environmentally friendly, step-economical strategies via the direct transformation of C–H bonds.[67] Toward this goal, ruthenium, rhodium, and palladium catalysts have been extensively explored for direct C–H arylation.[68] This section summarizes recent progress in copper-mediated direct C–H arylation with haloarenes or aryl organometallics, an area in which significant progress has recently been made.

An interesting hint of the feasibility of such copper-mediated process was actually published in 1960. Indeed, the Ullmann homocoupling of iodobenzene was reported to be significantly suppressed when 1,3-dinitrobenzene was used as a solvent at 195°C since the reaction furnished the expected biphenyl in a low 22% yield together with an unsymmetrical biaryl, 2,6-dinitrobiphenyl, and intact iodobenzene in 8% and 44% yields, respectively.[69a] 2,6-Dinitrobiphenyl was obviously produced by direct arylation of the C–H bond between the two nitro groups of dinitrobenzene with iodobenzene, and when 1,3,5-trinitrobenzene was used as the solvent, homocoupling was completely suppressed and the corresponding unsymmetrical biaryl was formed in 12% yield (Scheme 10.25, Eq. 1). Later, it was confirmed that the direct arylation of polynitroarenes with iodobenzene proceeded through a Meisenheimer intermediate that was formed from an intermediate phenylcopper reagent.[69b] Indeed, the reaction of 1,3,5-trinitrobenzene with 1,6-dimethoxyphenylcopper (**35**) in pyridine at 25°C resulted in a deep red solution, and acidification with acetic acid furnished the pyridinium salt of Meisenheimer anion **36** (37%), which was heated in vacuo at 110°C to afford biaryl **37** in 70% yield (Scheme 10.25, Eq. 2). Similar direct arylation of polynitroarenes was also observed when they were



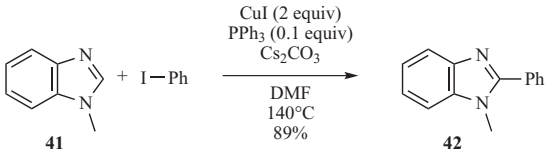
Scheme 10.25 Copper-mediated direct arylation of 1,3,5-trinitrobenzene with iodobenzene.



Scheme 10.26 Copper-mediated direct arylation of electron-deficient arenes with aryl iodides.

heated at 220°C with copper(I) oxide and *p*-iodoanisole in quinoline, the corresponding cross-coupling products of 1,3-dinitrobenzene or 1,3,5-trinitrobenzene being obtained in good yields (Scheme 10.26, Eq. 1).[70] While the formation of 2,6-dinitrophenylcopper (**38**) from the abstraction of the acidic 2-proton of 1,3-dinitrobenzene was proposed, attempts to prepare phenylcopper by this method failed (Scheme 10.26, Eq. 2).[70b] The cross-coupling reactions of preformed arylcopper reagents with iodoarenes were also reported,[27] and other aromatic compounds with sufficiently acidic protons were shown to undergo direct arylations via proton abstraction. Copper-mediated direct arylation of pentafluorobenzene and benzothiazole with nitrophenyl iodides was similarly performed to afford cross-coupling products **39** and **40** in 69% and 72% yields, respectively, the latter product being obtained in a higher yield (85%) using the highly sensitive copper(I) *tert*-butoxide as a promoter (Scheme 10.26, Eq. 3 and Eq. 4).[71,72]

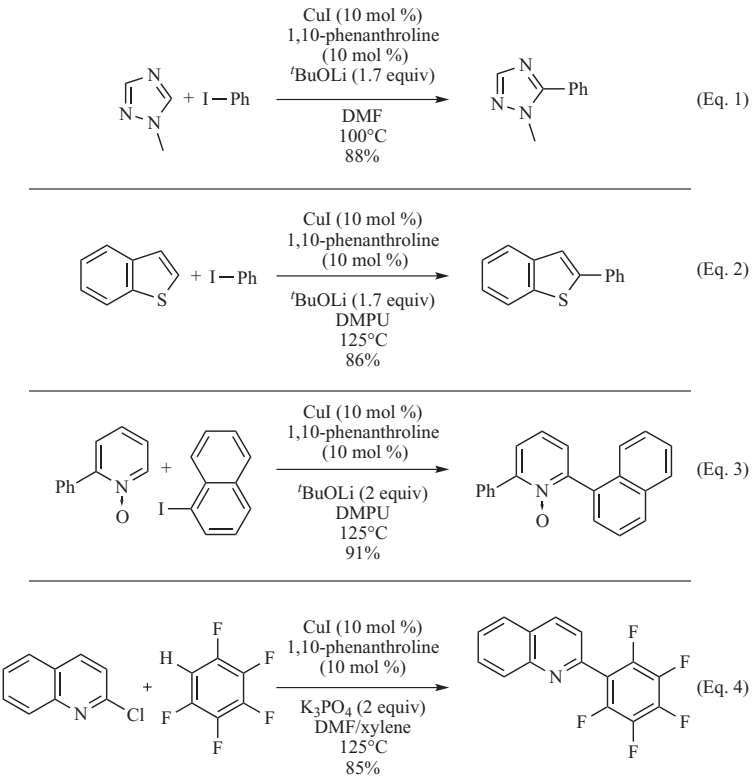
Although these above-mentioned methods have the practical advantage of producing unsymmetrical biaryls with predictable regiochemistry via simple procedures, stoichiometric loadings of copper promoters and harsh reaction conditions are required. After these early and remarkable reports, the copper-promoted direct C–H arylation with iodoarenes was neglected for more than two decades until a study published by Miura and coworkers on



Scheme 10.27 Copper-mediated direct arylation of 1-methyl-1*H*-benzimidazole with iodobenzene.

the palladium-catalyzed direct arylation of azole with haloarenes. In this publication, it was also shown that the combination of stoichiometric loading of copper(I) iodide, triphenylphopshine, and cesium carbonate as a base promotes the coupling of azoles with iodobenzene in DMF at 120–140°C to exclusively give 2-phenylazoles, albeit in low yields, while the palladium-catalyzed reactions produce mixtures of 5-phenylazoles and 2,5-diphenylazoles.[73a] The arylation of 1-methyl-1*H*-benzimidazole **41** with iodobenzene via treatment with copper(I) iodide, triphenylphopshine, and cesium carbonate for 8 hours resulted in the 2-phenylation product **42** in 89% yield (Scheme 10.27).[73a] After extensive optimizations, the scope of direct arylation with iodoarenes using this system was extended to include benzoxazole, benzothiazole, 5-aryloxazoles, 1,3,4-oxadiazoles, and 1,2,4-triazoles.[73b–d] It should be noted that the use of extra base and phosphine ligand enables the direct arylation of azoles under milder conditions.

A further breakthrough was reported in a series of publications by Daugulis and coworkers,[74] who demonstrated that a broad spectrum of heteroarenes and polyfluorobenzenes containing C–H bonds with pK_a values below 35 underwent catalytic direct arylation with (hetero)arylbromides and iodides using the copper(I) iodide/1,10-phenanthroline catalytic system in DMF or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (Scheme 10.28). The choice of the base again plays a pivotal role for the success of this transformation since the use of potassium *tert*-butoxide for the coupling involving *para*-substituted haloarenes resulted in a loss of regioselectivity due to the formation of benzyne intermediates, a side reaction that could be suppressed by switching to lithium *tert*-butoxide. For less-reactive substrates, a more hindered base, lithium 3-ethyl-3-pentanoxide, was shown to be beneficial to minimize the corresponding direct aromatic nucleophilic substitution, while a weaker base such as potassium phosphate can be used for the arylation of more acidic heterocycles such as benzothiazole, pyridine *N*-oxide, and penta- and tetrafluorobenzenes. Typical examples are shown in Scheme 10.28. These cross-coupling reactions are thought to proceed via the coupling of (hetero) arylcopper(I) intermediates with haloarenes, which is supported by the formation of a phenanthroline-ligated pentafluorophenylcopper(I) complex from copper(I) iodide, pentafluorobenzene, and phenanthroline in the presence of potassium phosphate in DMF at 125°C, the structure of which is confirmed by comparing its ^{19}F nuclear magnetic resonance (NMR) spectral data with those

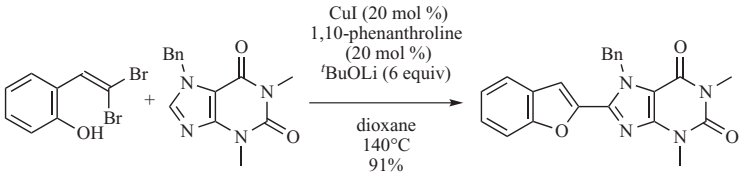


Scheme 10.28 Copper(I)-catalyzed direct arylation of heteroarenes and pentafluorobenzene.

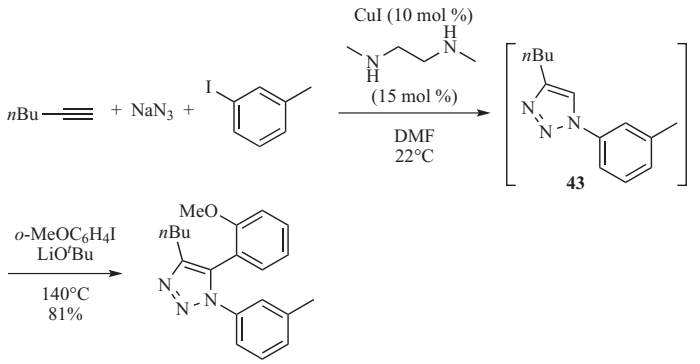
of an authentic sample. As an extension of this method, a one-pot sequential iodination/copper-catalyzed cross coupling was also accomplished, providing a direct route to unsymmetrical biaryls from two different (hetero)aromatic precursors.[74d]

The copper-catalyzed direct C–H arylation of caffeine with bromoarenes was also investigated in detail,[75] and just as a note, one of the obtained products, that is, the adduct with *p*-bromo-*N*,*N*-dimethylaniline, exhibited strong fluorescence in chloroform solution and in the solid state and is potentially applicable as a biological imaging probe. In addition, the direct coupling of a caffeine derivative was combined with an intramolecular copper-catalyzed Ullmann-type reaction from 2-(2,2-dibromovinyl)phenol to provide a successful, high-yielding tandem route to a caffeine-derived benzofuran (Scheme 10.29).[75b]

The direct C2-arylation of 1-(pyridin-2-yl)indole-3-carboxaldehyde with iodoarenes was also achieved using subcatalytic amounts of copper(I) oxide,[76] and Ackermann and coworkers established a sequential four-component coupling route to 1,2,3-triazoles, which involves a single copper catalyst-mediated



Scheme 10.29 Copper(I)-catalyzed tandem benzofuran cyclization/direct arylation.

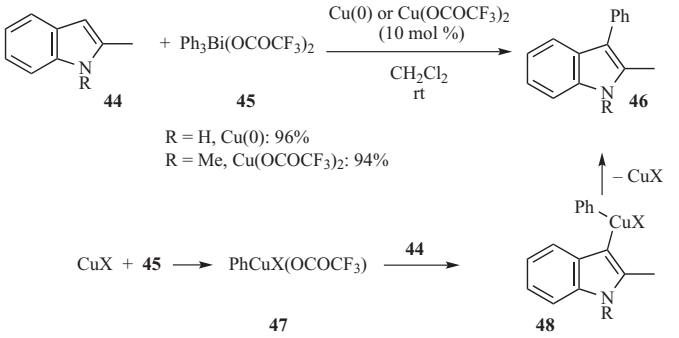


Scheme 10.30 Copper(I)-catalyzed tandem three-component azidation/dipolar cycloaddition/direct C–H arylation.

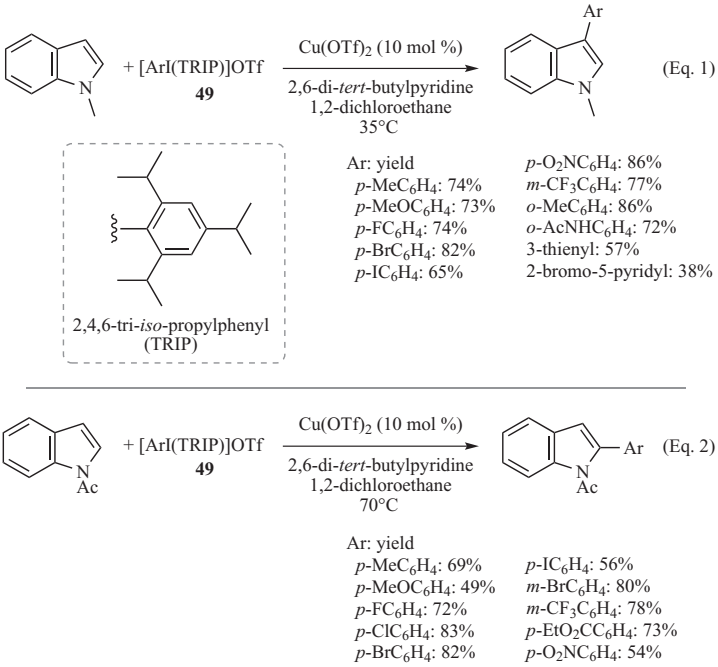
azidation of iodoarenes, [3 + 2] cycloaddition of the resulting arylazide with terminal alkynes, and subsequent direct C–H arylation of the resulting 1,2,3-triazole **43** (Scheme 10.30).[77]

As replacements for haloarenes, hypervalent compounds have been used for the copper-catalyzed direct C–H arylation of electron-rich aromatic substrates. Although these reagents are not commercially available and have to be prepared, their use typically allows for remarkably mild conditions as evidenced by results collected in this subsection.

A pioneering study published by Barton in 1988 involves the C3 arylation of indoles with triphenylbismuth bistrifluoroacetate.[78] As shown in Scheme 10.31, 2-methylindoles **44** were treated with hypervalent bismuth reagent **45**, prepared from triphenylbismuth bisacetate by ligand exchange,[78b] in the presence of copper catalysts (10 mol %) in dichloromethane at ambient temperature to afford 3-phenylindoles **46** in remarkably high yields. In the absence of the C2 methyl group, the reaction gave a *N*-phenylation product, which indicates the importance of steric shielding around the nitrogen atom. From a mechanistic perspective, indolylcopper(III) intermediates **48** were proposed to be produced from phenylcopper(III) complex **47** and indoles **44** (probably via electrophilic aromatic substitution), and this was followed by final reductive elimination to yield the C3-arylation products **46**.

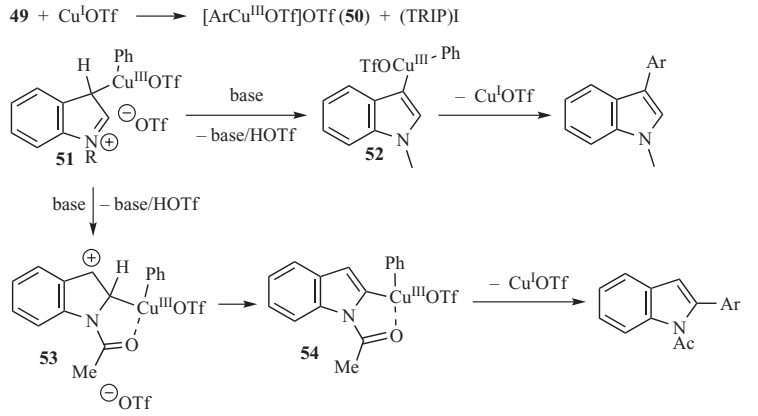


Scheme 10.31 Copper-catalyzed direct arylation of indole derivatives with triphenylbismuth reagent.



Scheme 10.32 Copper(I)-catalyzed regioselective direct arylation of indole derivatives with diaryliodonium salts.

Recently, a similar but regiocontrolled arylation of *N*-protected indoles using hypervalent iodine reagents was developed by Gaunt and coworkers (Scheme 10.32).[79a] The C3-arylation of *N*-methylindole was achieved using copper(II) triflate as the catalyst (10 mol %) and 2,6-di-*tert*-butylpyridine as the base in 1,2-dichloroethane. Nonsymmetrical diaryliodonium triflates **49**

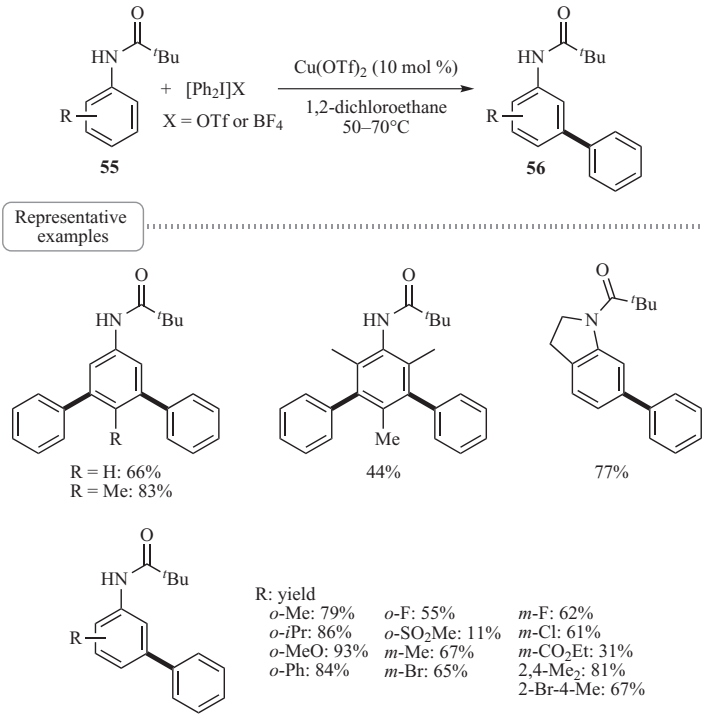


Scheme 10.33 Proposed mechanism for the copper(I)-catalyzed regioselective direct arylation of indole derivatives.

possessing a bulky 2,4,6-tri-isopropylphenyl (TRIP) as a sacrificial aryl group, were employed as arylating agents and substituted aryl and heteroaryl groups were selectively and efficiently introduced yielding the corresponding indoles in moderate-to-good yields and excellent regioselectivity. In contrast, *N*-acetylindole underwent C2-arylation under the same conditions, although the reaction had to be performed at 70°C, resulting in the corresponding products in 49–83% yields, the regioselectivity (C2 : C3 = 7:1–2.6:1) being lower than those of the C3 arylations (Scheme 10.32, Eq. 2).

Scheme 10.33 outlines plausible mechanisms. Hypervalent iodine reagent **49** first reacts with copper(I) triflate as the net catalyst to produce an electrophilic arylcopper(III) species (**50**), which is trapped by the indole, reacting preferentially at C3, to yield cyclic iminium intermediate **51**. Subsequent deprotonation then gives 3-indolylcopper(III) species **52** and final reductive elimination accounts for the formation of the 3-arylindoles and regenerates copper(I) triflate. In the case of *N*-acylindole, a 1,2-migration of the phenylcopper(III) fragment occurs due to the coordination of the amide carbonyl group in **53** and the resulting 2-indolylcopper(III) species (**54**) then undergoes reductive elimination to ultimately furnish the 2-arylation product and copper(I) triflate as in the previous case.

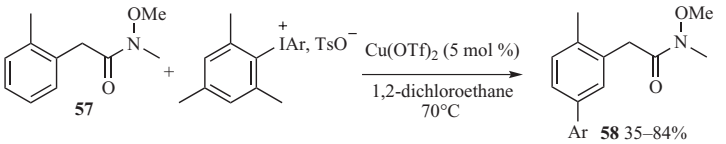
In an outstanding study, the copper-catalyzed direct arylation with hypervalent iodine reagents has been further extended to aniline derivatives. Friedel–Crafts-type electrophilic aromatic substitutions of aniline derivatives are expected to occur at *ortho*/*para*-positions due to the directing effect of the electron-donating amino group and the electrophilic attack by an arylcopper(III) species is also assumed to follow this trend. However, Phipps and Gaunt reported in 2009 an unprecedented *meta*-selective direct C–H arylation of *N*-acyl anilines with diphenyliodonium triflate or tetrafluoroborate under copper catalysis (Scheme 10.34).[79b] As acyl groups on the nitrogen



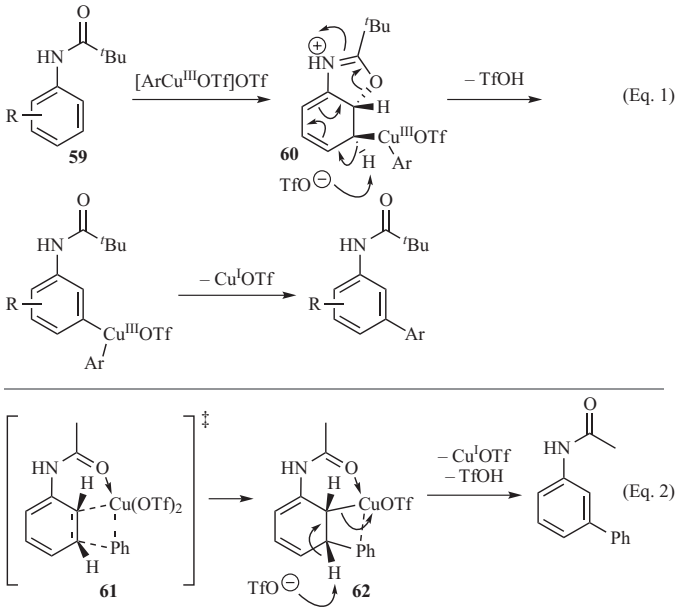
Scheme 10.34 Copper(I)-catalyzed, *meta*-selective direct arylation of aniline derivatives with diaryliodonium salts (bond formed shown in bold).

atom, benzoyl and pivaloyl groups provided the highest yields for *meta*-arylation. Pivaloyl anilides with various substituents (**55**) underwent arylation at 50–70°C to afford mono- or disubstituted products **56** in 11–93% yields. Electron-withdrawing substituents tend to diminish product yields, regardless of their position, and substrates with *ortho*-substituents were arylated at the less hindered of the two *meta*-positions. Substituted phenyl groups can also be introduced using nonsymmetrical diaryliodonium triflate possessing a bulky sacrificial mesityl group and this *meta*-selective arylation is applicable to α-arylacetamides and benzyl ketones.[79d] The *meta*-arylation of Weinreb amides **57** to obtain the *meta*-arylated products **58** is particularly useful because the amide moiety can be further transformed into aldehydes and ketones (Scheme 10.35).

This unusual *meta*-selectivity was ascribed to oxy-cupration, which involves the antiaddition of the amide carbonyl oxygen and arylcopper(III) species on the benzene ring (**59** → **60** in Scheme 10.36). Subsequent reductive elimination leads to the *meta*-arylation products and restoration of the catalytically active CuOTf species. A different mechanism involving four-membered transition state **61** was proposed on the basis of density functional theory (DFT)



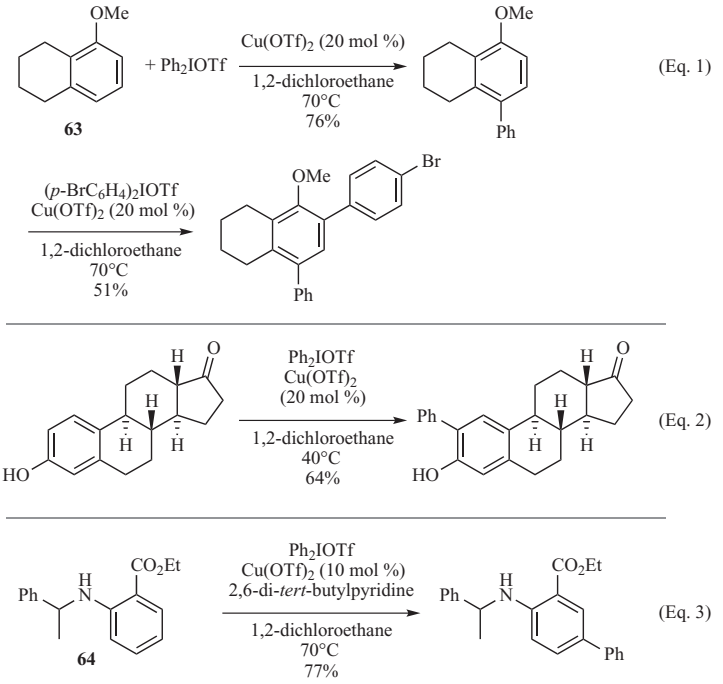
Scheme 10.35 Copper(I)-catalyzed, *meta*-selective direct arylation of Weinreb amide with diaryliodonium salts.



Scheme 10.36 Proposed mechanisms for the copper(I)-catalyzed *meta*-selective direct arylation of anilides.

calculations on the phenylation of acetanilide with a phenylcopper reagent.[79e] According to this proposed mechanism, the electrophilic copper(III) fragment is directed to the *ortho*-position and subsequent rearomatization of **62** via deprotonation restores copper(I) triflate as the net catalyst. It should be noted that the *meta*-arylation of Weinreb amide **57** proceeded without a copper catalyst at 80–90°C, while arylation at 70°C required the catalyst,[79d,f] which implies that the unprecedented *meta*-selectivity is attributable to a factor other than the copper catalyst. Thus, the mechanism of this remarkable transformation clearly necessitates further elucidation.

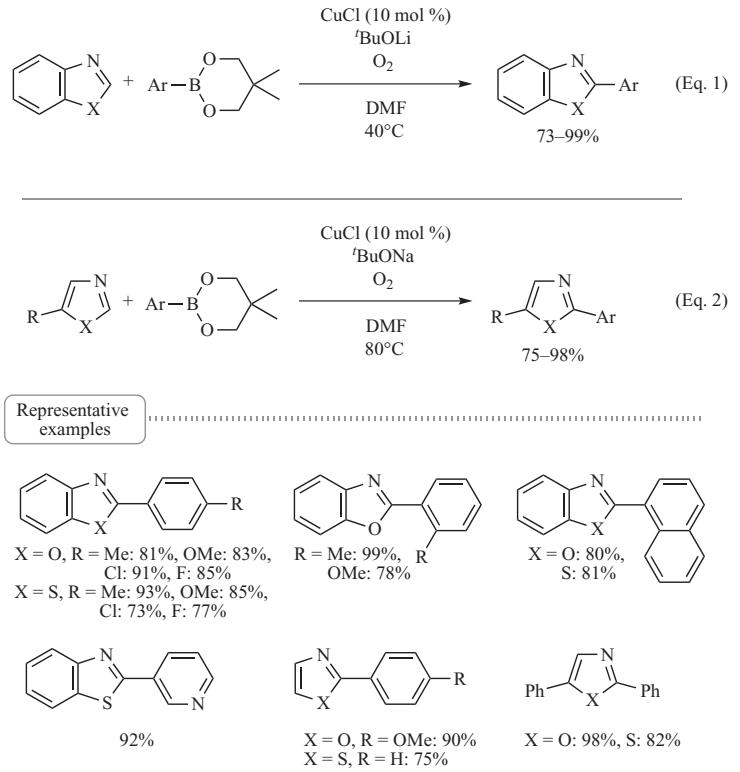
In contrast to these substrates, normal *para*-selectivity was observed for similar arylation of electron-rich phenol and anisole derivatives (Scheme 10.37, Eq. 1).[79c] When the *para*-position was blocked, arylation occurred at the *ortho*



Scheme 10.37 Copper(I)-catalyzed regioselective direct arylation of electron-rich arenes.

C–H bond (Scheme 10.37, Eq. 2), and consequently, regioselective introduction of two different aryl groups was achieved by performing sequential arylations of **63** (Scheme 10.37, Eq. 1). It was also revealed that *N*,*N*-dibenzylaniline underwent *para*-selective arylation in the presence of a base, 2,6-di-*tert*-butylpyridine,[79c] and that for *ortho*-substituted substrates such as **64**, a single phenethyl group provided effective protection (Scheme 10.37, Eq. 3).

In the above examples, which involve hypervalent reagents, highly electrophilic copper(III) species were generated, and their electrophilic reactions with electron-rich aromatics are the origin of the regioselective C–H arylations. Related direct C–H arylations were also achieved using readily available and easy-to-handle arylboronic acids.[80a] The ability to execute the reaction under air provides a significant practical advantage, although stoichiometric amounts of copper promoter and acidic conditions are required. Using this method, 1,3,5-trimethoxybenzene was monoarylated in moderate yields, and interestingly, excess amounts of copper(II) trifluoroacetate and phenylboronic acid enabled the multiple arylations of 1-methyindole and 1-methypyrrole. Moreover, catalytic arylation of azoles with arylboronate esters was achieved under basic conditions. In this reaction, copper(II) chloride was proposed to be a net catalyst and dioxygen was utilized as a terminal oxidant to reoxidize copper(I) chloride. Arylated oxazoles and thiazoles were obtained in high



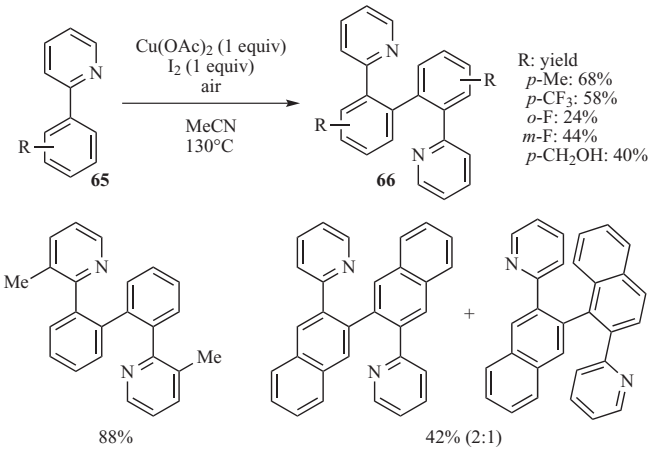
Scheme 10.38 Copper(I)-catalyzed direct arylation of azoles with arylboronates.

yields ranging from 73% to 99% and representative examples are shown in Scheme 10.38.[80b]

10.4.2 Direct C–H Arylation with Nonfunctionalized Arylating Agents

In the preceding section, the copper-mediated direct C–H arylations of arenes with haloarenes, hypervalent reagents, and arylboron reagents were shown to be reliable routes to biaryl compounds with predictable regiochemistry. They, however, require prefunctionalized aromatic compounds as arylating agents, and avoiding the use of these reagents would enable increased step economy and environmental benignancy. This section will outline the formation of biaryls that occurs via the fission of C–H bonds of both coupling components, reactions that are known as dehydrogenative or oxidative coupling reactions.

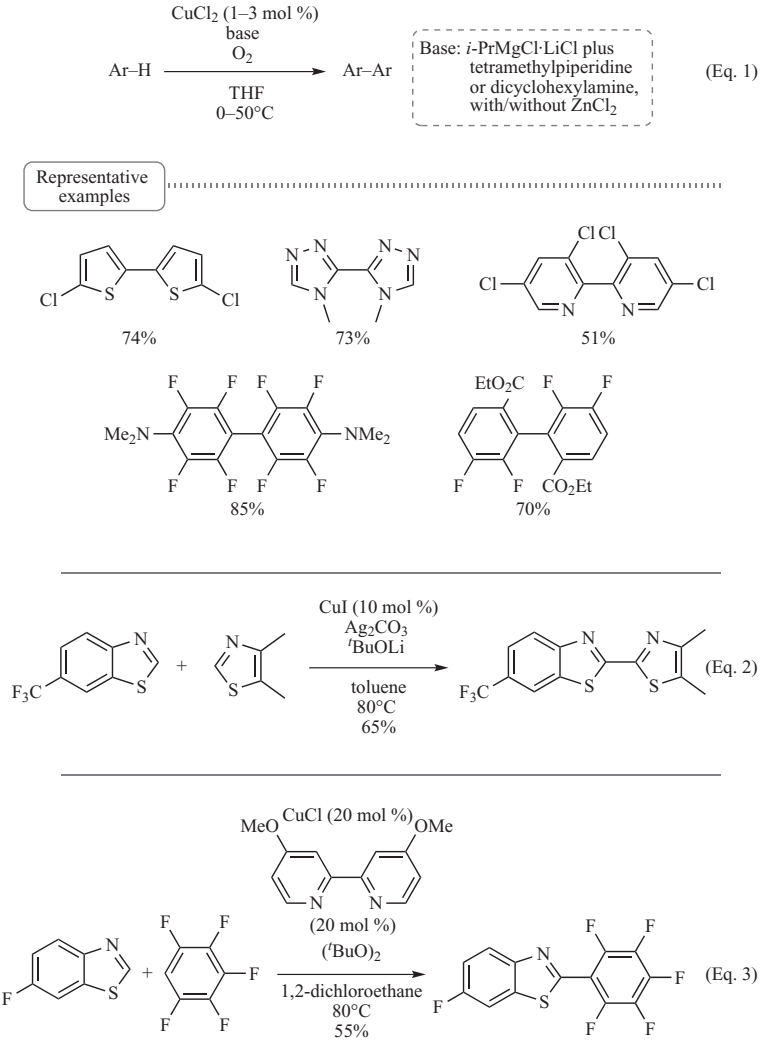
Ortho-lithiation is the conventional method for directly functionalizing aromatic C–H bonds *ortho* to the directing group,[81] and aryllithiums produced by this technique can undergo homocoupling via oxidation of cuprate



Scheme 10.39 Copper(II)-mediated dehydrogenative homocoupling of 2-arylpyridines.

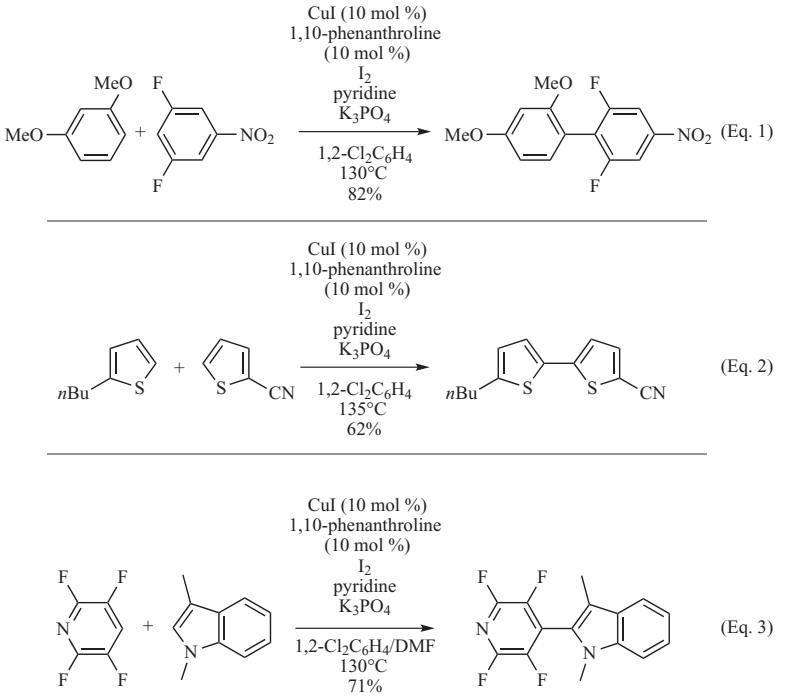
intermediates as described in Section 10.2.2.[34b] This method is superior to related homocouplings via cuprate oxidation since the preparation of haloarene precursors is unnecessary; however, the use of highly reactive alkyllithium reagents is incompatible with reactive functional groups. Recently, directed homocoupling, which is presumed to proceed via *ortho*-iodination and subsequent Ullmann coupling, was discovered by Yu and coworkers.[82] They treated 2-arylpyridines **65** with 1 equiv of copper(II) acetate and 1 equiv of iodine in acetonitrile at 130°C to obtain homocoupling products **66** in varied yields (Scheme 10.39). The aryl–aryl bond formation occurred at the position *ortho* to the 2-pyridyl group; this reaction is tolerant of unprotected hydroxy groups and the highest yield of 88% was obtained for the reaction of 2-phenyl-3-methylpyridine, while a 2:1 mixture of symmetrical and unsymmetrical coupling products was formed from 2-(2-pyridyl)naphthalene.

Catalytic oxidative homocoupling without relying on a directing group was accomplished by Do and Daugulis[83a] and Yamaguchi and coworkers[83b] using molecular oxygen as a more environmentally benign oxidant. As mentioned previously, heteroarenes and polyfluorobenzenes that feature C–H bonds with pK_a values below 35 undergo catalytic direct arylation with (hetero)aryl halides in the presence of a copper(I) iodide/1,10-phenanthroline catalytic system and an appropriate base such as lithium *tert*-butoxide.[74] As an extension of this strategy, oxidative homocoupling using a catalytic amount of copper(II) chloride and bases composed of isopropylmagnesium chloride and additive(s) was developed. The reaction conditions were tolerant toward heterocycles, ester, nitrile, and nitro moieties and selected examples are shown in Scheme 10.40, (Eq. 1). Zhang and coworkers[83c] reported a similar system based on copper(I) iodide (10 mol %) or chloride (20 mol %) using silver carbonate or *tert*-butyl peroxide as oxidants (Scheme 10.40, Eq. 2 and Eq. 3).

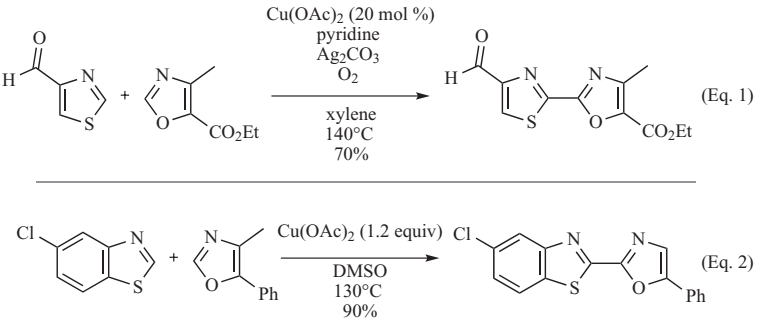


Scheme 10.40 Copper-catalyzed dehydrogenative homo- and hetero-cross coupling of heteroarenes and polyfluorobenzenes.

Subsequently, catalytic dehydrogenative cross coupling of arenes using iodine as a single oxidant was developed.[83d] The authors succeeded in suppressing undesired homocoupling by exploiting the selective iodination of one of the two coupling components followed by coupling of *in situ* formed iodoarenes with other coupling components. It is noteworthy that the single copper catalyst fulfills the dual role of promoting both the iodination of arenes and subsequent cross-coupling reactions in the presence of molecular iodine as an oxidant, and representative examples of this strategy are shown in Scheme 10.41 (Eq. 1, Eq. 2, and Eq. 3).

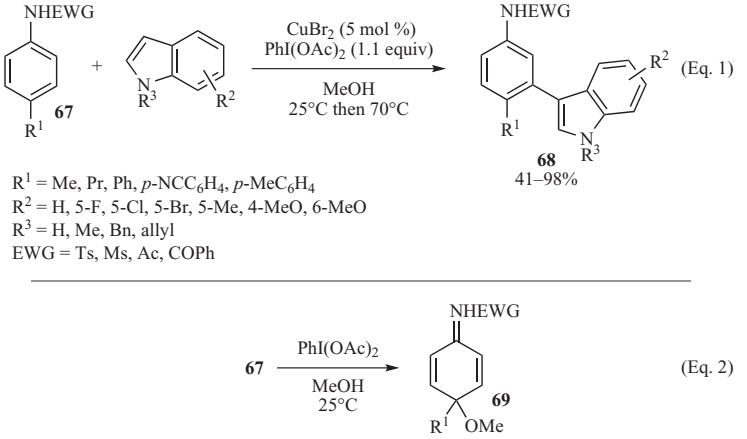


Scheme 10.41 Copper(I)-catalyzed dehydrogenative cross-coupling reactions between electron-rich (hetero)arenes and electron-deficient (hetero)arenes.



Scheme 10.42 Copper(II)-catalyzed or -mediated dehydrogenative cross-coupling reactions of heteroarenes.

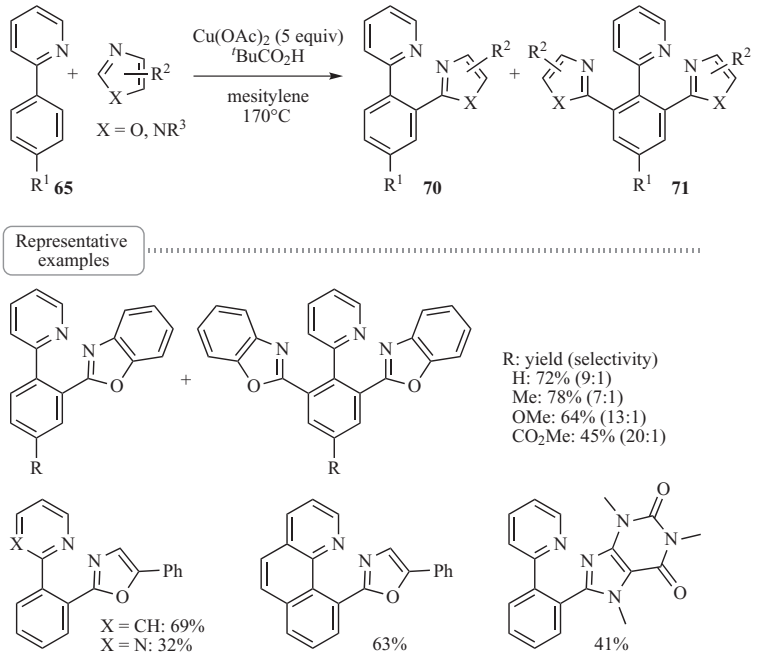
It should also be noted that copper-catalyzed or copper-mediated cross coupling of heteroarenes has been reported to occur with silver carbonate as an oxidant (Scheme 10.42, Eq. 1)[84a] or in the absence of any additives provided that stoichiometric amounts of copper(II) acetate are used (Scheme 10.42, Eq. 2).[84b]



Scheme 10.43 Copper(II)-catalyzed formal dehydrogenative cross coupling of anilides and indole derivatives.

An interesting and less common dehydrogenative C3–C3 cross coupling of aniline derivatives and indoles was developed in 2010, as shown in Scheme 10.43 (Eq. 1).[85] The amino group of **67** must be protected by electron-withdrawing groups such as sulfonyl or acetyl groups and the *para*-carbon should also be substituted by alkyl or aryl groups. In this reaction, the cross coupling is preceded by oxidative methoxylation of **67** with iodobenzene diacetate to form cyclohexa-2,5-dienimines **69** (Scheme 10.43, Eq. 2), which are then trapped by indoles at C3 in the presence of copper(II) bromide (5 mol %) to deliver **68**. Therefore, the copper catalyst is most likely acting as a Lewis acid activator for **69** in this process.

The cross coupling of arenes bearing a directing group and azoles possessing an acidic proton was achieved by Miura and coworkers, although excess amounts of copper(II) acetate were required (Scheme 10.44).[86a] They discovered that the treatment of 2-phenylpyridines **65** and benzoxazole (2 equiv) with copper(II) acetate (5 equiv) and pivalic acid (PivOH, 1 equiv) in mesitylene at 170°C for 2 hours produced mono- and double cross-coupling products **70** and **71** in 45–78% combined yields with selectivities in the 7:1–20:1 range. This cross-coupling reaction could also be applied to various combinations of 2-phenylazines and azoles to obtain 1:1 adducts in moderate-to-good yields. Typical examples are summarized in Scheme 10.44. Empirical evidences including the presence of an intramolecular kinetic isotope effect on *ortho*-deuterated 2-phenylpyridine, a minimal effect of radical scavengers, and rapid H/D exchange of benzoxazole under the reaction conditions imply that the cross coupling proceeds via reversible C–H cupration of azoles, *ortho*-C–H metallation of arylazines, and reductive elimination. The same group extended this methodology to a dehydrogenative cascade reaction that provides an efficient route to heterobiaryls.[86b] Instead of the directed aromatic C–H activation of 2-phenylazines, the latter method involves the annulative



Scheme 10.44 Copper(II)-mediated dehydrogenative cross coupling of 2-phenylpyridines and azoles.

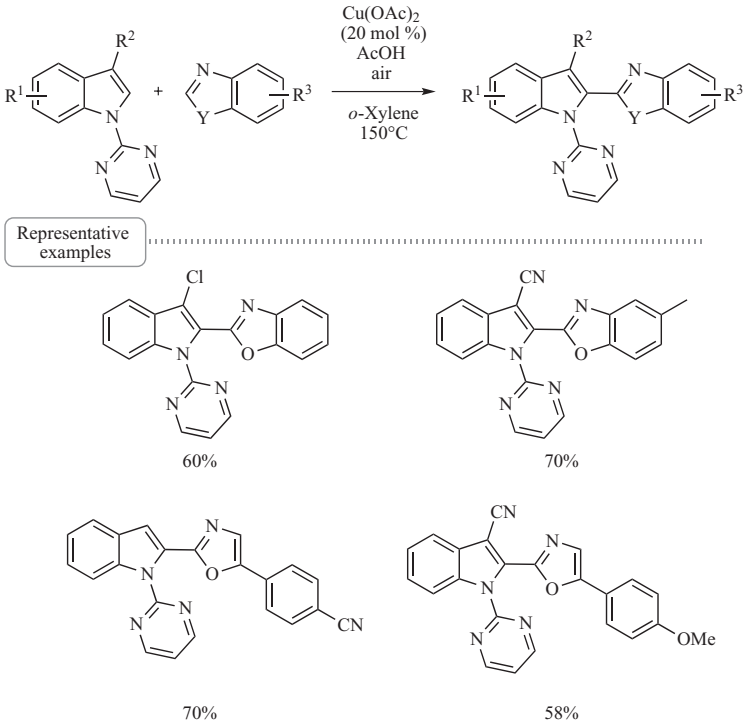
cupration of *o*-alkynylphenols to yield metallated benzofuran coupling components.

Hirano and Miura recently reported a very elegant extension of this concept to the copper-catalyzed cross-coupling reactions of substituted pyrroles and indoles with 1,3-azoles, under air. The directing group, a 2-pyrimidyl moiety, could be easily cleaved after the desired reaction by simple heating in DMSO at 100°C in the presence of sodium methoxide (Scheme 10.45).[87a] More recently, the same research group demonstrated that 8-aminoquinoline was also an excellent directing group for the copper-mediated coupling of benzoic acid derivatives with 1,3-azoles.[87b]

As seen in this section, efficient oxidative copper-catalyzed reactions are available to elaborate biaryls from nonfunctionalized arylating agents. Conceptually related is the decarboxylative coupling of benzoic acid derivatives that provides a straightforward access to biaryls from simple reagents. The recent advances in this domain are overviewed in the next subchapter.

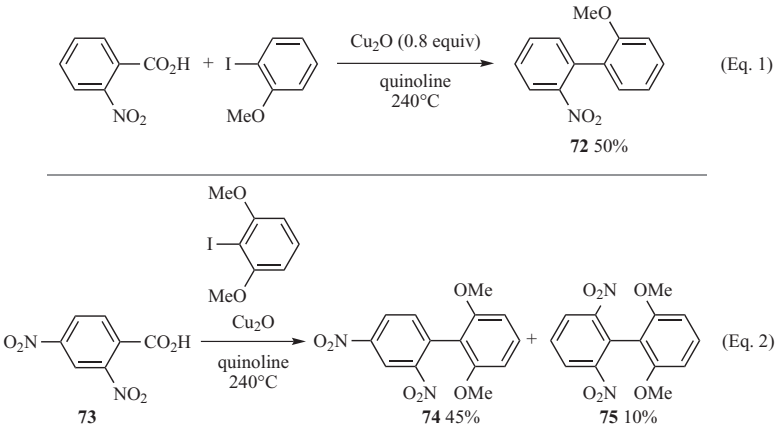
10.4.3 Decarboxylative Coupling of Benzoic Acid Derivatives

It has long been known that copper catalyzes the decarboxylation of aromatic carboxylic acids.[9,88] Nilsson revisited in 1966 the decarboxylation of benzoic acids to investigate the mechanism of the Ullmann coupling and eventually



Scheme 10.45 Copper(II)-catalyzed cross coupling of indoles and 1,3-azoles.

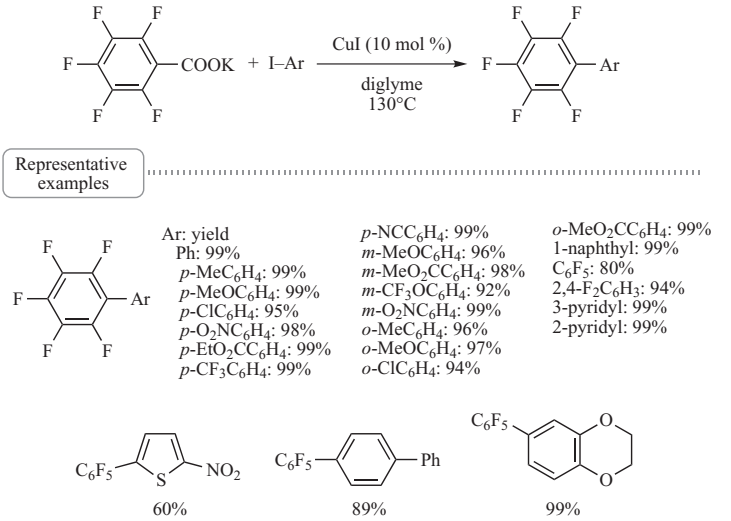
found that *o*-nitrobenzoic acid underwent a particularly rapid decarboxylation when it was boiled with copper(I) oxide in quinoline.[89a] Since he also noted that *o*-nitrohalobenzenes are excellent substrates for Ullmann coupling, he attempted the copper-mediated decarboxylation of *o*-nitrobenzoic acid in the presence of *o*-iodoanisole in boiling quinoline and obtained the corresponding cross-coupling product **72** in 50% yield and symmetrical homocoupling products were not detected (Scheme 10.46, Eq. 1). Similar reactions with benzoic acid derivatives and iodobenzenes resulted in lower yields. Thiophene-2-carboxylic and furan-2-carboxylic acids were also subjected to the copper-promoted decarboxylation in the presence of iodobenzenes; however, the cross-coupling products were obtained in low yields (<20%) and small amounts of diarylation products were observed.[89b] A similar reaction of 2,4-dinitrobenzoic acid (**73**) with 2,6-dimethoxyiodobenzene produced cross-coupling products **74** and **75** in 45% and 10% yields, respectively (Scheme 10.46, Eq. 2).[89c] The latter product was assumed to be formed via direct C–H arylation from *m*-dinitrobenzene, which was obtained by simple decarboxylation,[70] while the former product was obtained directly from carboxylic acid **73** via a 2,4-dinitrophenylcopper(I) species. Concrete evidence for the formation of arylcopper compounds from arylcarboxylic acids was later provided independently by Sheppard and coworkers.[90]



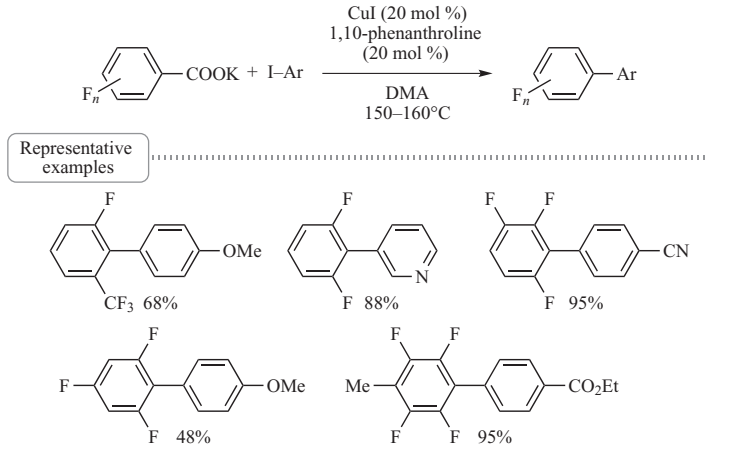
Scheme 10.46 Copper(I)-mediated decarboxylative cross-coupling reactions of benzoic acids and aryl iodides.

These early results demonstrated the feasibility of a copper-mediated decarboxylative cross coupling, and indeed, the use of readily available benzoic acids as environmentally benign surrogates for aryl organometallics or aryl halides is a fascinating tactic that is now frequently used in palladium-catalyzed (hetero)aryl–(hetero)aryl coupling.[91] Accordingly, Gooßen and coworkers developed a palladium/copper binary catalyst system for the decarboxylative cross coupling of benzoic acid derivatives with aryl halides, triflates, and tosylates, and the copper-catalyzed decarboxylation step plays a critical role in these processes.[92] Although these studies provide a powerful route to (hetero) biaryls from inexpensive benzoic acid derivatives, further improvements involving the replacement of palladium-based catalysts with inexpensive and less harmful metals should be addressed. Along this line, the decarboxylative cross coupling of potassium polyfluorobenzoates with aryl iodides and bromides was achieved using a copper catalyst (Scheme 10.47).[93] This method enabled the synthesis of various unsymmetrical (hetero)biaryls from potassium pentafluorobenzoate and iodoarenes in high yields. The cross coupling with bromoarenes was also achieved but required increased catalyst loadings and 1,10-phenanthroline as the ligand. Other fluorobenzoates were used to obtain the corresponding cross-coupling products at higher temperatures in good yields, except for monofluoro- and 2,3,4-trifluoro derivatives, which resulted in low yields. Selected examples are shown in Scheme 10.48.

The arylation reaction involving arene carbon–hydrogen or carbon–carbon bond fission detailed in this subchapter is thus a very efficient strategy to elaborate biaryls from nonfunctionnalized reagents. The impressive efficiency and selectivity of copper catalysts in this area augur well for future developments aiming at even milder conditions and functional-group tolerance. Another vibrant area of investigations is the oxidative coupling of naphthols



Scheme 10.47 Copper(I)-catalyzed decarboxylative cross coupling of potassium pentafluorobenzoate and aryl iodides.



Scheme 10.48 Copper(I)-catalyzed decarboxylative cross coupling of potassium polyfluorobenzoate and aryl iodides.

that has found numerous applications in asymmetric synthesis. This exciting domain is overviewed in the next subchapter.

10.5 BIARYL SYNTHESIS BY OXIDATIVE COUPLING OF 2-NAPHTHOLS

Since they are extraordinarily versatile chiral scaffolds for the design of chiral ligands and auxiliaries in asymmetric synthesis[94] and functional materials with

chiral recognition abilities,[95] an enantioselective synthetic route to 1,1′-binaphthyl-2,2′-diol (BINOL) and its derivatives has been actively sought. Among the established synthetic methods, the oxidative C1–C1′ coupling of 2-naphthols and congeners is one of the most efficient.[94b,c,96] Although various transition-metal catalysts have been developed for this method, copper-based mediators are cost-effective and highly reliable and, therefore, have led to practical applications. This section is devoted to a survey of the copper-mediated oxidative coupling of 2-naphthols with particular emphasis on enantioselective processes.

Copper-mediated oxidative transformations have been extensively studied as models for enzymatic oxidations[97] and advanced tools in modern organic synthesis.[98] The oxidation of phenols using copper complexes has been reported to produce various products including catechols, *o*/*p*-quinones, polyethers, and *cis*,*cis*-muconic acid, depending on the ligands, substrate structures, and reaction conditions. Aryl–aryl coupling products such as 4,4′-dihydroxybiphenyls and their oxidation products, diphenoquinones, and Pummerer's ketone from *p*-cresol have been reported in addition to 2,2′-biphenols. Therefore, selective coupling at the *ortho*-carbons of phenols is limited to appropriately designed reactions such as the reaction of 2,4-di(*tert*-butyl)phenol with elaborated binuclear complexes or intramolecular coupling of tethered phenols.[99] Similarly complicated reactions were also observed for the catalytic oxidations of 1- and 2-naphthols.[100] For example, in the presence of copper nitrate (2 mol %) and excess 2,4,6-collidine, 2-naphthol was oxidized in methanol under an oxygen atmosphere for 14 hours to obtain a mixture of various coupling products (Fig. 10.1) including a copper BINOL complex and collidine (yields are not shown).

The first major breakthrough that demonstrated the synthetic utility of such a process was reported by Feringa and Wynberg and involved the stoichiometric oxidation of 2-naphthol with a copper(II)/chiral amine complex.[101a] Upon treatment with 1 equiv of copper(II) nitrate and racemic α-phenethylamine ((±)-**76**, 3 equiv) in methanol at ambient temperature for 20 hours, 2-naphthol was selectively converted to BINOL in 62% yield (Scheme 10.49). This stoichiometric oxidative dimerization is quite sensitive to the substrate structure

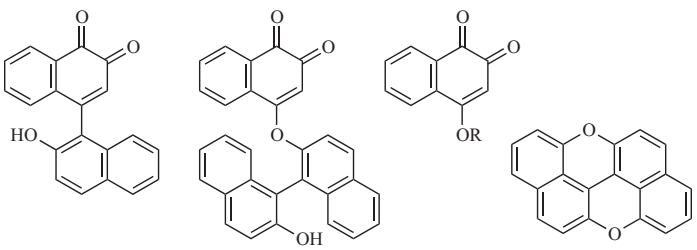
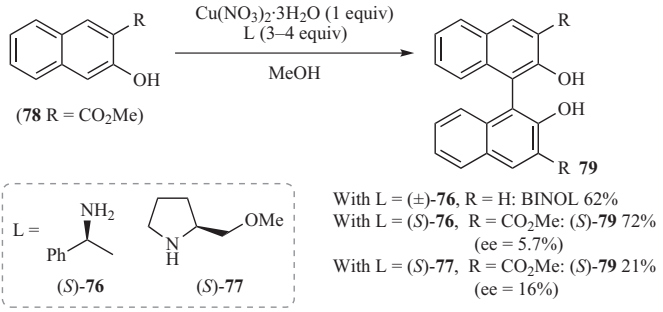


Figure 10.1 Coupling products produced by copper(I)-catalyzed aerobic oxidation of 2-naphthol.

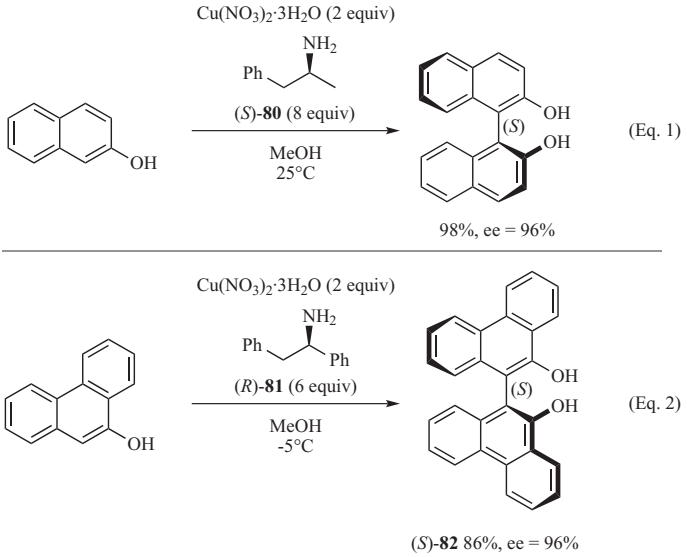


Scheme 10.49 Oxidative homocoupling of 2-naphthol derivatives mediated by copper(II) nitrate and chiral amine ligands.

as evidenced by the fact that 2,7-dihydroxynaphthalene and 3-hydroxyphenanthrene gave significantly lower yields of 20% and 25%, respectively. However, the same reaction was applied to the oxidative dimerization of 7-isopropoxy-4-methoxyphenanthren-2-ol to give the diisopropyl ether of a natural product (−)-blestriarene C in 92% yield.[102]

Naturally, it is expected that the copper(II) salt/chiral amine complex promoter could be applied to an asymmetric version of this oxidative homocoupling using enantiopure amines. Accordingly, Feringa and Wynberg attempted an asymmetric homocoupling and the use of (*S*)-**76** as an enantiopure ligand for the coupling of 2-naphthol resulted in the formation of (*S*)-BINOL with a low optical purity of 2.5% and with a moderate chemical yield of 63%.[101b] Higher, but still unsatisfactory, enantioselectivities were observed for the transformation of methyl 3-hydroxy-2-naphthoate (**78**) into **79** using (*S*)-**76** and (*S*)-2-methoxymethylpyrrolidine ((*S*)-**77**) with copper(II) chloride (Scheme 10.49). It was concluded that neither kinetic resolution nor a second-order asymmetric transformation (see below) is responsible for the observed enantioselectivity since the reaction of racemic BINOL under the same conditions resulted in 90% recovery of the racemic starting material.

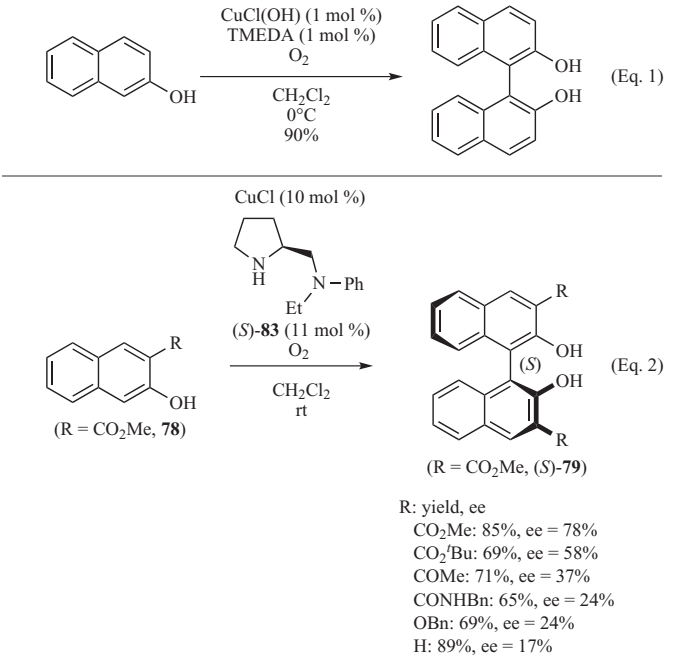
The second significant improvement was the discovery of highly enantioselective oxidative homocouplings by Brussee and coworkers who employed (*S*)-(+)-amphetamine ((*S*)-**80**) in place of (*S*)-α-phenethylamine to obtain (*S*)-BINOL in 98% yield with a remarkable 96% enantiomeric excess even though these chiral amines have very similar structures (Scheme 10.50, Eq. 1).[103] Optimization of this reaction revealed that a 2-naphthol:Cu(II):amine ratio of 1:2:8 is optimal and that the enantioselectivity is dependent on the reaction temperature, the enantiomeric excess dramatically increasing from 5% to 96% within the narrow temperature range of 10–20°C. This result implies that the oxidative homocoupling step is not responsible for the high enantioselectivity, which was further confirmed by the asymmetric transformation of racemic BINOL. Indeed, the treatment of racemic BINOL with copper(II) chloride and (*S*)-**80** in methanol at 25°C for 20 hours resulted in the formation of



Scheme 10.50 Enantioselective oxidative homocoupling of 2-naphthol derivatives mediated by copper(II) nitrate and chiral amine ligands.

precipitates. After filtration, 87% of (–)-BINOL with 91% ee was obtained from the precipitates, while 13% of (+)-BINOL with 12% ee was recovered from the filtrate. In addition, this deracemization was not observed at 0°C. These results led to the conclusion that a second-order asymmetric transformation involving the copper(II)-mediated atropisomerization of BINOL and kinetic resolution via the selective crystallization of a copper/(–)-BINOL complex accounts for the observed high enantioselectivity. Meanwhile, a highly enantioselective homocoupling of 9-phenanthrol was achieved using a similar protocol with (*R*)-1,2-diphenylamine (**81**) as the chiral ligand (Scheme 10.50, Eq. 2).[104] In striking contrast to Brussee's report, coupling product **82** was obtained with high enantioselectivity even at –5°C. No mechanism for the observed stereoselectivity was given in this report.

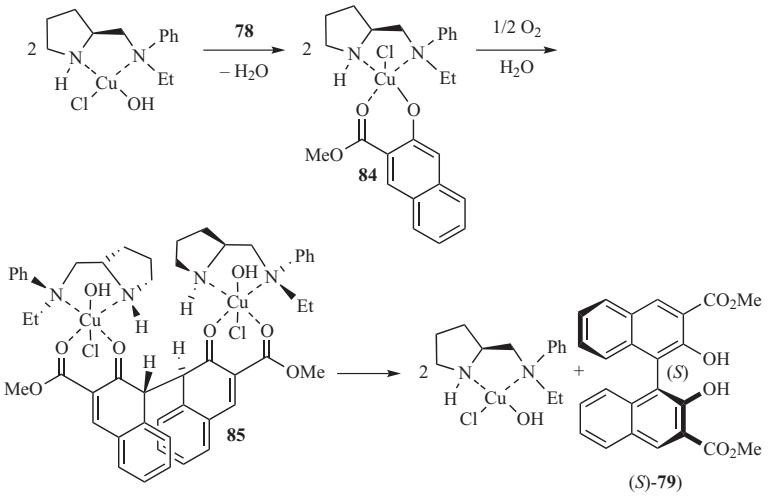
Ever since highly enantioselective oxidative couplings were achieved, catalytic versions of these reactions have been sought. An initial attempt revealed that the catalytic aerobic oxidation of 2-naphthol using a copper(II) nitrate/collidine complex produced a complex product mixture.[100] Significant contributions were made by Nakajima and coworkers, who developed a new aerobic oxidation protocol using a copper chloride(hydroxyde)/TMEDA complex, which is readily prepared from copper(I) chloride and TMEDA under an oxygen atmosphere.[105] In the presence of 1 mol % catalyst, 2-naphthol underwent homocoupling in dichloromethane under an oxygen atmosphere to afford BINOL in a high yield (Scheme 10.51, Eq. 1).[105a] The same reaction can be performed under air with a prolonged reaction time, and this method



Scheme 10.51 Copper(II)-catalyzed enantioselective oxidative homocoupling of 2-naphthol derivatives using chiral diamine ligand.

proved to be readily scalable and was applied to the synthesis of 50–60 g of racemic BINOL without difficulty.[106a] Moreover, the reaction can be carried out under mild conditions, that is, without solvent at 50°C under air.[105c] In terms of the mechanism of the reaction, a gas-phase study suggested that binuclear copper complexes play an important role in the C–C bond-forming step.[106c]

Although Lipshutz and coworkers showed that 7,7′-linked bis(2-naphthol) with a chiral tether underwent a CuCl(OH)/TMEDA-catalyzed intramolecular oxidative coupling in excellent yields with reasonable diastereoselectivity,[106b] a catalytic enantioselective process was still desired and the use of chiral diamine ligands instead of TMEDA provides a viable route to this goal. Nakajima and coworkers found that (*S*)-*N*-ethyl-*N*-phenyl-2-pyrrolidinemethanamine ((*S*)-**83**) was an optimal chiral diamine ligand and successfully transformed 3-hydroxynaphthoate **78** into (*S*)-**79** in 85% yield with 78% ee (Scheme 10.51, Eq. 2).[105b,d] They also revealed that the ester substituent is indispensable for obtaining a high enantioselectivity. A bulkier *tert*-butyl ester derivative led to decreased yields and enantioselectivity, which indicates that the ester substituents act as coordinating groups. Indeed, the use of the parent 2-naphthol (R = H) as a substrate resulted in a dramatic decrease in enantioselectivity, although the chemical yield remained high (89%). As coordinating groups,

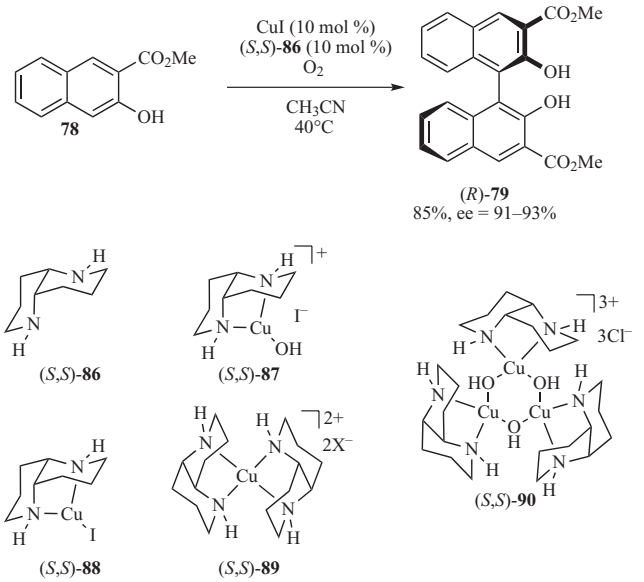


Scheme 10.52 Proposed mechanism for the copper(II)-catalyzed enantioselective oxidative homocoupling of 2-naphthol-3-carboxylate.

acetyl, *N*-benzylamide, and benzyloxy substituents were less effective than esters in terms of both yield and enantioselectivity.

According to these observations, the proposed mechanism would involve the oxidative coupling of two molecules of chiral copper complex **84**, which features a bidentate naphtholate ligand, to yield diketone intermediate **85** (Scheme 10.52). Subsequent tautomerization would convert the central chirality to axial chirality along with the dissociation of the CuCl(OH)/diamine complex to ultimately furnish (*S*)-**79**. A similar central-to-axial chirality transfer was exploited in the recently reported synthesis of axially chiral biphenols. Copper(II) chloride indeed promoted the oxidative coupling of enolates, which were derived from nonaromatizable cyclohexenones bearing a chiral tertiary carbon β to the carbonyl group.[107a] This method enables the highly enantioselective synthesis of bihydroquinones and was applied to the total synthesis of bismurrayaquinone A.[107b]

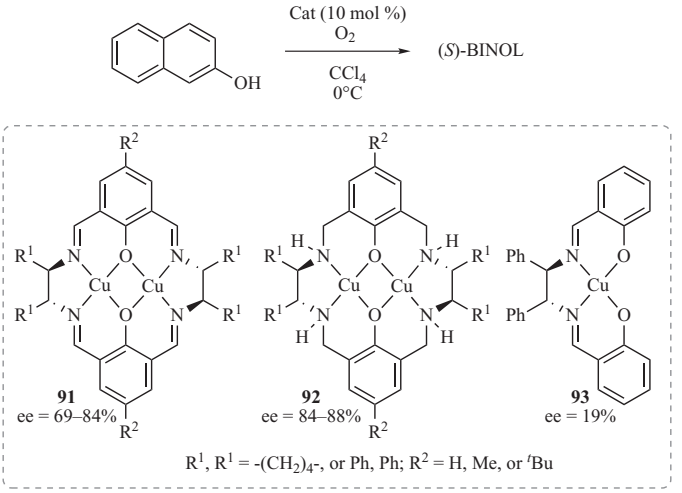
Since Nakajima's report, the copper-catalyzed asymmetric aerobic oxidative homocoupling has been significantly improved. Kozlowski and coworkers designed an efficient new chiral diamine ligand, 1,5-diaza-*cis*-decalin (**86**), for this asymmetric transformation and they identified the optimal conditions to rely on the use of 10 mol % of copper(I) iodide/(*S*,*S*)-**86** in 1,2-dichloroethane or acetonitrile at 40°C under an atmosphere of oxygen. After stirring for 2 days, naphthoate **78** was transformed into the corresponding dimer (*R*)-**79** in 85% yield with up to 93% ee (Scheme 10.53).[108] In contrast, the analogous reaction with the parent 2-naphthol afforded BINOL with only 16% ee, although the chemical yield was good (80%), which demonstrates once again the importance of the ester moiety as a coordinating group. In addition to



Scheme 10.53 Oxidative homocoupling of 2-naphthol-3-carboxylate using copper(I)/1,5-diaza-*cis*-decalin complexes as catalysts.

esters, secondary amides, ketones, phosphonates, and sulfones were also effective coordinating groups and gave moderate-to-high enantioselectivities. Cationic copper(II) hydroxide **87**, which was derived from neutral complex **88**, is considered to be the catalytically active species, and other complexes including monometallic **89** and trimetallic **90** were also isolated. However, $[(\mathbf{86})_2\mathrm{Cu}]\mathrm{Cl}_2$ proved to be catalytically inactive and the ligand:copper ratio of 1:1 is therefore critical for catalytic asymmetric oxidation. This highly enantioselective aerobic oxidative homocoupling has been applied to the total synthesis of natural products that contain axial chirality, and representative examples will be described in Chapter 18.[109] The enantioselective synthesis of binaphthyl polymers via tandem Glaser coupling/asymmetric oxidative coupling was also achieved using Kozlowski's catalyst[110] and similarly, a highly enantioselective aerobic oxidative homocoupling of naphthoate **78** leading to diester **79** in 95% yield with 94% ee was achieved using copper(II) chloride and an octahydrobinaphthyl-2,2′-diamine ligand.[111]

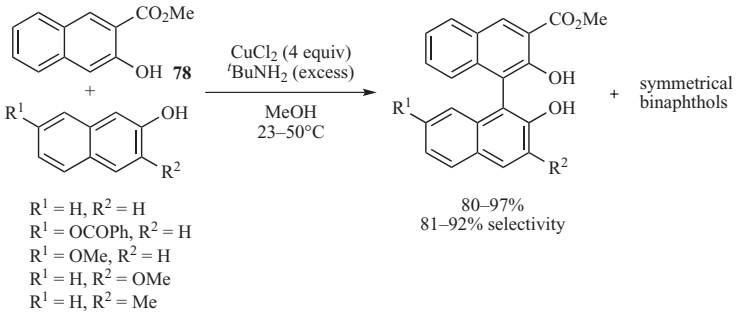
Schiff base complexes of copper have also been reported to be efficient catalysts for the aerobic oxidative homocoupling of 2-naphthols.[112,113] In particular, dinuclear cyclic bis(salen) complexes **91** were found to catalyze the asymmetric homocoupling of 2-naphthol to furnish (*S*)-BINOL in 79–80% yields with 69–84% ee (Scheme 10.54).[113] Closely related macrocyclic polyamine complexes **92** were superior to **91** in terms of reproducibility and stability, and gave (*S*)-BINOL with higher yields (84–92%) and enantioselectivity



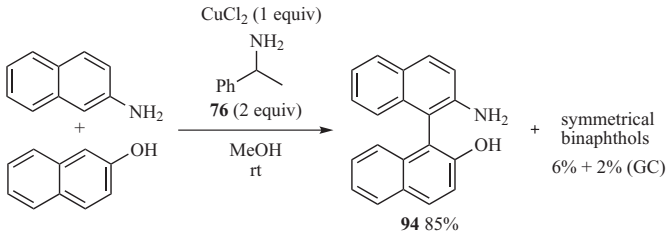
Scheme 10.54 Enantioselective oxidative homocoupling of 2-naphthol using dicopper(I)/Schiff base complexes as catalysts.

(84–88% ee). The high enantioselectivity achieved without an extra coordinating group on the 2-naphthol substrate is ascribed to the rigid dinuclear platform and accordingly, mononuclear Schiff base complex **93** gave a considerably lower enantioselectivity (19% ee).

Besides the homocoupling of naphthol derivatives, the copper-mediated oxidative cross coupling of 2-naphthols has also been investigated since the first report involving the coupling of 9-phenanthrol and 3-methoxymethoxy-2-naphthol.[114] Hovorka and coworkers generalized the cross coupling by investigating the reactivity of combinations of relatively electron-rich 2-naphthols and electron-deficient naphthoate **78** and obtained cross-coupling products with selectivities superior to 80%, while combinations of electron-rich or electron-deficient substrates led to decreased pair selectivity (around 30%) (Scheme 10.55).[115] *tert*-Butylamine was assumed to act as a base to abstract a proton from the 2-naphthols and the authors showed that copper chloride(methoxide) (4 equiv) efficiently promoted the cross-coupling reaction of 2-naphthol with **78** at 50°C in the absence of the amine, the corresponding unsymmetrical product being isolated in 86% yield. The treatment of 2-naphthol substrates with sodium methoxide followed by reaction with copper(II) chloride led to a similar result.[115c] From a mechanistic point of view, it was proposed that a radical derived from the more easily oxidized, electron-rich 2-naphthol attacks the copper naphtholate electrophile, derived from **78** (i.e., via a radical insertion mechanism). Alternatively, it was considered that cross coupling might occur in a concerted fashion via a dicopper complex with two naphtholate bridges. The authors concluded that distinction



Scheme 10.55 Copper(II)-mediated oxidative cross coupling of 2-naphthol derivatives.

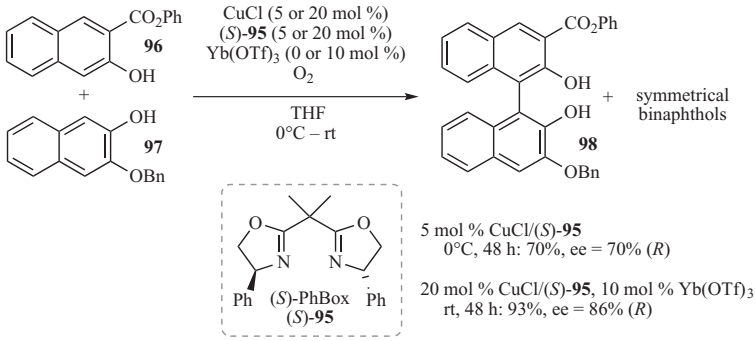


Scheme 10.56 Copper(II)-mediated oxidative cross coupling of 2-naphthol and 2-naphthylamine.

between the homolytic and heterolytic couplings or radical insertion mechanisms is futile in the latter situation.[115d]

The Kočovský group also investigated the copper-mediated couplings of 2-naphthols with 2-naphthylamine.[116] As depicted in Scheme 10.56, the highly selective cross coupling of 2-naphthylamine and 2-naphthol using 1 equiv of copper(II) chloride and α-phenethylamine (**76**) as a promoter in methanol at ambient temperature resulted in the isolation of cross-coupling product **94** in 85% yield. Interestingly, kinetic crystallization was observed albeit with moderate enantiomeric excesses, when (*R*)-(+)-**76** was used as the ligand.

Recently, N-heterocyclic carbene copper complexes were also reported to catalyze the oxidative cross coupling of 2-naphthols with 3-hydroxy-2-naphthoates using Oxone® as the terminal oxidant.[117] Habaue and coworkers introduced a chiral bisoxazoline ligand, (–)-2,2-isopropylidenebis[(4*S*)-4-phenyl-2-oxazoline] ((*S*)-PhBox, **95**), to enable catalytic asymmetric oxidative cross coupling of 2-naphthol derivatives (Scheme 10.57).[118] The aerobic oxidative cross coupling of phenyl 2-hydroxynaphthoate (**96**) and 3-benzyloxy-2-naphthol (**97**) proceeded in THF at 0°C to give (*R*)-**98** in 70% yield and 70% ee. The combination of copper(I) chloride (20 mol %), (*S*)-PhBox (20 mol %) with ytterbium(III) triflate (10 mol %) as a Lewis acid catalyst resulted in

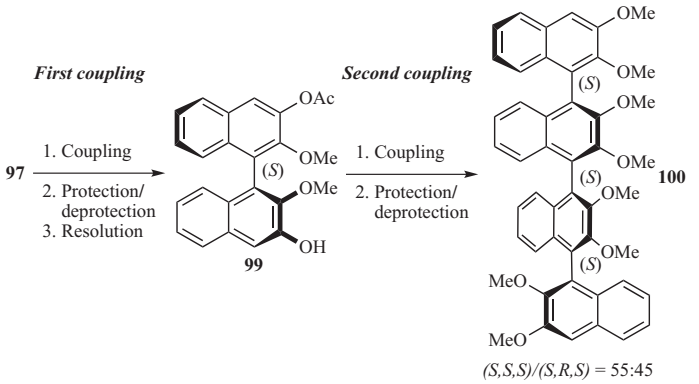


Scheme 10.57 Effect of Lewis acid catalyst on the copper(I)-catalyzed enantioselective oxidative cross coupling of 2-naphthol derivatives.

a higher yield (93%) and enantioselectivity (86% ee).[118d,e] Similarly, a selective cross coupling proceeded for the corresponding amides, which acted as electron-deficient coupling partners, although the enantioselectivity was lower.[118c,e] It was assumed that a radical species was derived from the copper catalyst and the more oxidizable naphthol **97** selectively coupled with electrophilic **96** upon activation by the Lewis acid catalyst.

These developments in the copper-mediated oxidative homo- and cross couplings of naphthol derivatives have led to many applications including the controlled synthesis of macromolecules.[110,119] Indeed, Okamoto and coworkers achieved the asymmetric oxidative coupling polymerization (AOCP) of enantiopure 3,3′-dihydroxy-2,2′-dimethoxy-1,1′-binaphthyl using copper/chiral amine catalyst systems based on the use of (*S*)-(+)-1-(2-pyrrolidinylmethyl) pyrrolidine and (−)-spartein as chiral diamine ligands.[120a] This method provides polymers with molecular weights up to 5.2×10^3 g mol^{-1}, which corresponds to approximately 24 naphthalene units. The same group extended the AOCP to various monomers including 2,3-dihydroxynaphthalene, ter-, and quarternaphthyls, a binaphthyl crown ether, and tetrahydroxybinaphthyl derivatives,[120b–h] and dinuclear copper complexes with tethered diamine ligands were examined for the polymerization of 2,3-dihydroxynaphthalene.[120f]

Bis(oxazoline) ligands proved to be effective for the oxidative coupling polymerization of 2-naphthol-derived monomers[120] and as described earlier, the copper(I) chloride/PhBox catalytic system showed high cross-coupling selectivity.[118] Accordingly, Habaue and coworkers achieved selective oxidative cross-coupling polymerizations using chiral bis(oxazoline) ligands.[121] They investigated a variety of monomers including those bearing electron-rich 2-naphthol (D: donor) and electron-deficient 3-hydroxy-2-naphthoate (A: acceptor) moieties (i.e., D–A type) and those with two electron-rich (D) or electron-deficient (A) units (i.e., D–D and A–A types). The analysis of the resultant polymers revealed that oxidative coupling proceeded in a highly selective manner in favor of cross coupling, although the enantioselectivity

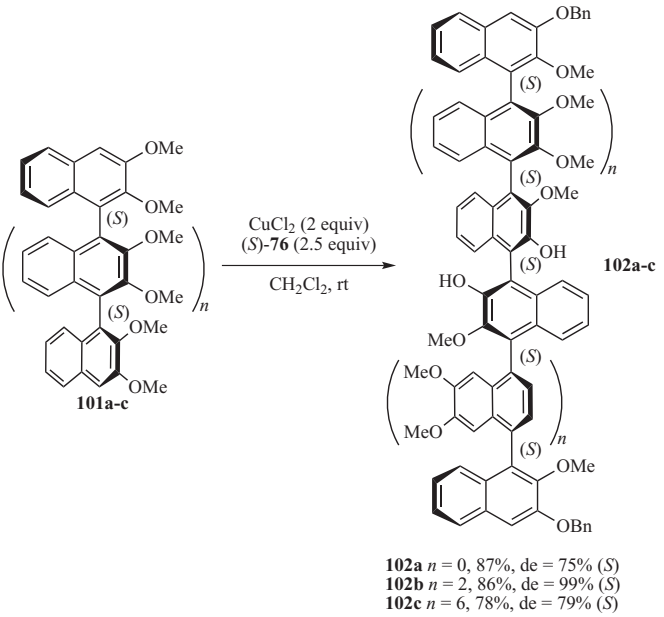


Scheme 10.58 Synthesis of quaternaphthyl derivative via repetitive oxidative homocoupling.

was estimated to be low to moderate from the model coupling reactions. Hyperbranched polymers were also obtained via the copper(I) chloride/PhBox-catalyzed oxidative coupling polymerization of monomers bearing three 2-naphthol units (i.e., D–D–D, D–D–A, and D–A–A types),[121d] and the cross-coupling selectivity was improved using a binary catalyst system composed of copper complexes and Lewis acids.[121e]

Configurationally defined oligonaphthalenes have also been synthesized using an iterative oxidative coupling method.[122] For example, the homocoupling of 3-benzyloxy-2-naphthol (**97**) afforded the homocoupling product from which optically active binaphthyl **99** was obtained as a binaphthyl substrate for the subsequent oxidation and the second homocoupling furnished a diastereomeric mixture of the corresponding quaternaphthyl derivative **100** (Schemes 10.58). Therefore, although separation of diastereomers is required at every step to obtain configurationally defined oligonaphthalenes, a highly diasteroselective homocoupling synthesis of oligonaphthalenes was achieved by exploiting asymmetric transformations provided by the copper(II) chloride/α-phenethylamine system.[122c]

Binaphthyl precursor **101a** (n = 0, Scheme 10.59) was subjected to homocoupling with (*S*)-α-phenethylamine ((*S*)-**76**) to afford quaternaphthyl product **102a** (n = 0) in 87% yield with 75% diastereomeric excess. Interestingly, the desired product (**102a**) was obtained in 58% yield with 93% diastereomeric excess from precipitates formed during the reaction, which were isolated by filtration, while the remnant filtrate yielded the same product in 15% yield with a much lower diastereomeric excess of 17%. In contrast, the use of (*R*)-**76** led to a lower yield (69%) and decreased diastereoselectivity (26% de). These results clearly imply that the observed diastereoselectivity can be attributed to atropisomerization of the newly formed axis and kinetic crystallization. The diastereoselectivity was improved to 99% for the coupling of quaternaphthyl precursor **101b** (n = 2), whereas the coupling of octinaphthyl precursor **101c**



Scheme 10.59 Enantioselective synthesis of oligonaphthyls using chiral copper(II) catalyst.

($n = 6$) gave diastereomeric excess comparable to that of binaphthyl substrate **101a**, the latter coupling affording configurationally defined hexadecanaphthyl **102c** ($n = 6$) in 70% yield after purification via silica gel chromatography. After further modifications involving hydroxy protecting groups and copper catalysts, enantiopure dotriacontanaphthalene was ultimately synthesized via this bottom-up strategy, the absolute configuration of this naphthalene oligomer being unambiguously determined using the CD exciton chirality method.[122g] A wide variety of applications are expected for monodisperse, nanometer-sized molecules; hence, configurationally defined oligonaphthyls are fascinating scaffolds for functional materials.[123]

As shown earlier, the copper-mediated oxidative coupling of 2-naphthols is a highly useful tool for natural product synthesis and materials sciences. Nevertheless, residual metal contamination of the final products can be a serious problem. Accordingly, various copper catalysts supported on alumina,[124a,c] montmorillonite,[124b] mesoporous aluminosilicates,[124d,f] and polymers[124e,g] have been developed.

10.6 CONCLUSIONS AND OUTLOOK

Since the discovery of Ullmann coupling in 1901, various copper-mediated aryl–aryl coupling methods have been devised and continuously evolved into

highly sophisticated tools for natural product synthesis and materials sciences. The copper-catalyzed protocols for homo- and cross coupling of organostannanes, organoboranes, or organosilanes enable the selective synthesis of functionalized biaryls under relatively mild conditions. Moreover, the development of copper-catalyzed direct C–H arylations and decarboxylative arylations result in a significant paradigm shift due to the improved accessibility to highly valuable biaryl scaffolds from inexpensive and environmentally benign starting materials and catalysts. Moreover, relatively conventional oxidative coupling of 2-naphthols has been dramatically improved to provide enantioselective access to axially chiral building blocks. Consequently, axially chiral natural products and configurationally defined naphthyl polymers and oligomers became accessible due to advances in copper-catalyzed asymmetric oxidative coupling. The exploitation of supported copper catalysts and efficient catalyst-recycling systems is becoming increasingly important in light of the focus on green chemistry. With further progress in this area, copper catalysts will ultimately play a central role in cross-coupling chemistry and may even supplant palladium catalysts in the near future.

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