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C-S Cross-Coupling Reactions Catalyzed by Well-Defined Copper and Nickel Complexes

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Abstract

This review presents well-defined copper and nickel complexes that have been used in the formation of C-S bonds. The use of Cu or Ni catalysts represent an advantage in comparison with those based on precious metals such as Pd, by being two of the most abundant metals in the earth's crust and thus cheaper. As can be expected the catalytic activity of the different Cu and Ni complexes is strongly dependent on the nature of the ligands used. Thus, multidentate and strong electron-donating ligands are of common use to design highly active species since such ligands are capable to stabilize species in high oxidation states which are key intermediates in the reaction mechanisms of these processes. This being particular true in the case of copper, where Cu(III) produces unstable and reactive species that require an "extra stabilization" during the reaction mechanism. Hence, the reaction mechanisms using copper and nickel complexes as catalysts are also discussed in this paper, including the role of the different ligands during the catalytic processes. Although there are an increasing number of reports on C-S cross coupling reactions, due to the relevance of this transformation, they are often difficult to reproduce and not of general use due to the fact that the actual catalytic species are not identified, thus we hope that this report will help to promote the search and synthesis of new ligands for the design of more active well defined complexes that can be used as catalysts in a more rationale manner in the formation of valuable C-S bond containing species.

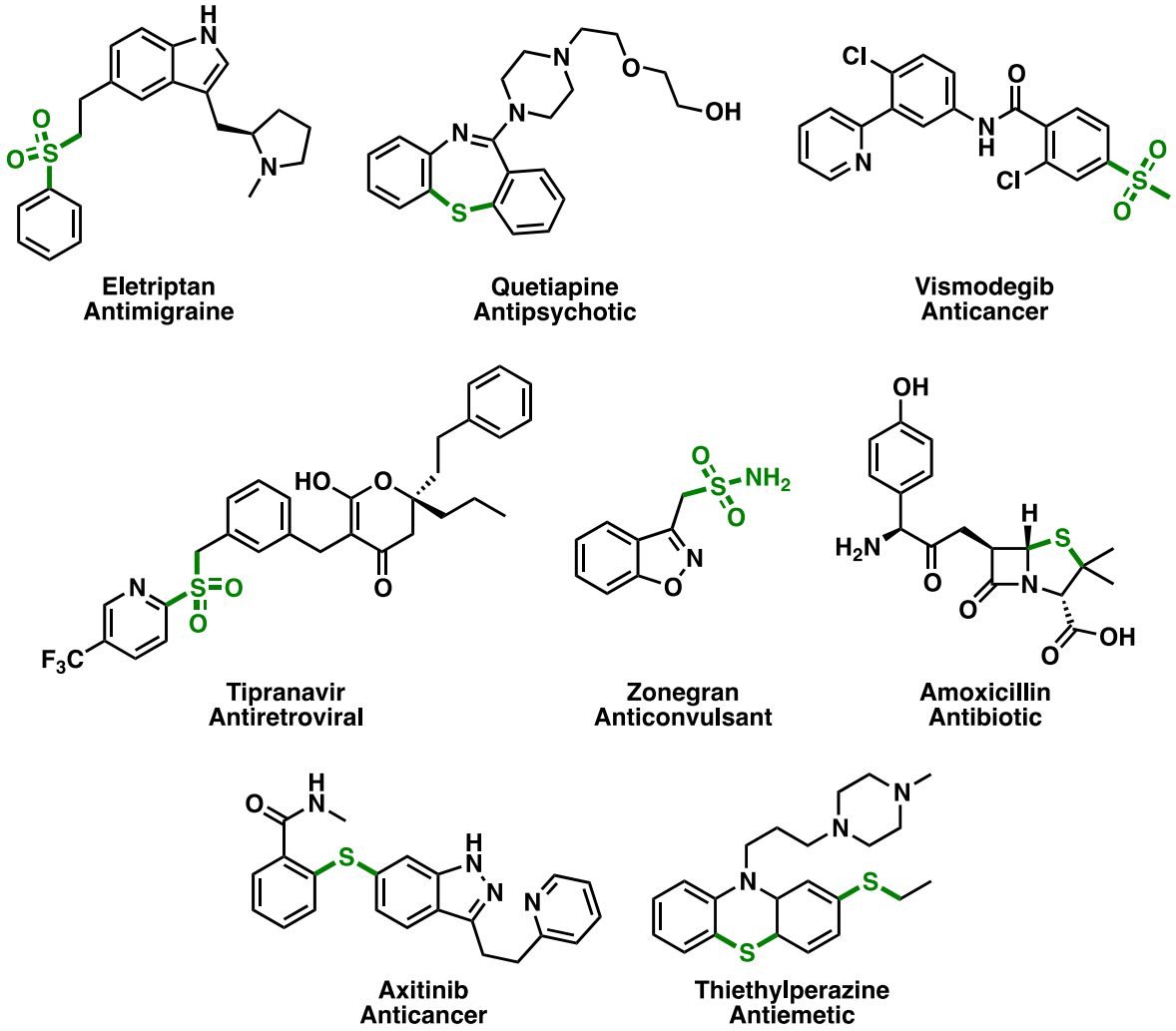
Keywords: Thiolation, C-S cross-coupling, Ni catalyst, Cu catalyst, NHC complexes, pincer complexes, reaction mechanism, catalysis.

1. Introduction

C-heteroatom cross-coupling reactions are considered an essential tools in organic chemistry.[1-6] In particular, the formation of C-S bonds is a key step in the synthesis of pharmaceuticals[7] and advanced materials.[5] For instance, C-S bond is present in more than 300 FDA approved drugs.[7] Scheme 1 shows some representative examples of drugs containing C-S fragments.[8-9] Their uses are very wide, ranging from antibiotics to anticancer agents, including antipsychotics, antiretroviral, antimigraine and anticonvulsant. Thus, the demand of organosulphur compounds increases constantly, demanding safer, cleaner, and cheaper methodologies. In this sense, C-S cross-couplings catalyzed by transition metals is probably one of the strategies that is close to convene these actual requirements.

C-S cross-coupling is carried out by the reaction of an inexpensive organothiol or disulphide with an arylmagnesium halide, aryl boronic acids or aryl halides in the presence of a catalyst. In addition, there are some examples of direct thiolation through C-H bond activation, however a directing group is required.[10-12] As in other catalyzed reactions, the design of the catalyst is fundamental to get good results, and since organosulphur compounds exhibit a strong tendency to coordinate to transition metals, leading to a rapid catalyst poisoning, and consequently, depleting the catalyst performance, this becomes paramount. In this sense, the reaction has been catalyzed by some transition metals, such as Cu, Ni, Pd, Ru, Ir, Co and Au. Usually, multidentate or strong σ-donor ligands are employed for catalyst design.

Recently, C-S cross-coupling reactions catalyzed by heterogeneous catalysts, ligand assisted catalysts, supported catalysts and photocatalysts, were compressively reviewed.[1, 10, 13-28] Thus, in this review we have summarized the most recent examples of C-S cross coupling catalyzed by well-defined Cu and Ni complexes.



Scheme 1. Representative examples of commercially available drugs containing C-S bonds.

2. Copper Catalysts

The C-S cross-coupling reactions catalyzed by copper, can be performed between a thiol or disulfide, and an aryl- or aryl-halide. Also, some authors have taken advantage of the ability of copper to perform transmetalation reactions with organoboron reagents, and have described the use of aryl-boronic acids instead of the organohalide.[29-30] In Scheme 2 are summarized some representative examples of well-defined Cu-based catalysts and their use in C-S cross-coupling reactions. When a thiol and an aryl-halide is used the reaction requires a base. The base can be omitted using a sodium thiolate salt or when the reaction is carried out in water.

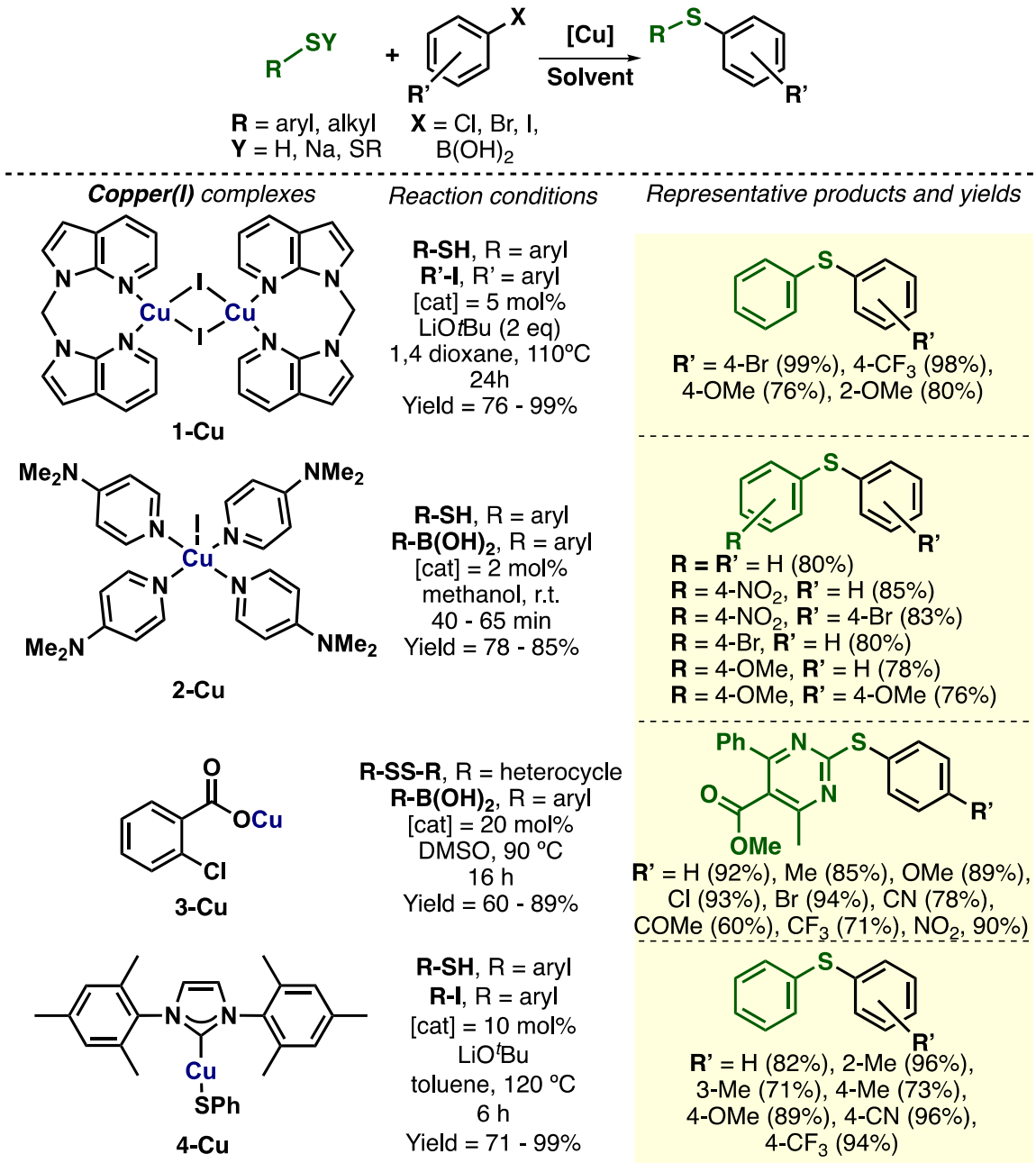
In 2009, Perez and Nicasio described the catalytic activity of two dinuclear Cu(I) complexes bearing two isomeric ligands based on bis(7-azaindolyl)methane (**1-Cu**).[31] After a long optimization, they found that using 5 mol% of catalyst and LiO^{t}Bu in dioxane at 110 ºC the cross-coupling of arylthiols and aryl iodides proceed from moderate to excellent yield (76 –

99%). They found out that the electronic nature of different functionalities in the aryl iodide does not affect the reaction. The catalytic conditions tolerated the presence of sterically hindered groups at the *ortho* position of the aryl iodide.

Besides, Phukan and co-workers employed a Cu(I) complex based on dimethylamino pyridine (DMAP) **2-Cu** as catalyst for the cross-couplings between thiols and boronic acids.[32] The reaction was carried out under mild conditions, using 2 mol% of catalyst in methanol at room temperature. In this case the authors found that the presence of electron-withdrawing groups attached to the thiol, lead to an increase in the yield of the products.

In addition, Quan and Wang described the coupling of different boronic acid compounds with 1,2-di(pyrimidin-2-yl) disulfide catalyzed by complex **3-Cu**.[30] The reaction was carried out in the absence of a base, under air. Although the reaction requires high catalyst loading (20 %), the products were obtained in high yields going from 60% to 89%. The catalytic conditions tolerated well some functional groups such as OMe, Cl, Br, CN, NO_2, CF_3 and COMe.

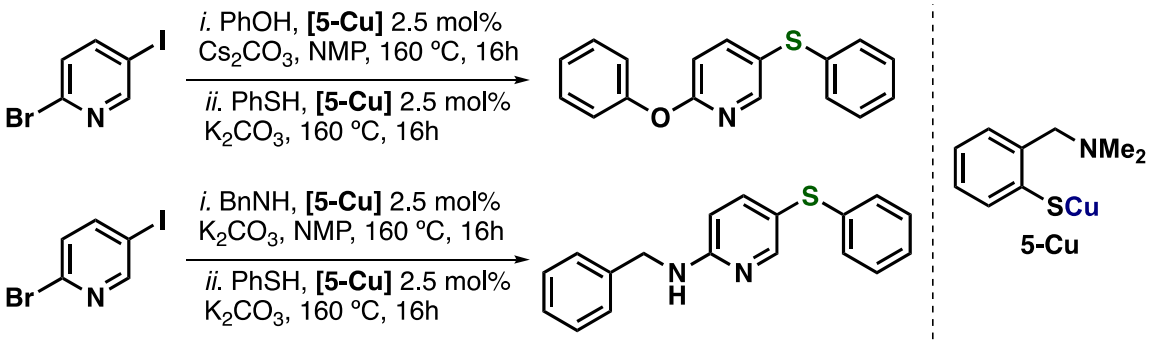
Furthermore, The use of strong σ-donor ligands such as N-heterocycle carbenes (NHC) to prepare Cu(I) catalysts was explored by Hsu, Han and Shyu.[33] They employed **4-Cu** to catalyze the C-S cross-coupling of a series of arylthiols and iodo-aryls in the presence of lithium *tert*-butoxide (LiO^tBu). The reaction was carried out in toluene at 120 ºC for 6h. By using the latter conditions, the thioether products were isolated in yields >71%. Some functional groups such as OMe, CN and CF_3, were tolerated.



Scheme 2. C-S cross-coupling reactions catalyzed by Cu(I) complexes with mono-dentated ligands, optimized reaction conditions and representative products were prepared using optimized conditions.

In 2010, van Koten and coworkers expanded the applicability of the C-S cross-coupling reaction and developed a new strategy to perform a sequential C-heteroatom cross-coupling reactions (Scheme 3).[34] First, they carried out the C-O cross-coupling on 2-bromo-5-iodopyridine with phenol using a Cu(I) catalyst (**5-Cu**). The reaction was selective on the substitution of the bromine atom for phenol. Then over the same reaction mixture, they added the second set of reagents, performing a C-S cross-coupling on the iodide. A similar approach

was also functional to perform a sequential C-N/C-S cross-coupling, both catalyzed by Cu(I) species.



Scheme 3. Sequential C-heteroatom cross-coupling catalyzed by Cu(I) (**5-Cu**).

The disposition of the donor-atoms in 1,10-Phen-type ligands is suitable to produce Cu(I) complexes, due to the fact that the nitrogen atoms, after coordination to the metal center, yields a 5-member metallocycle. Furthermore, the literature is abundant on several strategies to functionalize 1,10-phen compounds giving access to sophisticate structures. Hence, in 2004, Venkataraman and co-workers described the cross-coupling of vinyl iodides and aryl-iodides catalyzed by three Cu(I) complexes with ligands derived from 1,10-phenanthroline (phen) (**6a-Cu, 6c-Cu**) and 2,9-dimethyl-1,10-phenantrhroline (Me_2phen) (**6b-Cu**) (Scheme 4).[35] The catalytic reactions were carried out using 5 mol% of catalyst in the presence of K_3PO_4 in toluene at 110 ºC. Under these conditions a wide range of thiols with electron-rich and electron-poor donating groups, including sterically hindered moieties, were tolerated. The cationic Cu(I) complex **6c-Cu** showed high yields, ranging from 80 to 99 %. Noteworthy the fact that using a mixture of CuI/phen as catalyst afforded the C-S product albeit in lower yield in comparison with the well-defined copper complex. Furthermore, the stereochemistry of the vinyl iodides was retained after the catalytic reaction.

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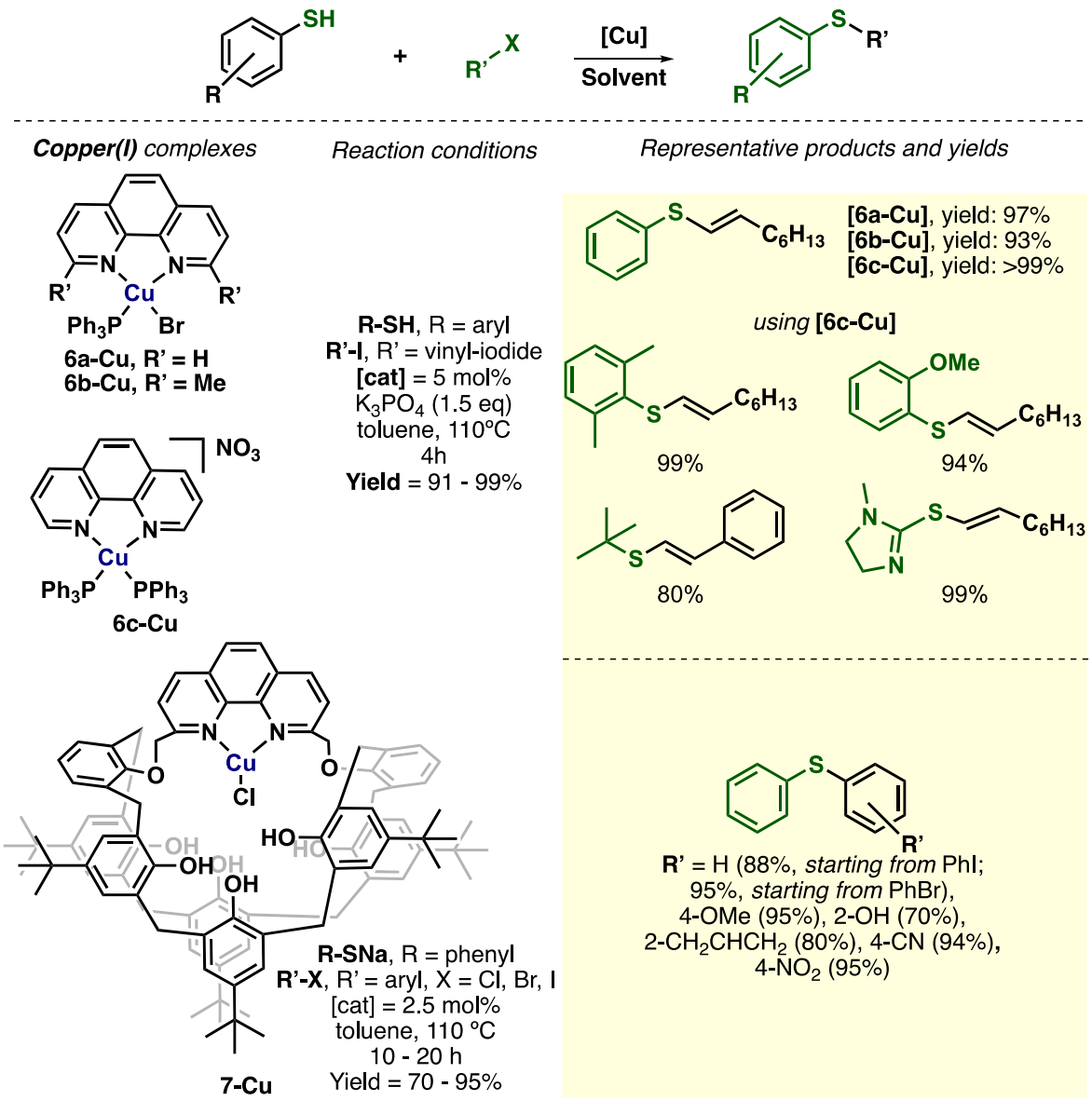

Scheme 4. C-S cross-coupling reaction catalyzed by Cu(I) complexes with bi-dentated ligands, optimized reaction conditions and representative products that were prepared using optimized conditions.

In other relevant work, phen was merged with a calix[8]arene compound.[36] This class of ligand was useful for the preparation of a Cu(I) complex (**7-Cu**) that was used to catalyze the cross-coupling between aryl-halides and sodium thiophenol (**Scheme 2**).[37] The reactions were carried out in toluene at 110ºC for 10-20 h, obtaining from moderate to excellent yields (70 to 95 %). More interestingly is the fact that this sophisticated ligand allows the isolation of the corresponding mono-thiophenolate species, which can stoichiometrically react with one equivalent of haloarene to quantitatively produce the corresponding aryl thioether in few hours.

Copper(II) is capable to catalyze the C-S cross-coupling reactions between thiols and aryl halides.[38-40] Pathak and co-workers synthesized two new Cu(II) complexes (**8a-Cu** and **8b-Cu**) derived from benzoylhydrazine (Scheme 5).[38] The complexes catalyzed the couplings using bromo- and iodo-aryl substrates and thiols bearing heterocyclic fragments. As expected, when the reaction was performed with bromoaryls (83-86%) the yields were lower than using iodoaryl derivatives (88-92%). The complex with the methoxy group (**8b-Cu**) performed better than their NO_2 analogue (**8a-Cu**), this being probably due to electronic effects. The general reaction conditions consist in using 0.5 mol% of catalyst, K_2CO_3 and ethylene glycol at 80 ºC. On the other hand, Islam, Felix, San Martin and Das described an ONO pincer complex (**9-Cu**) and its reactivity in C-S cross-couplings in water.[39] The catalyst exhibited a typical behavior; *i.e.* using electron-withdrawing groups in the aryl iodides the yields were higher than those having electron-donating groups. And, regarding the aryl halides, the reactivity showed the expected trend: PhI > PhBr > PhCl, being two-fold more reactive the PhI in comparison with PhCl (95% for PhI, 53% for PhBr, 36% for PhCl). Finally, very recently, Ghosh et al. observed similar trends using a bis[2-(4,5-diphenyl-1H-imidazol-2-yl)-4-nitrophenolato] copper(II) dehydrate complex (**10c-Cu**) as catalyst (Scheme 5).[40]

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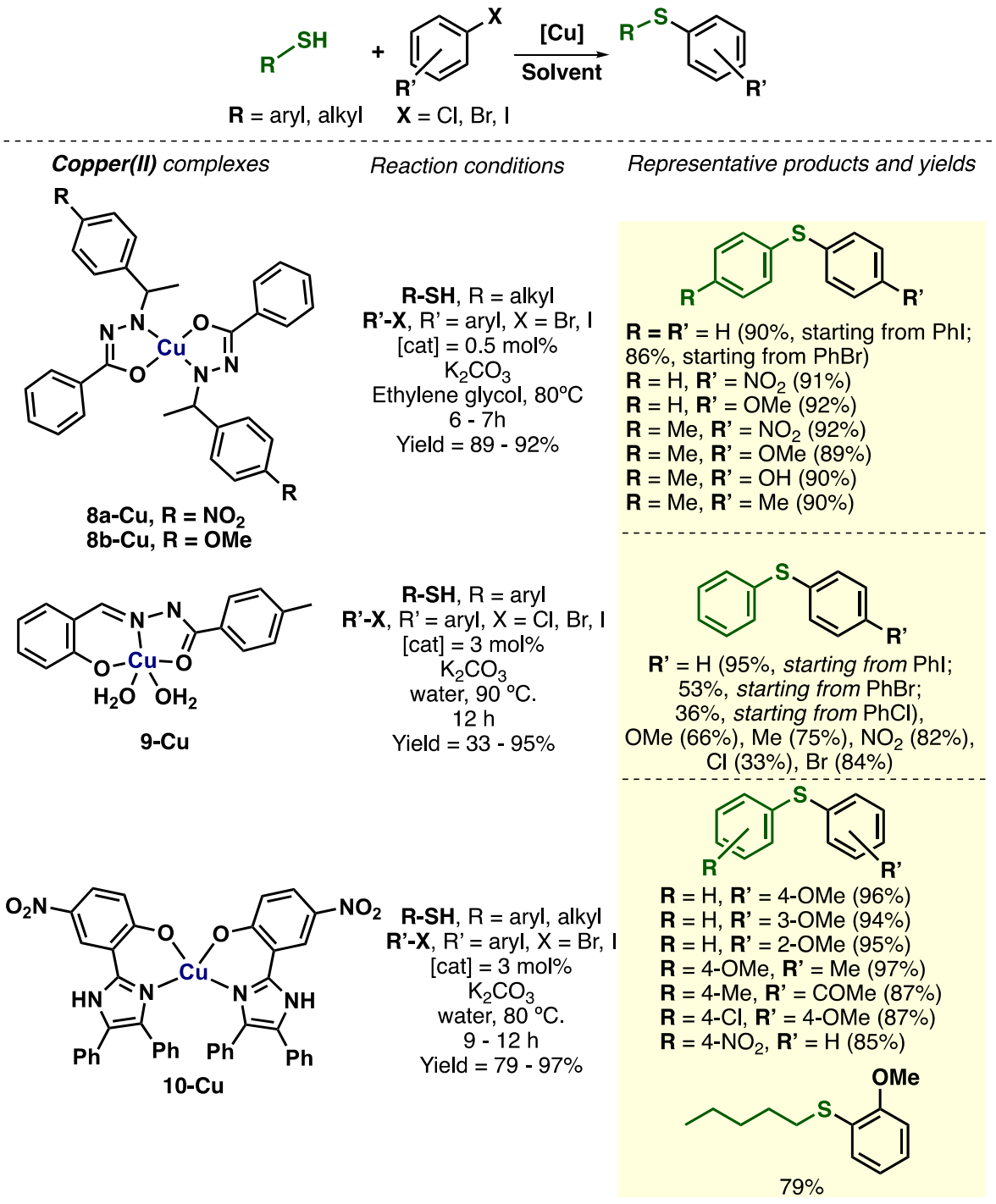
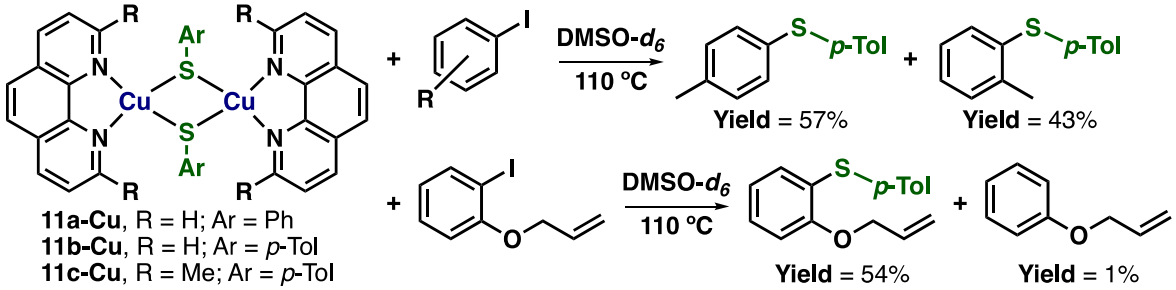


Scheme 5. C-S cross-coupling reactions catalyzed by Cu(II) complexes with bi- and tri-dentated ligands, optimized reaction conditions and representative products were prepared using optimized conditions.

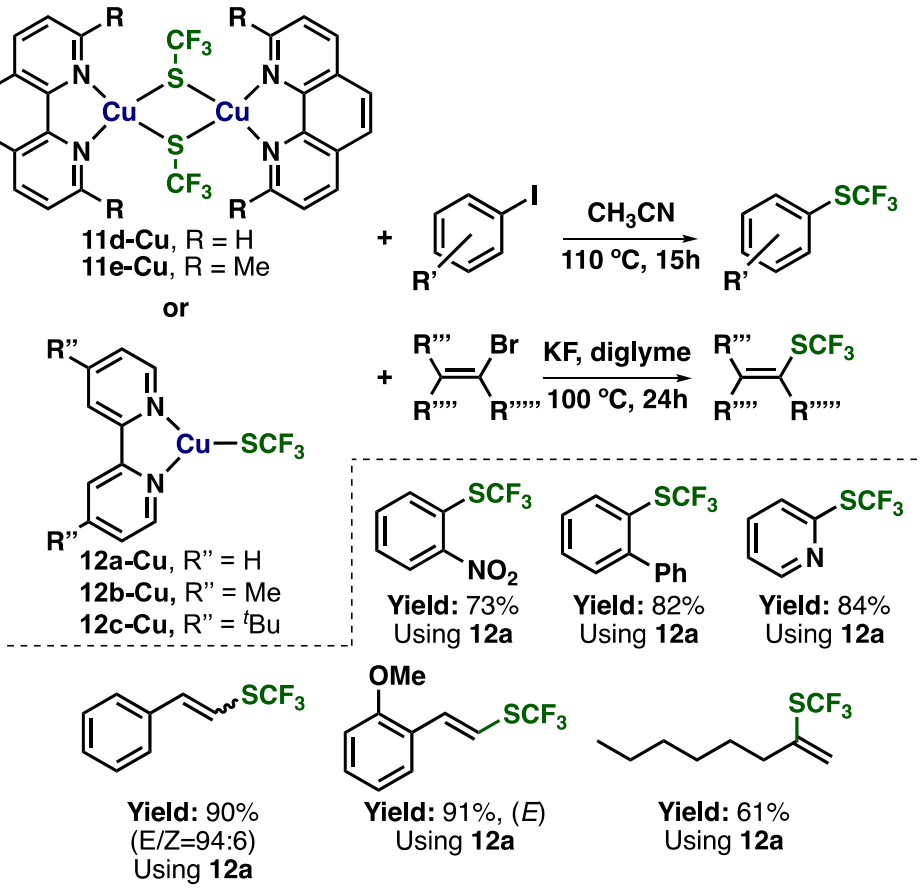
Mechanistic considerations

Weng and Hartwig made a substantial progress in the understanding of the reaction mechanism of C-S cross-couplings with well-defined Cu complexes.[41] Their approach consisted in the preparation of a series of Cu(I) thiophenolato complexes of the type $[Cu(SAr)(phen)]_2$ (**11a-Cu – 11c-Cu**) and the exploration of their reactivity towards aryl-iodides (Scheme 6). They found that the formation of the arylsulfide occurs after heating a stoichiometric amount of the thiophenolato complex and the corresponding iodo-aryl at 110ºC in DMSO-d_6. The complex with the Me_2phen ligand (**11c-Cu**) resulted to be less active than those having the phen ligand, this being probably due to a steric effect of the methyl groups. Also, they discarded the possibility of the formation of radical species during the reaction mechanism by reacting the thiophenolato Cu(I) complexes with *o*-(allyloxy)iodobenzene. This substrate is known to undergo fast cyclization to form 2-dihydrobenzofuran *via* a radical pathway. So, the reaction yields the C-S cross-coupling product in 54 % yield, and the dehalogenation product in 1% yield.



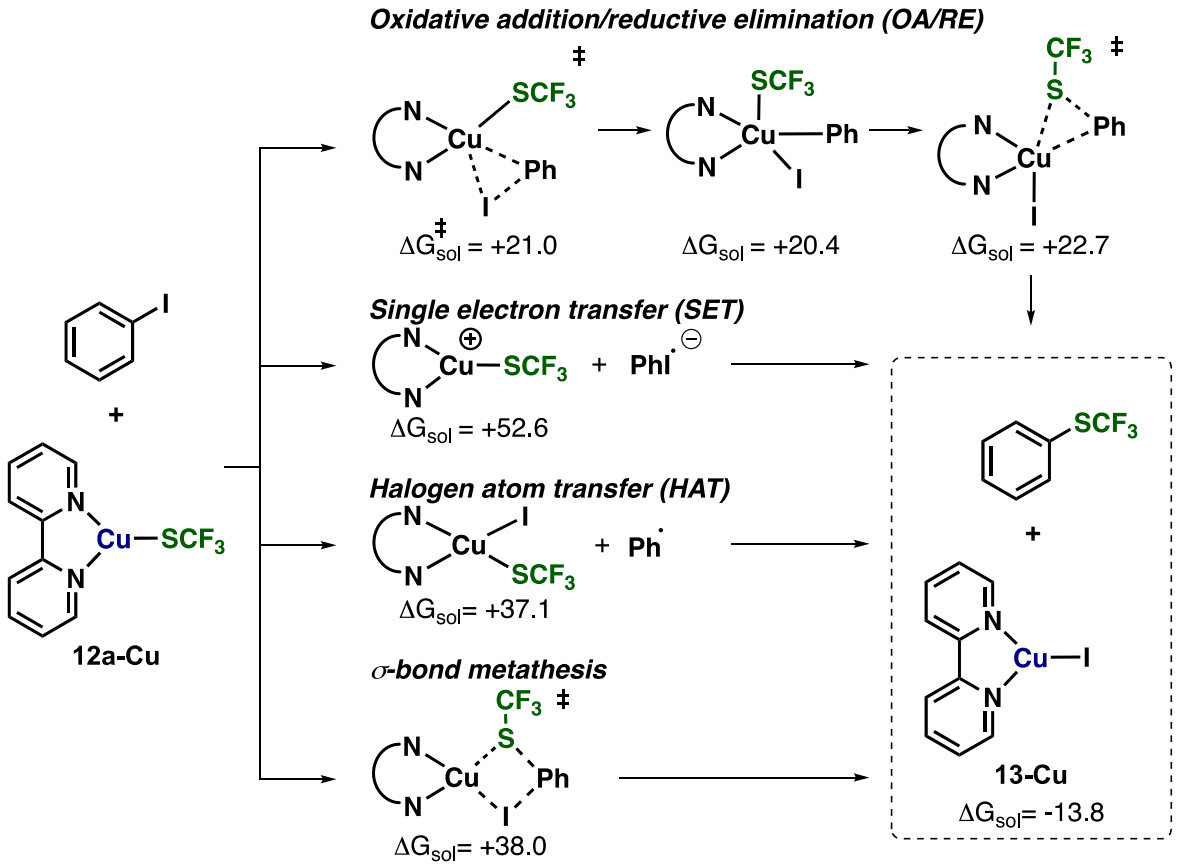
Scheme 6. Reactivity of Cu(I) thiophenolato complexes towards iodo-aryl compounds.

Following a similar approach, Weng and Huang prepared a series of trifluoromethylthiolato Cu(I) complexes containing bipyridine and phen ligands (Scheme 7).[42] The use of bipyridine produced a change in the molecular structure of the complexes. And three-coordinate copper complexes were isolated, where the metal is coordinated to one neutral bidentate bipyridine ligand and one anionic -SCF_3 group (**12a-Cu – 12c-Cu**). In contrast, the use of phen ligand produced a dimeric species and both types of complexes were reacted with aryl-halides to produce the sulfide compound (**11d-Cu**, **11e-Cu**). A significative higher reactivity was observed with the monomeric complexes. The reaction turned out to be very versatile, tolerating a wide range of aryl and heteroaryl halides, as well as vinyl bromides with various functional groups, such as cyano, nitro, trifluoromethyl, alkoxy, amino, halide and heterocyclic groups. Interestingly, when the reaction of the vinyl bromides with a trifluoromethylthiolate Cu(I) complex was carried out in the presence of a radical inhibitor such as BHT and TEMPO, where the sulfide product was observed, no cyclisation was observed, suggesting the absence of radicals in the reaction.[43]



Scheme 7. Reactivity of trifluoromethylthiolato Cu(I) complexes towards aryliodide and vinyl bromide compounds.

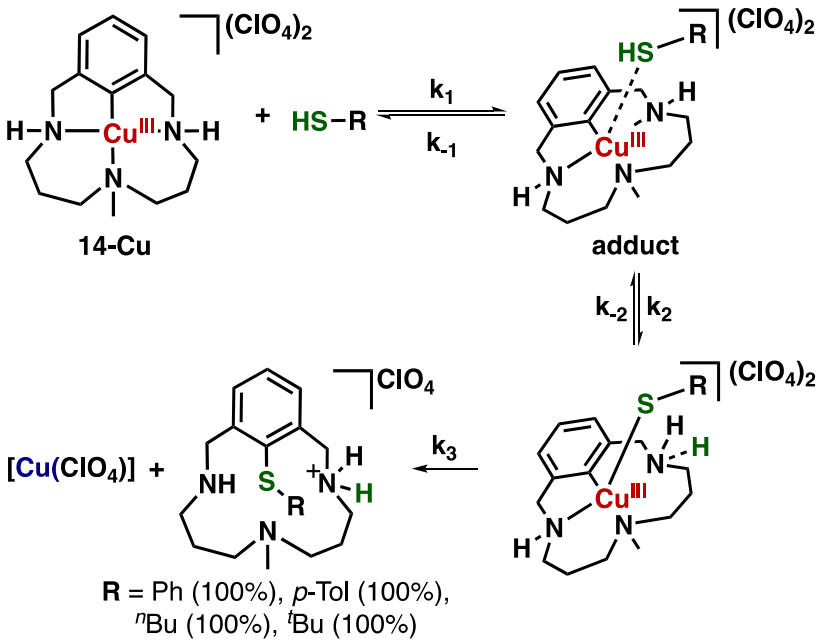
Moreover, Weng and Huang studied the reaction mechanism by DFT calculations.[42] They calculated the free energies (ΔG) of four possible routes (Scheme 8): i. Oxidative addition/reductive elimination (OA/RE), ii. Single electron transfer (SET), iii. halogen atom transfer (HAT) and iv. σ-bond metathesis. They found that the most plausible route is the OA/RE. The trifluoromethylthiolato Cu(I) complex undergo an oxidative addition of the aryliodide, giving place to a Cu(III) species. Then by a reductive elimination process the desired product is formed. Cu(III) species have been proposed in other reaction mechanisms, and they are considered as highly unstable compounds. Nevertheless, in the literature there are some examples of Cu(III) compounds bearing fluorinated ligands.[44-50] Besides, the OA/RE pathway has been proposed by other authors.[51]



Scheme 8. Possible reaction mechanism for the C-S coupling.

In a similar way, Zhang and Fan performed systematic DFT studies on the reaction mechanism of C-S cross-couplings catalyzed by Cu(I) complexes of the type $[Cu(SAr)(phen)]_2$.[52] Their study considered the four possible routes analyzed by Weng and Huang: OA/RE, SET, σ-bond metathesis and HAT, and the effect of the polarity of the solvent. They found that in non-polar solvents, such as toluene, the catalytic active species is a monomeric thiophenolate Cu(I) complex [(phen)Cu(SAr)], while in polar solvents, such as DMSO, the most favored species is the anionic $[Cu(SAr)_2]^-$. In principle, both species are in equilibrium, and the HAT is the most favored route. According to the DFT calculations, the rate-limiting step is the halogen atom transfer from the aryl halide to the Cu(I) center, leading to the formation of the Cu(II) species [(phen)Cu(SAr)(I)] and a phenyl radical. This latter radical reacts very fast with the sulfur atom, affording the C-S cross-coupling product and a [(phen)Cu(I)] species. Then, the halogen ligand is exchanged by the aryl thiol, regenerating the catalytic active species. This proposal contrast with the OA/RE route proposed by Weng and Huang, thus suggesting that both mechanisms operate at the same time. Although, if there are nucleophiles stabilizing Cu(III) species the OA/RE is preferred over the HAT pathway.

In the same line, the reductive elimination step of the C-S cross-coupling was studied by Ribas and co-workers.[53] They prepared a complex with a macrocycle ligand that was able to stabilize a Cu(III) metal center. The reaction of this complex with thiols at room temperature, leads to the C-S bond formation (Scheme 9). Thus implying that the Cu(III) center is capable to perform a rapid reductive elimination in the presence of nucleophiles. A significative difference in the reaction rate was observed between aryl-thiols and aliphatic thiols, the firsts being faster than the second ones. Also, they performed competence experiments with other nucleophiles by reacting the Cu(III) complex with 4-mercaptophenol and 4-mercaptobenzoic acid. When 4-mercaptophenol was used only the C-S coupled product was observed. Whereas, using 4-mercaptobenzoic acid the C-S product was observed in 45% yield and the C-O coupled product in 55% yield. Furthermore, the C-S cross-coupling between the macrocyclic ligand precursor and thiols was catalyzed by $[Cu(CH_3CN)_4](CF_3SO_3)$, affording the sulfide product quantitively. In this reaction was not necessary the presence of a base since the macrocyclic is a non-innocent ligand, capable to deprotonate the thiol. Hence, the OA/RE pathway operates in this case.

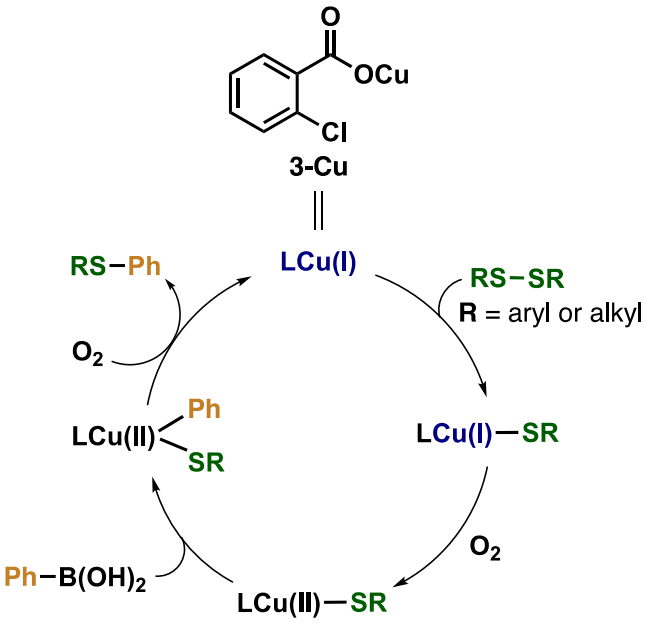


Scheme 9. Reaction mechanism of C-S cross-coupling by Cu(III).

Besides, Hsu, Han and Shyu studied the reaction mechanism of the C-S cross-coupling reaction catalyzed by a Cu(I) complex including a NHC ligand (Complex **4-Cu**, Scheme 2).[33] First, the nature of the catalytic active species was established by theoretical and experimental studies, since Cu complexes may transform to other Cu species through disproportionation, dimerization and ligand dissociation. The latter are endergonic processes for [(NHC)Cu(SAr)] complexes, with free energies differences of 14-69 kcal mol^{-1}, even in polar solvents such as DMF. Also, the kinetic and DOSY experiments suggested that the

[(NHC)Cu(SAr)] species dominates in the reaction media. This is remarkably because, as we mentioned above, using phen instead of NHC ligands, the most favorable species in polar solvents is the anionic $[Cu(SAr)_2]^-$ complex.[52] According to experiments using radical scavengers the contribution of free radicals is negligible, as previously observed by Weng, Huang and Hartwig.[41, 43] Hence, Hsu, Han and Shyu considered two possible routes: the OA/RE and the σ-bond metathesis. The first proceed *via* a radical path, while the second is considered a free-radical path. As expected, the rate-determining-step is the oxidative addition of the iodo-aryl to [(NHC)Cu(SAr)]. DFT calculations using the B3LYP functional revealed that the activation energy for the σ-bond metathesis is ~3 kcal mol^{-1} higher than that calculated for the OA/RE (43.18 kcal mol^{-1} for σ-bond metathesis *vs* 40.61 kcal mol^{-1} for OA/RE). Thus, the OA/RE is slightly more predominant, which agrees also with the fact that NHC's are strong σ-donor ligands capable to stabilize transition metals in high oxidation states.

Up to here, we have described the reaction mechanism using aryl-halides and thiols. However, a different reaction mechanism for the C-S cross-coupling operates when the substrates are aryl boronic acids and disulfides (Scheme 10).[29-30] The mechanism starts with the reaction between a Cu(I) complex (**3-Cu**) and the disulfide, to form the catalytic active species [LCu(SR)]. The S-S cleavage probably occurs through an electrophilic and nucleophilic attack by complex **3-Cu** and water or boronic acid, respectively.[54-58] The [LCu(SR)] reacts with molecular oxygen and the boronic acid, forming the Cu(II) species [LCu(SR)(Ph)]. Finally, the wanted product is released by a reductive elimination, and the catalyst is regenerated by a rapid re-oxidation with molecular oxygen.[29-30] Remarkably, the reaction does not proceed under inert atmosphere due to the active role of molecular oxygen during the mechanism.

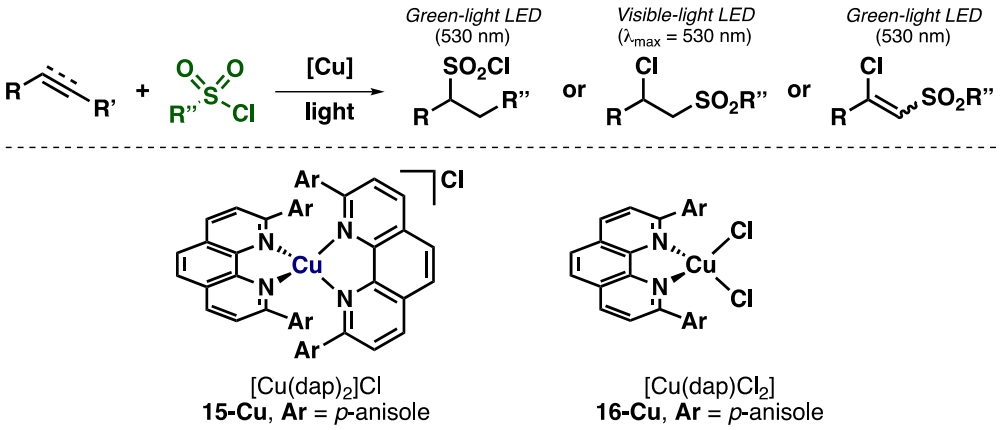


Scheme 10. C-S cross-coupling reaction mechanism between disulfides and boronic acids catalyzed by Cu(I).

C-S cross-coupling photocatalyzed by well-defined copper complexes

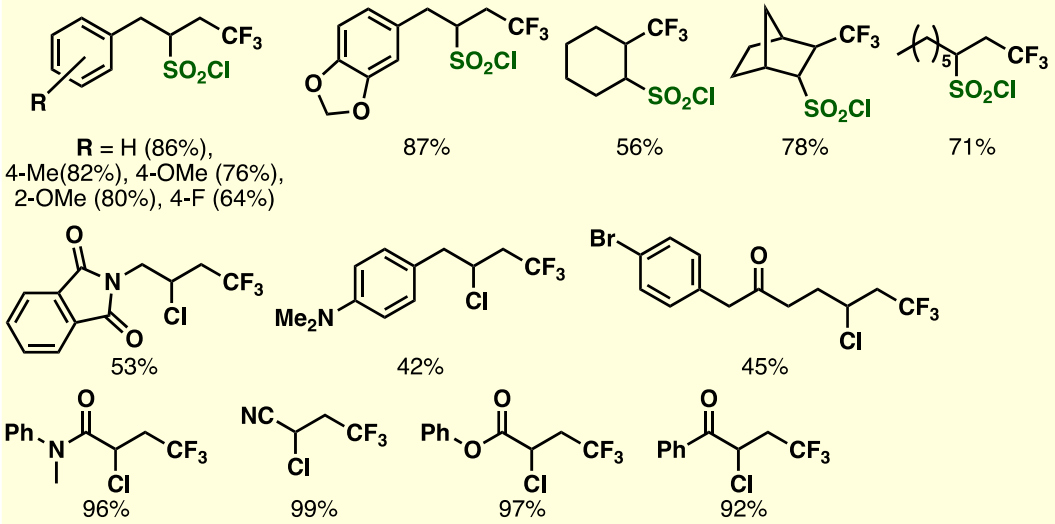
The first example of a photoinduced C-S cross-coupling reaction catalyzed by copper was described by Fu and Peters in 2013,[59-60] and consisted on reacting aryl-thiols with aryl-bromides or aryl-iodides in the presence of a copper salt (CuI) and a base (NaO^{t}Bu) at 0 ºC. The latter mixture was irradiated with a 100 W Hg lamp, from 5h to 24h depending on the substrates. The aryl-bromides required longer reaction times (12-24h) than the aryl-iodide substrates (5-8h). These unusual soft conditions worked well with a wide range of substrates, including heterocycles such as 4-mercaptopyridine, iodothiophenes, 5-iodoindole, and arenes with functional groups such as ethers, nitriles and nitro. This pioneer report showed the high potential of the use of photocatalysis methodologies catalyzed by copper salts.[61-67] In the literature there some recent and interesting reviews about photocatalysis using copper,[68-79] but the use of well-defined copper-based catalysts for the photoinduced C-S cross-coupling remains scarcely explored.

Well-defined complexes [Cu(dap)$_2$]Cl (15-Cu) or [Cu(dap)Cl$_2$] (16-Cu), where dap is 2,9-di(*p*-anisole)-1,10-phenanthroline, have been employed to photocatalyze the sulfonylation of alkene and alkynes (Scheme 11).[80-83] In 2015, Reiser and co-workers described that alkenes can be sulfonylated with trifluoromethanesulfonyl chloride (CF_3SO_2Cl) in the presence of K_2HPO_4 and 14-Cu, and irradiation with green light LED (530 nm). The sulfonyl fragment was bonded in a regioselective fashion to the carbon with least hydrogen atoms (Markovnikov product), and the -CF_3 fragment to the terminal carbon atom. The reaction tolerates some functional groups such as aryls and ethers. However, when electron-deficient alkenes such as α,β-unsaturated ketones, amides, esters, carboxylic acids, sulfones and phosphonate were used,[84] or a donor atom is close in proximity to the alkene, the bonding of -Cl to alkene occurs instead of the -SO_2Cl fragment. Interestingly, the regioselectivity of the reaction was inverted by irradiation with visible light (λ_{max} = 520 nm) in the presence of Na_2CO_3. Under the latter conditions sulfonyl chlorides with electron-rich or electron-poor substituents such as aryls, fluorinated-aryls or thiophenes were used, as well as inactivated alkenes. In a similar way, using either 15-Cu or 16-Cu complexes activated alkynes were sulfonylated under green LED irradiation (λ_{max} = 530 nm) in good yields, while inactivated alkynes such as 1-hexyne were inactive. The reaction affords in all cases a mixture of *E* and *Z* isomers near to 1:1 ratio.[83]



Representative products and yields

- Starting from alkenes and irradiating with green-light LED

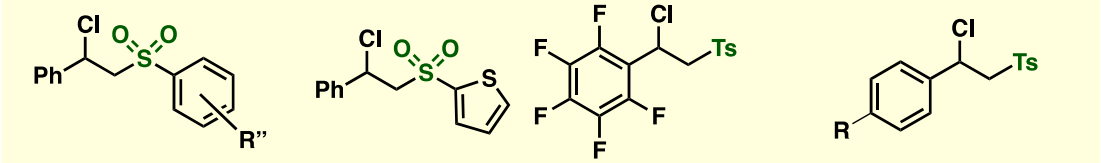


R = H (86%), 4-Me(82%), 4-OMe (76%), 2-OMe (80%), 4-F (64%) | 87% | 56% | 78% | 71%

53% | 42% | 45%

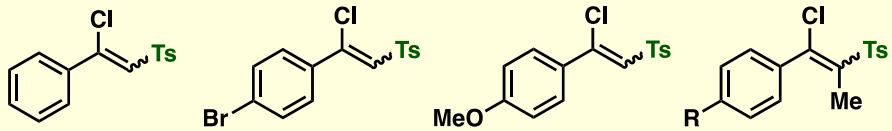
96% | 99% | 97% | 92%

- Starting from alkenes and irradiating with visible-light LED



R" = H (95%), 2-Me (95%), 4-Me (95%), 4-OMe (97%), 4-F (95%), 4-CF_3 (95%), 4-NO_2 (81%), 2,3,4,5,6-F (77%) | 95% | 91% | **R** = Me (96%), ^{t}Bu (97%), Cl (87%), NO_2 (38%), CN (90%)

- Starting from alkynes and irradiating with green-light LED



Using **15-Cu** =	**90% (*E*:*Z* = 51:49)**	**97% (*E*:*Z* = 52:48)**	**96% (*E*:*Z* = 45:55)**	**46% (*E*:*Z* = 65:35)**
Using **16-Cu** =	**87% (*E*:*Z* = 64:36)**	**93% (*E*:*Z* = 52:48)**	**97% (*E*:*Z* = 63:37)**	**45% (*E*:*Z* = 60:40)**

Scheme 11. Sulfonylation photocatalyzed by Cu(I) complexes with bi-dentated ligands and representative products that were prepared under different light frequencies.

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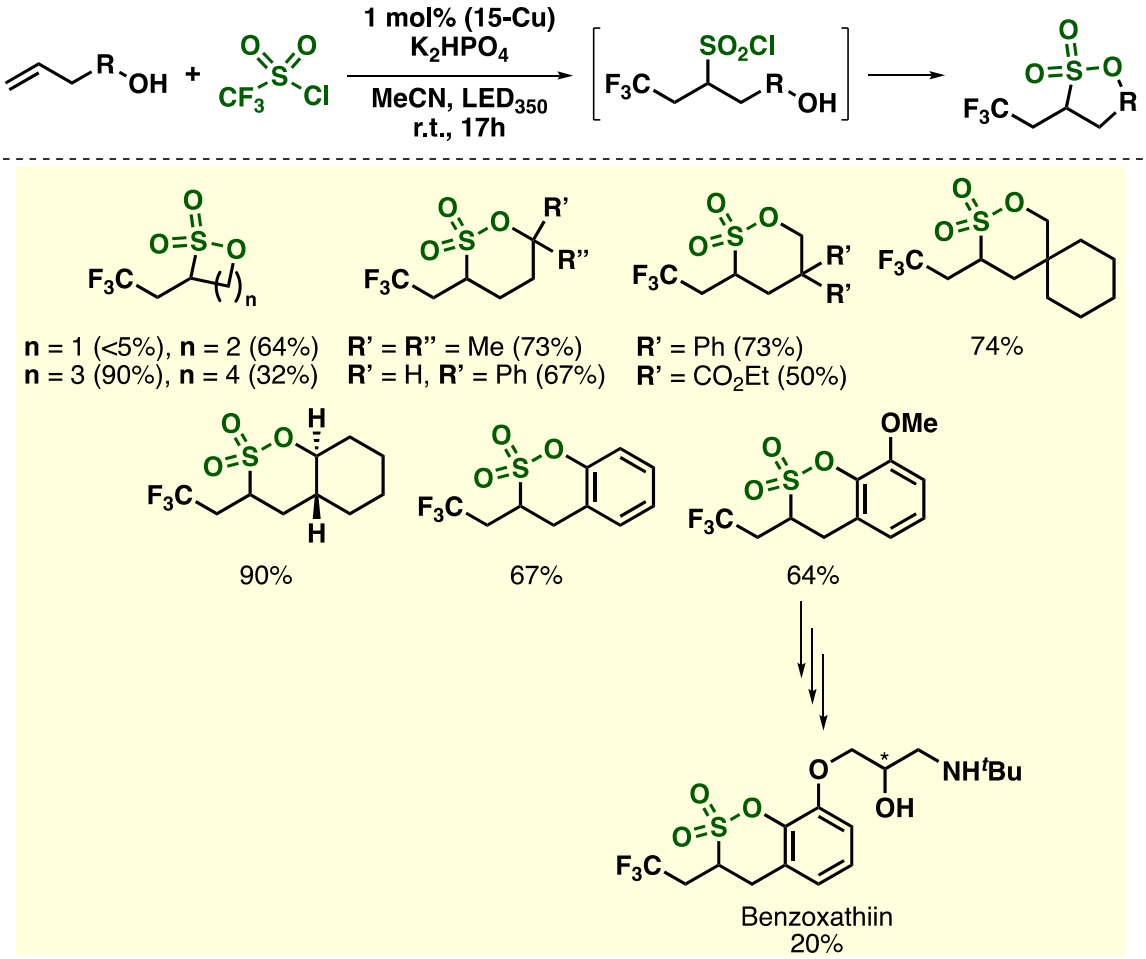
In a similar approach, Reiser and coworkers described the synthesis of sultones from alkenols and trifluoromethylsulfonyl chloride (Scheme 12), photocatalyzed by 15-Cu. [85] The reaction proceeds in the presence of K_2HPO_4, and by irradiation with blue LED (455 nm). The use of but-3-en-1-ol and pent-4-en-1-ol gives high yield of the sultone (64% and 90%, respectively), while the use of shorter or longer alkenols, afford lower yields; <5% using allyl alcohol and 32% using hex-5-en-1-ol. Others commercially available alkyl-fluorinated sulfonyl chlorides such as trifluoromethanesulfonyl chloride or nonafluoro-1-butanesulfonyl chloride required longer reaction time to generate the sultone (17-48h), while pentafluorobenzenesulfonyl chloride or trichloromethanesulfonyl chloride did not show any reactivity. Interestingly, the authors showed the synthesis of a novel benzoxathiin derivative using this synthesis of sultones as the key step.

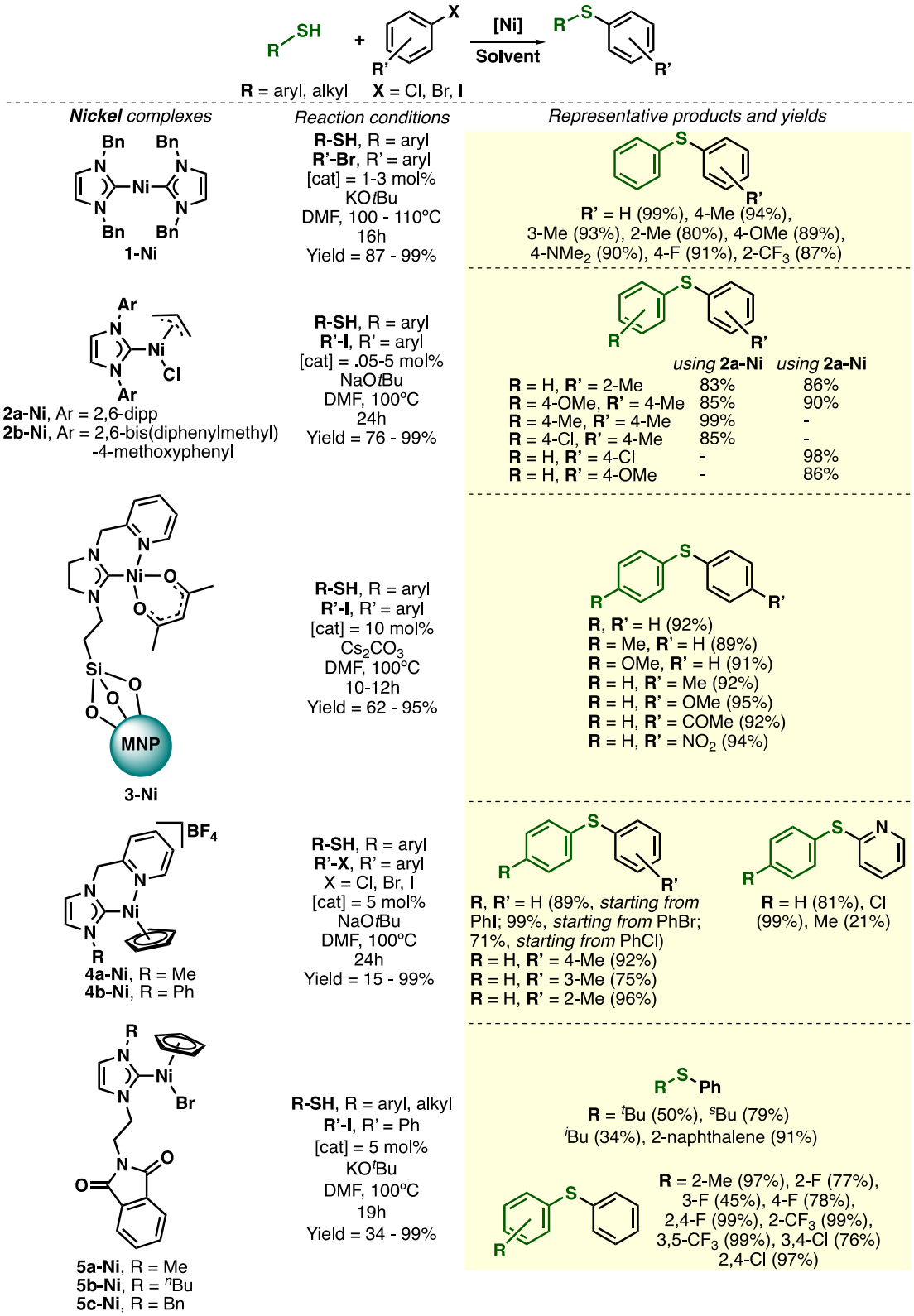


Scheme 12. Synthesis of sultones from alkenols photocatalyzed by **15-Cu.**

3. Nickel Catalysts

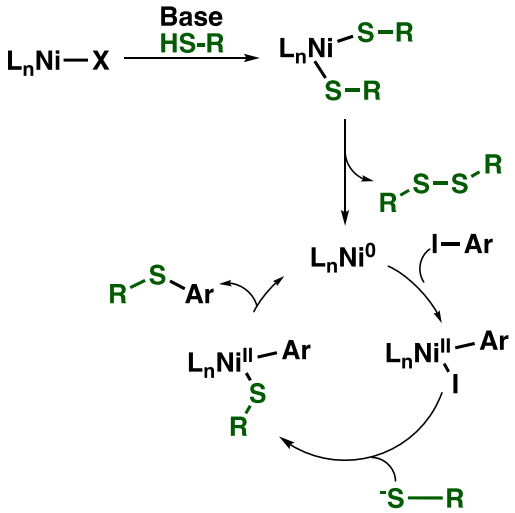
Nickel is a useful transition metal to prepare well-defined catalysts for cross-coupling reactions.[86-87] Some examples of NHC-Ni complexes are shown in Scheme 13. In 2007 Zhang and Ying described the first NHC-based Ni(0) catalysts for C-S cross-couplings. The catalyst was produced *in situ* from the reaction of the corresponding azolium salt, $[Ni(COD)_2]$, and KO^{t}Bu in DMF. In principle, this reaction produces a complex of the type $[Ni(NHC)_2]$, which is the catalytic active species.[88] Three years later Nicasio and co-workers described one of the first examples of well-defined Ni(II)-NHC catalyst for the C-S cross-coupling reactions. The catalyst was based on the well-known 1,3-bis(2,6-diisopropylphenyl)imidaol-2-ylidene (IPr). In this case the reaction conditions were similar, *i.e.* 1-5 mol% of catalyst, iodo-aryl, thiol-aryl, base (KO^{t}Bu or NaO^{t}Bu), DMF, 100 – 110ºC, and reaction times between 10 and 16 h to get >80% yields.[89] Then, by using the bulkier IPr* ligand (N,N′-bis[2,6-bis(diphenylmethyl)-4-methoxyphenyl]imidazol-2-ylidene) a slightly improvement in the catalytic activity was achieved.[90] Under similar reaction conditions but using lower catalyst loading (0.5 – 2 mol%) similar yields were obtained.

Jun and Lee immobilized on magnetite/silica a Ni(II)-NHC complex (3-Ni), which was active for C-S cross-couplings between aryl halides and thiols.[91] Interestingly, the catalyst can be recovered and reused for thee cycles. Puerta y Valerga contributed to the development of well-defined catalysts by describing the synthesis and catalytic evaluation of two Ni(II) complexes using a bidentate NHC-N ligand (4a- and 4b-Ni).[92] The catalytic reactions were performed at room temperature, however longer reaction times (24h) were required to obtained good yields. Interestingly, the electronic properties of the different substituents in the thiol did not affect the catalytic activity of the complexes.



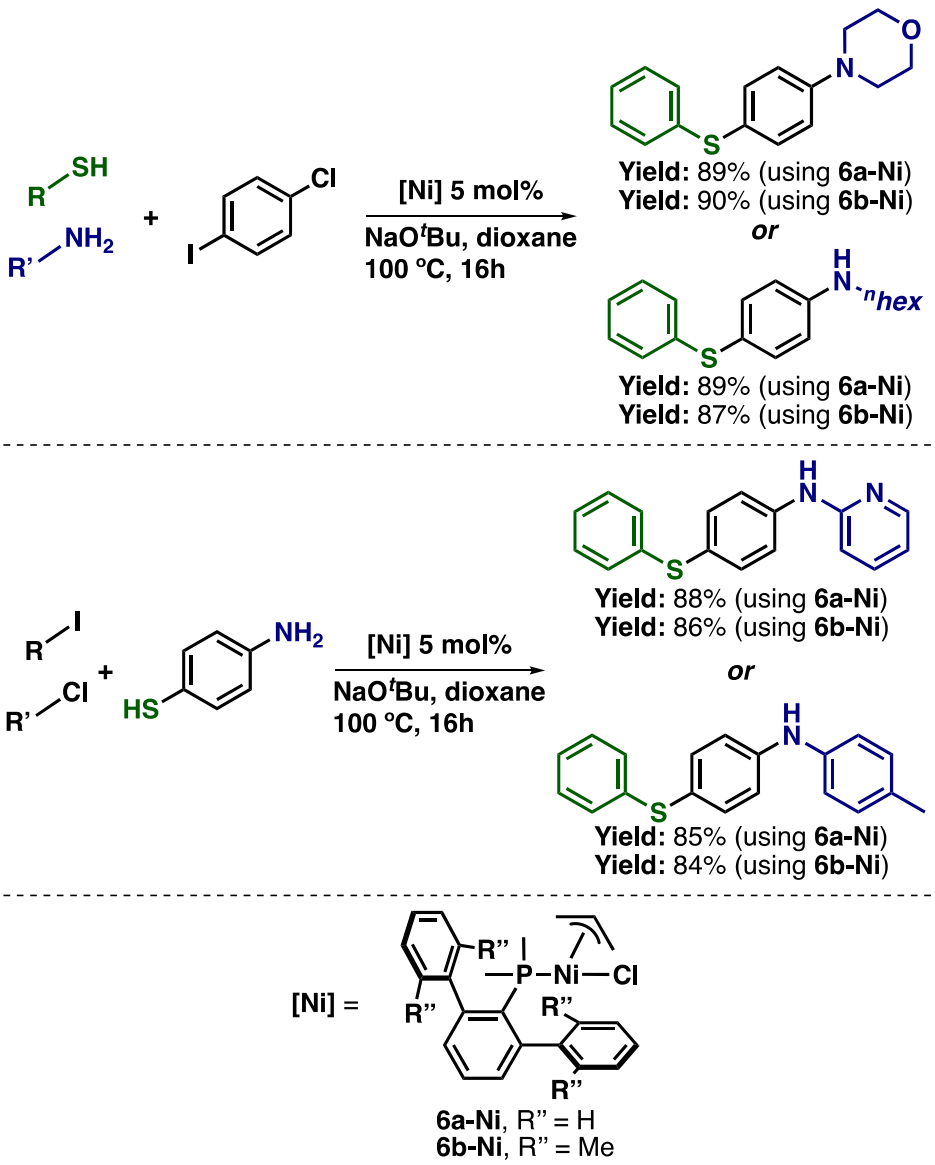
Scheme 13. C-S cross-coupling reactions catalyzed by Ni complexes with NHC-based ligands, optimized reaction conditions and representative products were prepared using optimized conditions.

On the other hand, Morales-Morales *et al.* contributed to the development of this field.[93] They prepared and evaluated a series of Ni(II) complexes of the type [(NHC)Ni(Cp)(Br)] on C-S cross-coupling reactions of thiols and iodo-aryls. The reactions were carried out using 5 mol% at 100ºC in DMF. The most active complex was that with the more electron donating NHC ligand (5b-Ni). In fact, the complexes followed a trend according to the N-substituent: -N^{n}Bu > -NMe > -NBn. The proposed reaction mechanism (Scheme 14) starts with the reduction of Ni(II) to Ni(0) through the coordination of the thiolate followed by a reductive elimination, to form a disulfide compound, which has been experimental observed.[94] Then, the Ni(0) species undergo an oxidative addition, producing a [(L)$_n$Ni(Ar)(X)] complex. The halogen ligand is then exchanged by a thiolate. Finally, the catalyst is regenerated, and the product is released through a reductive elimination.



Scheme 14. Reaction mechanism of C-S cross-coupling catalyzed by Ni-NHC complexes.

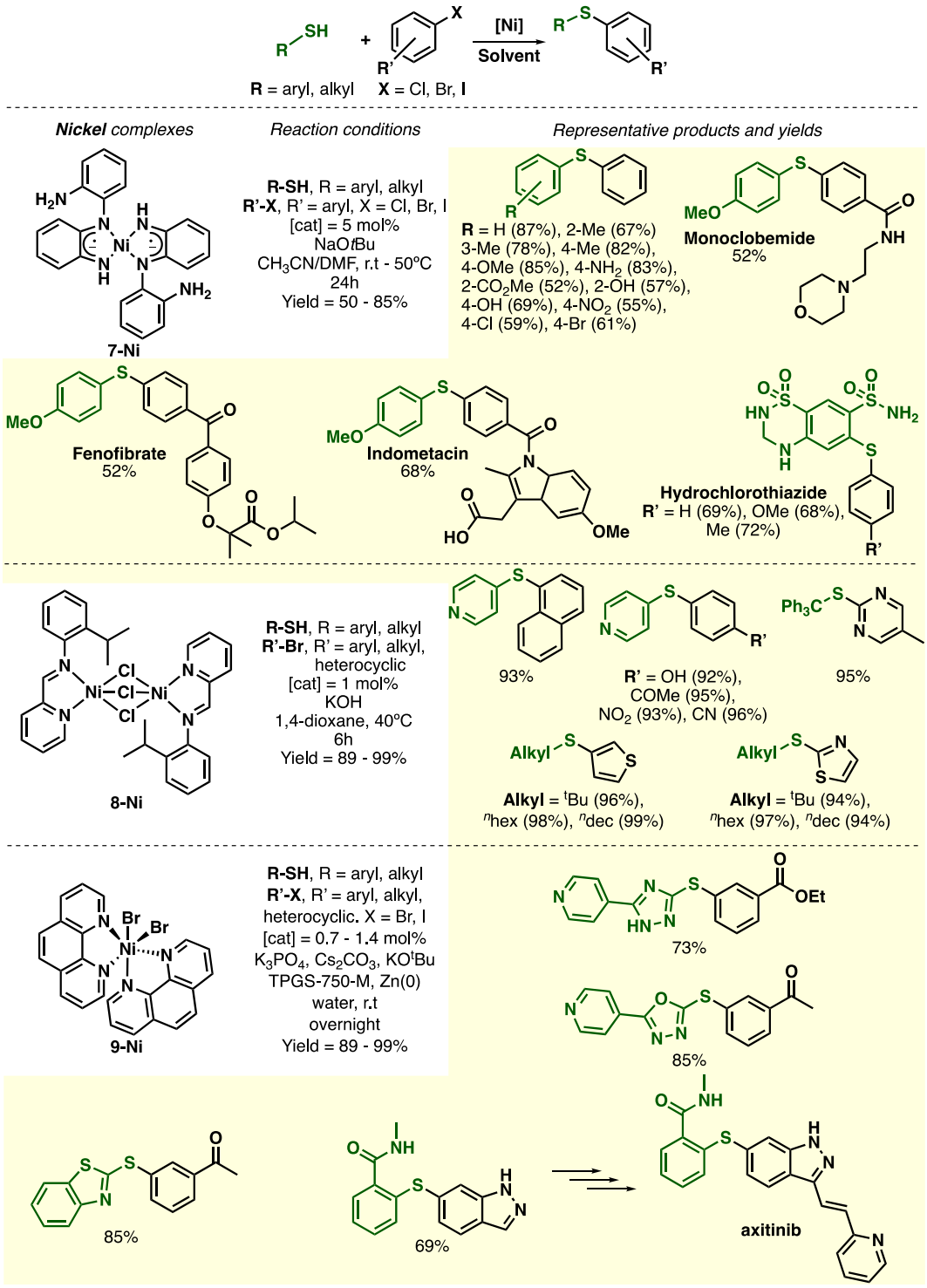
In a more recent example Nicasio and Prieto described a well-defined Ni(II) phosphine-based complex with a strong electron-donating and sterically crowded dialkylterphenyl phosphine ligand.[95] This ligand is particularly effective to sterically protect the metal center, and provides and extra stabilization through a weak M-C$_{aryl}$ interaction. The Ni(II) phosphine-based complexes were able to promote the C-S cross-couplings of thiols and alkenyl tosylates or aryl-halides, including the less reactive aryl-chlorides. These catalysts were also able to promoted a *tandem* C-S/C-N cross-coupling of multi-electrophile/nucleophile combinations in a chemoselective manner (Scheme 15).



Scheme 15. *tandem* C-S/C-N cross-coupling of multi-electrophile/nucleophile by Ni(II) complex.

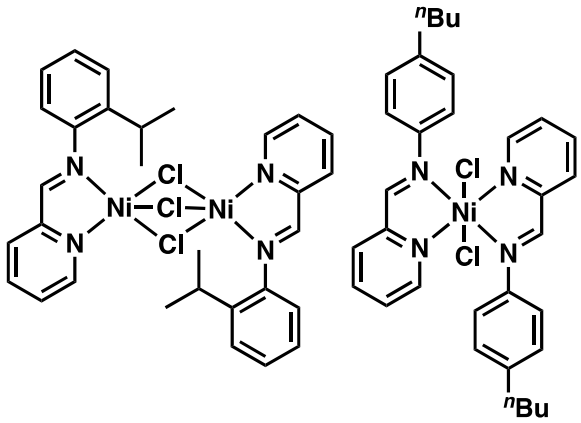
Further, multi-dentated ligands have also been used for the design of Ni catalysts. In particular bi-dentated N,N-ligands have shown interesting features (Scheme 16).[96-101] For instance, some 1,2-phenyldiamine derivatives are considered non-innocent ligands since they exhibit one electron oxidized redox properties. This particularity enhances the catalytic activity of their Ni complexes derivatives. In fact, complexes of the type [Ni(L)$^{-}_{n}$] (**7-Ni**) promote the C-S cross-couplings at room temperature of bromo- and iodo-arenes, leading to good yields even using chloro-arenes at 55 °C.[36] The presence of the N,N-non-innocent ligands does not modify the essential steps of the mechanism, following a typical OA/RE pathway. However, the predominant oxidation states of the metal center varies from II to III, instead of the typical 0 to II. According to DFT calculations, the Ni(II) center and one of the

coordinated ligands participates in a synergistic manner during the oxidative addition, involving Ni(II)/Ni(III) and $\{(L)^{2-}\}/\{(L)^{-}\}$ redox pairs.



Scheme 16. C-S cross-coupling reactions catalyzed by N,N-Ni(II) complexes, optimized reaction conditions and representative products were prepared using optimized conditions.

The effect of the steric properties of α-diimine Ni(II) complexes and its relationship with their catalytic activity was study by Stefan and co-workers.[102] They calculated the ligand bite angle and the percent buried volume (%V_{bur}) of two Ni(II) complexes (Scheme 17). They found that in both ligands the bite angle was very similar (78.13(6) º vs 79-02(8)º), but a clear difference in %V_{bur} was determined; the *iso*-propyl derivative showing a %V_{bur} of 52.1, while that of the of the *butyl*-derivative was %V_{bur} = 34.5. This difference influencing the catalytic activity of the corresponding complexes. The Ni(II) complexes with the highest steric bulk ligand afforded *quasi* quantitative yields in the C-S cross-couplings using alkyl, heteroaryl thiols and aryl and heteroaryl bromides. Thus, the reductive elimination and oxidative addition are promoted by greater steric bulk (steric hindrance) and ligand bite angle.



	8-Ni	10-Ni
Ligand bite angle (N1-Ni-N2)	79.02(8)°	78.13(6)°
%V_{bur}	52.1	34.5

Scheme 17. Ligand bite angle and the percent buried volume (%V_{bur}) of two Ni(II) complexes described by Stefan and co-workers.

Phen type ligands form robust catalysts when they are coordinated to Ni(II). Thus, Lipshutz and co-workers demonstrated that the well-defined complex of the type [Ni(phen)$_2$Br$_2$] is more catalytically active than the plain mixing of [NiBr$_2$] and phen.[103] Furthermore, the [Ni(phen)$_2$Br$_2$] complex catalyzes the C-S cross-coupling reactions in water in the presence of DL-α-tocopherol methoxypolyethylene glycol succinate (TPGS-750-M), which acts as surfactant. Remarkably, the synthesis of a key intermediate for the Pfizer's antitumor agent axitinib was achieved in gram scale, and more important, was the fact that the residual nickel found in the axitinib precursor was 9.8 ppm, which is a value below the FDA accepted guidelines of ≤25 ppm.

Pincer ligands have played an important role in the development of C-S cross-coupling reactions (Scheme 18). Thus, in 2005 Morales-Morales and co-workers reported the catalytic activity of a series of N,N,N-Ni(II) pincer complexes with fluorinated fragments.[104-105] The

thiolation reactions were carried out using disulfides and iodoarenes, Zn (0) in DMF at 110ºC for 4h. Interestingly, the performance of the N,N,N-Ni(II) pincer was affected by the steric hindrance of the substituents in the disulfide. The bulkier was the substituent the lower activity was observed, following the trend: methyl > *n*-butyl > *iso*-propyl > *sec*-butyl > *tert*-butyl. A similar behavior was more recently observed using PYCOP-Ni(II) (Y = O or S)[106-108] or SPS-Ni pincer complexes.[109]

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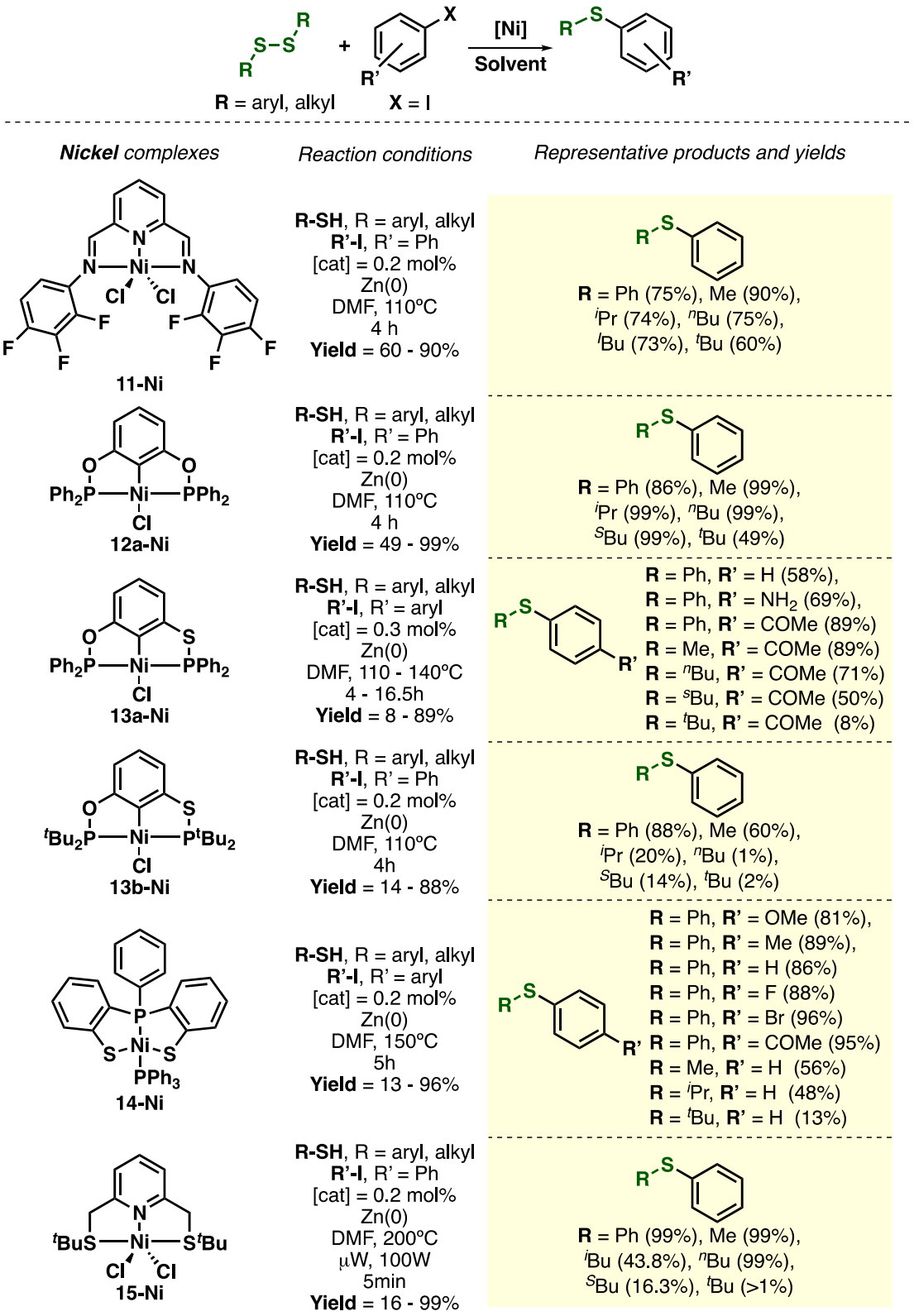
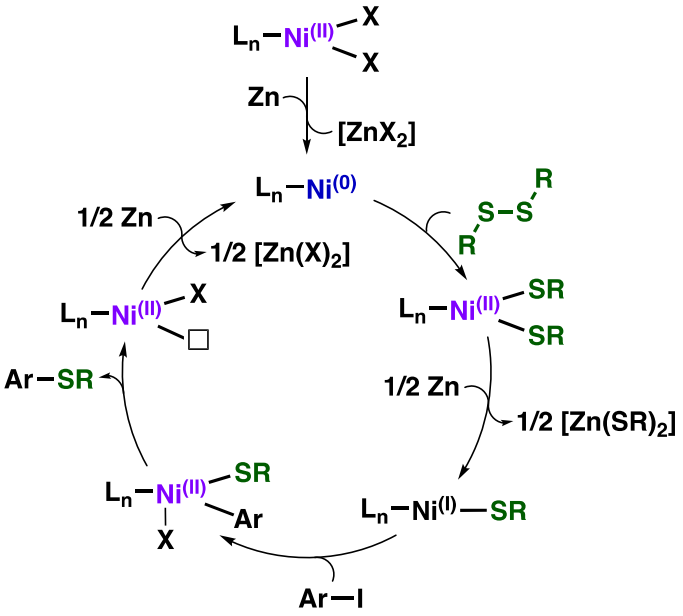


Scheme 18. C-S cross-coupling reaction of disulfides and aryl-halides catalyzed by pincer Ni(II) complexes, optimized reaction conditions and representative products that prepared using optimized conditions.

Microwave irradiation has appeared as a green alternative to traditional heating, improving some methodologies and promoting some challenging reaction. In this sense, the SNS-Ni(II) pincer complex catalyzed the C-S cross-coupling of disulfides and iodobenzene in just 5 min under microwave irradiation (100 W).[110] Thus, quantitative yields were observed using methyl-, *n*Bu-, and phenyl-disulfide, while using a more crowded disulfide (*tert*-butyl-disulfide) only afforded < 1% yield of the desired product.

As expected, the reaction mechanism is different due to the use of disulfides and Zn(0) (Scheme 19). Hence, the disulfide undergoes oxidative addition to the Ni(0) species, affording a Ni(II) dithiolate complex, which is then reduced to a Ni(I) thiolate compound. Then, the iodoarene is oxidatively added to the Ni(I) species, forming a Ni(III) complex, that further undergoes a reductive elimination to generate the product and a Ni(II) complex. Finally, the excess of Zn(0) causes the reduction of this latter complex to regenerate the catalyst.[104]



Scheme 19. Reaction mechanism of the C-S cross-coupling of disulfides and aryl-halides catalyzed by pincer Ni(II) complexes.

Furthermore, POCOP-, PNP- and POP-Ni(II) pincer complexes have showed a great performance in C-S cross-couplings of aryl halides and aryl-thiols (Scheme 20).[111-113] The catalytic reactions are usually carried out in DMF for 2-6h at 80ºC in the presence of KOH, obtaining yields from 76% to >99%. These catalytic conditions tolerate functional groups such as methoxy, cyano, heterocycles and CF_3. Despite this high activity and versatility, the coupling reactions did not proceed using chloro-aryl substrates, this being probably due to high energy involved in the C-Cl bond activation. Although this drawback can be

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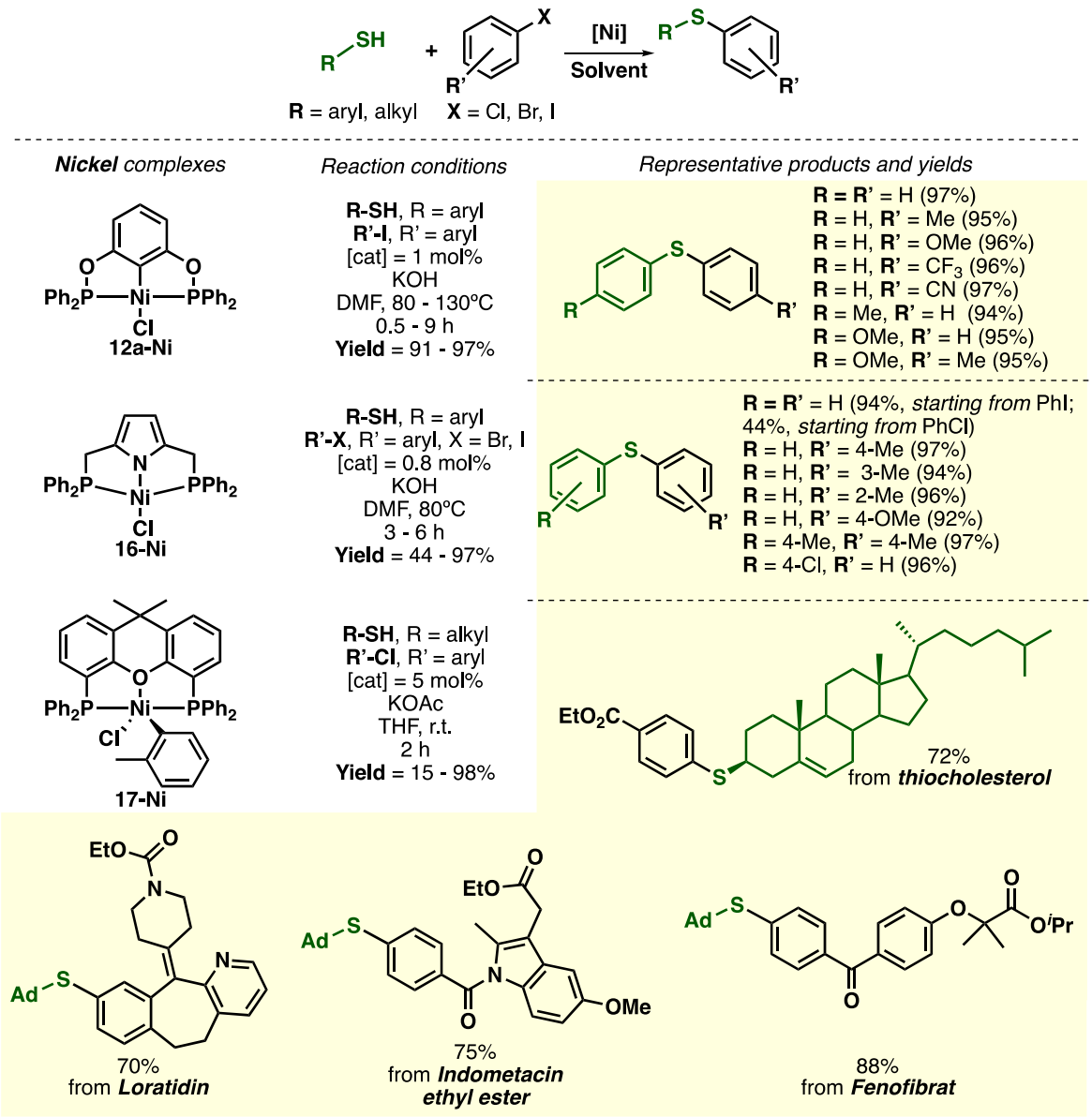
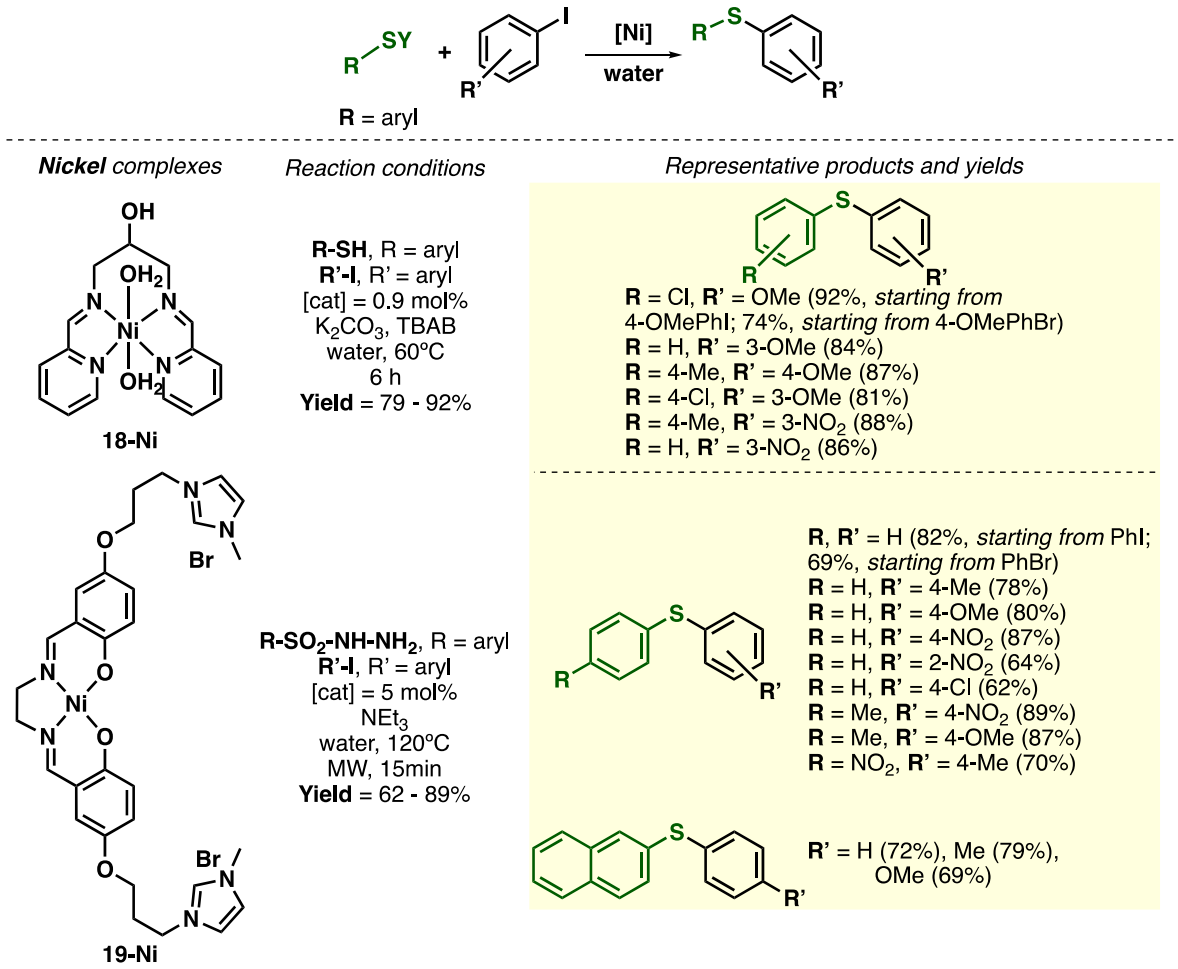
circumvented by the correct choice of the catalyst and base. Actually, using a xanphos-Ni(II) pincer complex (**17**-**Ni**) and potassium acetate [$K(CH_3COO)_2$] the reaction proceeds at room temperature in only 2h.[113] In a comparative study, using chlorobenzene, bromobenzene and iodobenzene the yields were similar (81%, 89% and 85%, respectively), in fact using phenyl triflate allowed to reach 96% yield of the desired product. Besides, primary, secondary and a variety of sterically challenging alkyl thiols were coupled with chloro-arenes. The catalytic reaction conditions tolerated functional groups such as ketones and esters, but a notable limitation was observed using aldehydes, acids, or primary amines. Very interestingly is the dual key role of the [$K(CH_3COO)_2$], since it acts as halogen scavenger after the oxidative addition of the chloro-arene, and acts as an internal-base by deprotonating the approaching thiol in an internal manner. Other Ni(II) complexes including ONS-type ligands also catalyze the coupling of thiols and alkyl- or aryl-chlorides, however requiring higher temperatures.[114]



Scheme 20. C-S cross-coupling reaction of thiols and aryl-halides catalyzed by pincer Ni(II) complexes, optimized reaction conditions and representative products were prepared using optimized conditions.

Finally, greening of C-S couplings based on the design of water-soluble catalysts has allowed the use of water as solvent[115] (Scheme 21). For example the N,N,N,N-Ni(II) complex (**18-Ni**) catalyzed the coupling of aryl-halides and thiols in water at 60 ºC in 6h.[116] The reaction tolerates functional groups such as methoxy and nitro, but the reaction did not proceed using chlorobenzene as substrate. Further, the salen-based Ni(II)-complex (**19-Ni**) catalyze the coupling of sulfonyl-hydrazines and aryl-halides in water.[117] The reaction was promoted by microwave irradiation and a base was required (NEt_3). Interestingly, under this reaction

conditions chlorobenzene can be used yielding 49% of the C-S cross-coupling product. Moreover, the aqueous catalytic system can be reused 5 times without apparent loss of activity or deactivation of the catalyst.

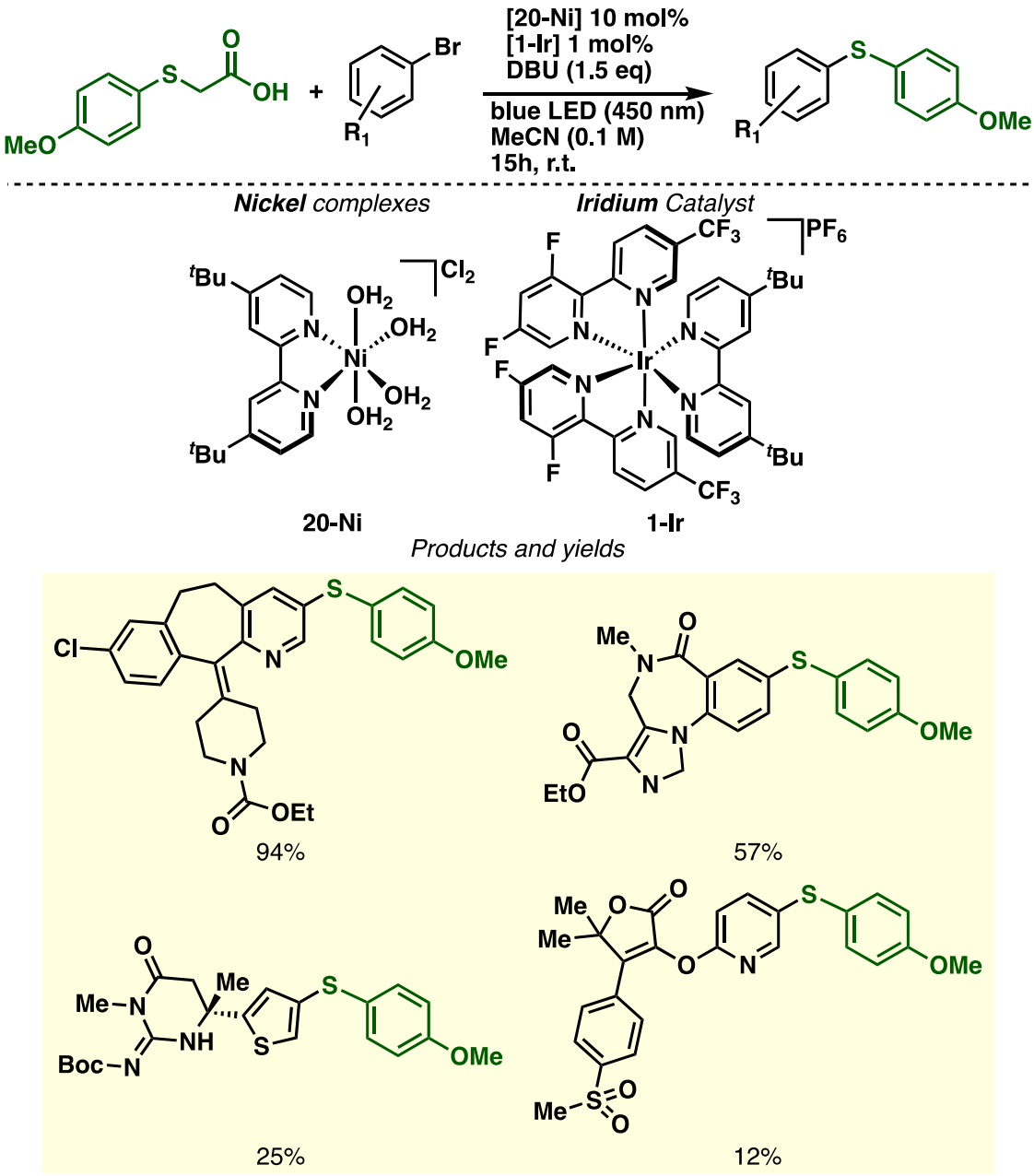


Scheme 21. C-S cross-coupling reaction in water catalyzed by Ni(II) complexes with multi-dentated ligands, optimized reaction conditions and representative products were prepared using optimized conditions.

C-S cross-coupling photocatalyzed by well-defined nickel complexes

Recently, the use of light to promote C-C[118] and C-heteroatom cross-coupling reactions has attracted much attention, but the use of nickel remains uncommon.[119-120] In the particular case of the C-S cross-coupling reactions some examples have been described using a photoredox catalyst and nickel, being the so-called *metallaphotoredox* approach,[97-98, 121-124] where the photoredox catalyst is an iridium-based complex that is able to perform excited-state single-electron transfer (SET) processes[125] to drive the C-S cross-couplings together with the nickel catalyst.[97] In this line, Christian applied this strategy to functionalize some

pharmaceutically relevant heteroaryl bromides (Scheme 22).[99] The use of complexes **20-Ni** (10 mol%) and **1-Ir** (1 mol%) in the presence of DBU and irradiated with a blue LED at room temperature, afford the desired thioether derivative in yields that range from 12% to 94%, demonstrating a good tolerance to different functional groups.



Scheme 22. C-S cross-coupling reaction of pharmaceutically relevant heteroaryl bromides, catalyzed by Ir/Ni metallaphotoredox strategy.

4. Conclusions

The C-S cross-coupling reaction can be efficiently catalyzed by two non-precious transition metals, copper and nickel. Copper is one of the most abundant metals in the earth curst, and consequently is one of the cheapest. In a similar way, nickel is also accessible. The catalytic performance of the metal center can be tuned by different ligands. Nitrogen-based ligands are very common, and they form readily stable Cu(I) complexes. In particular, multidentate N-based ligands have provided a suitable chemical environment to prepare active catalysts, besides they have helped to the isolation of some key Cu(III) intermediates, allowing a deep study of the C-S cross-coupling reaction mechanism. In fact the stabilization of copper(III) species has been a breakthrough in copper chemistry that has permitted the establishment of some catalytic mechanism.[126-127] Nowadays, it is very well-accepted that in the C-S cross-coupling reaction Cu(III) species are involved. Further, the use of nickel as catalyst has also a long history and represents a good alternative to some other expensive metals such as palladium. The construction of highly active catalyst based on nickel has consisted in the use of very strong σ-donor, multidentate ligands or a combination of both. The different scaffolds of well-defined Ni-NHC complexes have helped to design more active catalysts. Increasing the σ-donor capacity of the ligands improves the catalytic activity since electron-rich metal centers favor the first step of the reaction mechanism, oxidative addition. The steric factors of the ligands have also played an important role, favoring the oxidative addition and the reductive elimination processes, both being essential steps in the accepted reaction mechanism. The use of simple multidentate ligands such as phen is also relevant to design highly active catalytic systems. Noteworthy the fact that the very robust pincer ligands have played an important role in the development of cross-coupling reactions. Their unique coordination fashion provides a suitable environment to stabilize Ni complexes, thus producing highly active catalysts for C-S cross-couplings. In practice, POP-Ni(II) pincer complex catalyze the coupling of chloroarenes and thiols at room temperature in 2h, being one of the most active catalysts described this far. Processes that can be nicely complemented using alternative sources of energy such as microwaves, allowing the SNS-Ni pincer complex to promote C-S couplings in 5 min under microwave irradiation.

Based on the results presented in this review is highly probable that we will continue to observed and abundant amount of reports on the coming years regarding the better design of new, well defined, more active catalysts based on earth abundant metals, supported by different ligand scaffolds to promote C-S cross couplings in a more efficient manner thus expanding the application scope of this foremost industrially relevant transformation.

5. Outlook

One of the advantages on the use of well-defined catalysts for the C-S cross-coupling is the control of its reactivity. Simple, cheap and commercially available ligands such as phen, 2-chlorobenzoyloxy and pyridines provide a suitable environment around the metal to prepare catalytically active complexes. The use of phen-based ligands and Cu(I) (see Scheme 11)

enable the sulfonylation of alkenes and alkynes promoted by light. Remarkably, the well-define [Cu(dap)$_2$]Cl photocatalyst did not require the presence of any photosensitizer, avoiding the use of expensive Ir- or Ru-based complexes. Tridentated ligands such as pincers, has showed to be excellent platforms to design catalysts with an outstanding catalytic performance that facilitate the preparation of sophisticate organic compounds, see Scheme 20. Whereas macrocycles ligands have helped to stablish some key steps of the C-S reaction mechanism catalyzed by Cu. Thus, we hope that this review will further inspire and help researchers to design novel, yet more active and selective, well-defined catalysts to efficiently catalyze the C-S cross-coupling reaction.

Acknowledgments

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Table of Contents Entry

The uses of well-defined coordination and organometallic copper and nickel complexes in the formation of C-S bonds by C-S cross coupling reactions is described. Representing an advantage in comparison with those based on precious metals such as Pd, by being two of the most abundant metals in the earth's crust and thus cheaper. The design and selectivity of different ligand scaffolds as well as involved reaction mechanisms of these complexes on these processes is also discussed.

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Biographies

Hugo Valdés received his bachelor's in Chemistry from the National Autonomous University of Mexico (UNAM) in 2011 and completed his PhD degree with honors at University Jaume I in 2015, under the supervision of Prof. Eduardo Peris and Dr Macarena Poyatos. Then, he moved to the group of Prof. David Morales-Morales, at the Institute of Chemistry, UNAM for postdoctoral studies. Thereafter he joined the group of Prof. Xavi Ribas at the University of Girona as post-doc. His research interest involves the development of catalysts for C–C and C-heteroatom cross-coupling reactions through C–H activation.

Ernesto Rufino-Felipe (Guerrero, México, 1981) received his MSc and PhD degrees in chemistry from the Universidad Autónoma del Estado de Morelos under the supervision of Prof. Miguel A. Muñoz-Hernández in 2008 and 2016 respectively. In February 2016, he joined the team of Prof. Virginia Montiel-Palma as postdoctoral fellow. In October 2018, he joined the group of Prof. David Morales-Morales as postdoctoral researcher. His research interests are in the field of medicinal and organometallic chemistry, as well as the developed of new catalysts for C-S cross-coupling reactions.

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