

Transition Metal Catalysis and Cross-Coupling Reactions

Palladium-catalyzed cross-coupling of aryl halides and boronic acids (Suzuki coupling), organostannanes (Stille), organosiloxanes (Hiyama), organozinc compounds (Negishi), Grignard reagents (Kumada-Corriu), alkynes (Sonogashira) or olefins (Heck) have found widespread popularity in synthetic chemistry. Recent efforts have provided highly active transition metal catalysts that allow one to replace aryl iodides, which are often not commercially available or relatively expensive, by less reactive aryl chlorides and bromides. We have developed multiple palladium, nickel and copper catalyzed C-C, C-N and C-S bond forming reactions and frequently rely on cross-coupling methods as part of our daily synthetic routine.

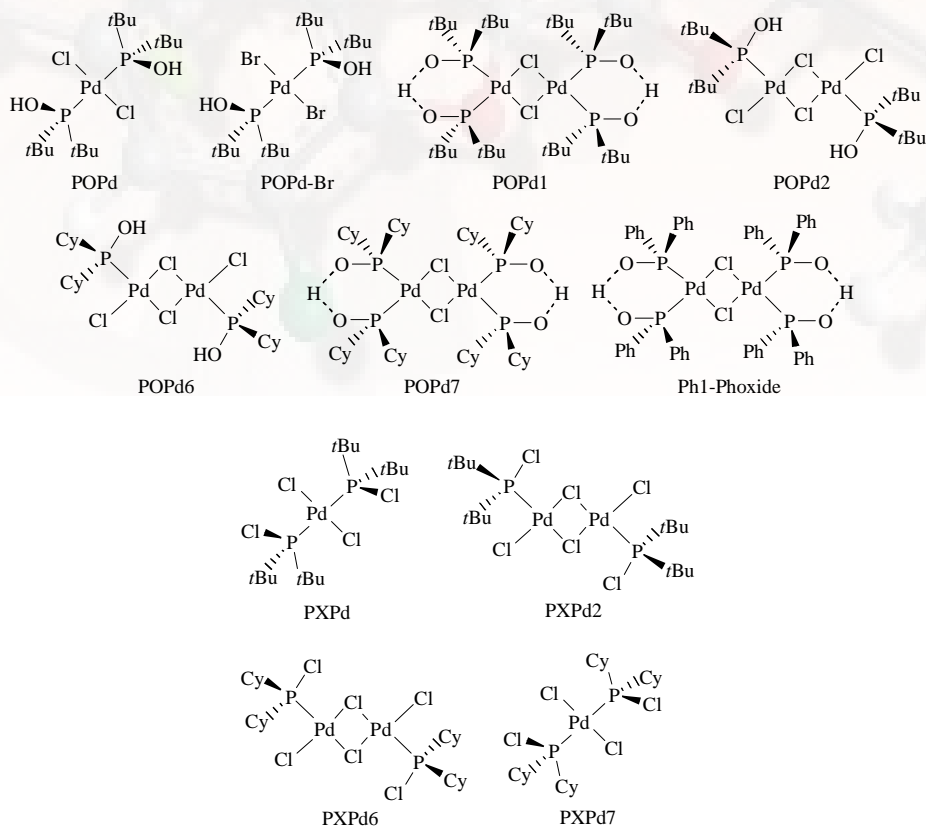
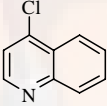
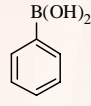
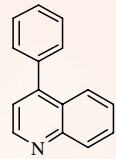
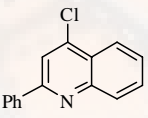
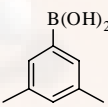
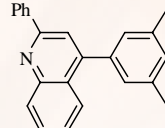
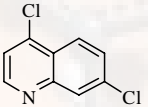
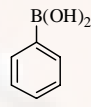
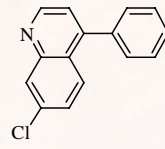
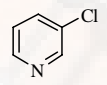
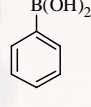
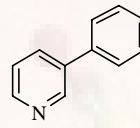
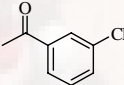
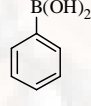
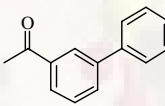

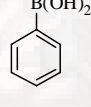
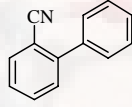

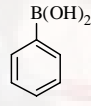
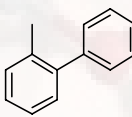
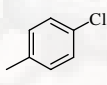
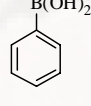
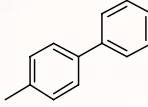
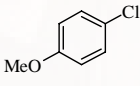
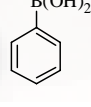
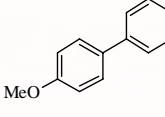
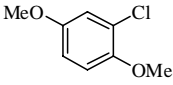
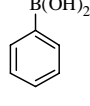
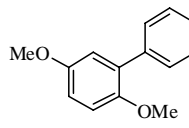


Figure 1. Structures of palladium-phosphinuous acids (top) and dialkylchlorophosphine-derived palladium catalysts (bottom).

We and others have reported the usefulness of highly active palladium-phosphinous acids including $[(t\text{-Bu})_2\text{P}(\text{OH})]_2\text{PdCl}_2$ (POPd), $[[t\text{-Bu})_2\text{P}(\text{OH})(t\text{-Bu})_2\text{PO}]]\text{PdCl}_2$ (POPd1) and $[(t\text{-Bu})_2\text{P}(\text{OH})\text{PdCl}_2]_2$ (POPd2) and dialkylchlorophosphine-derived palladium catalysts such as PXPd, Figure 1. General features of palladium-phosphinous acid catalysts include simple preparation from readily available phosphine oxides, $\text{RR}'\text{P}(\text{O})\text{H}$, and Pd complexes such as $\text{Pd}_2(\text{dba})_3$, $\text{Pd}(\text{cod})\text{Cl}_2$ or $\text{Pd}(\text{OAc})_2$, stability to air, and high catalytic activity in cross-coupling reactions. The catalysts can be stored at air for a long time without loss in activity and can be employed directly in *C-C*, *C-N*, and *C-S* coupling reactions. Moreover, palladium-phosphinous acid-catalyzed coupling reactions do not have to be performed in anhydrous solvents or under an inert atmosphere. The high catalytic activity of palladium-phosphinous acids in the presence of base can be attributed to (a) the presence of bulky phosphine ligands and (b) the formation of anionic Pd complexes that undergo accelerated oxidative addition to aryl halides including electron-rich chlorides. Some results of POPd-catalyzed Suzuki cross-coupling with aryl chlorides are summarized in Table 1.

Table 1. POPd-catalyzed Suzuki cross-coupling of aryl chlorides.

Entry	Aryl chloride	Boronic acid	Coupling product	Yield (%)
1				93
2				98
3				97
4				74
5				86

6				99
7				94
8				84
9				65
10				85
11				72
12				75
13				72
14				80
15				78

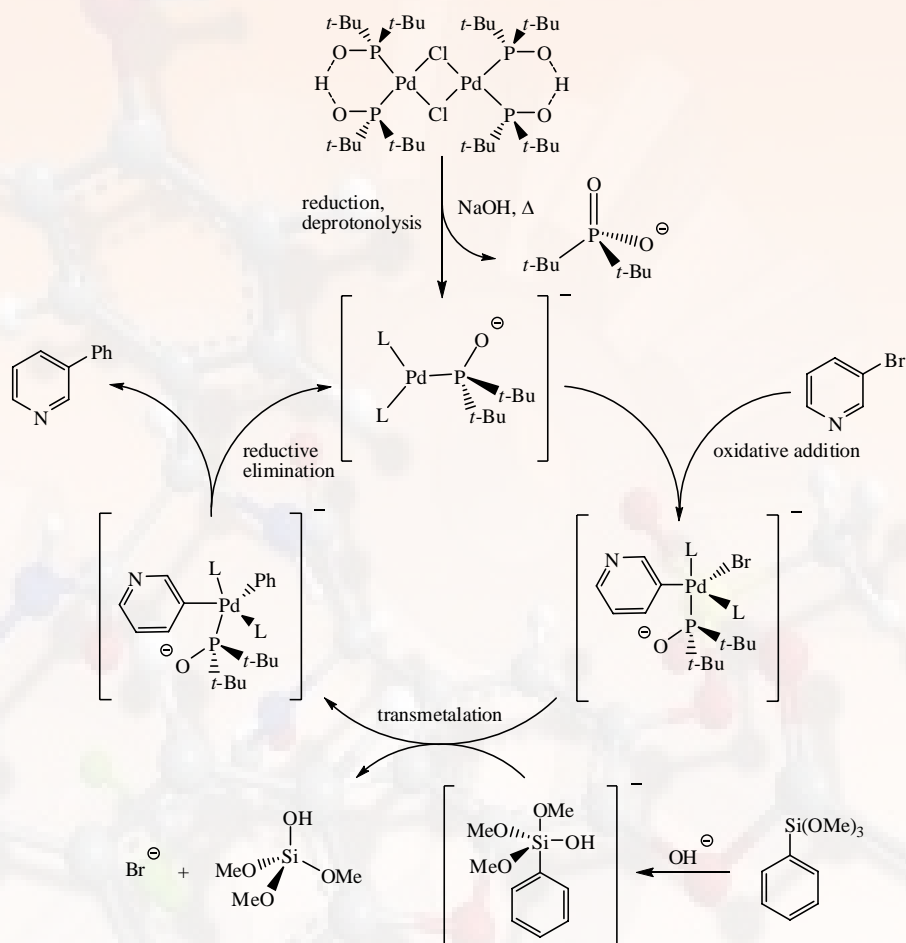
We have become increasingly interested in developing cross-coupling methods that proceed in pure water without the presence of commonly used additives such as surfactants or organic co-solvents. We obtained excellent results with palladium-phosphinous acid-catalyzed Stille, Hiyama and Sonogashira reactions. In general, good to high yields of coupling products can be obtained from a wide range of aryl halides while operation and catalyst recycling are simplified. Some results of POPd1-catalyzed Hiyama coupling and a proposed mechanism are shown in Table 2 and Scheme 1.

Table 2. POPd1-Cross-coupling of arylsiloxanes and aryl halides in water.

Ar1-X + Ar2-Si(OMe)3 >>[Pd(0), H2O] Ar1-Ar2

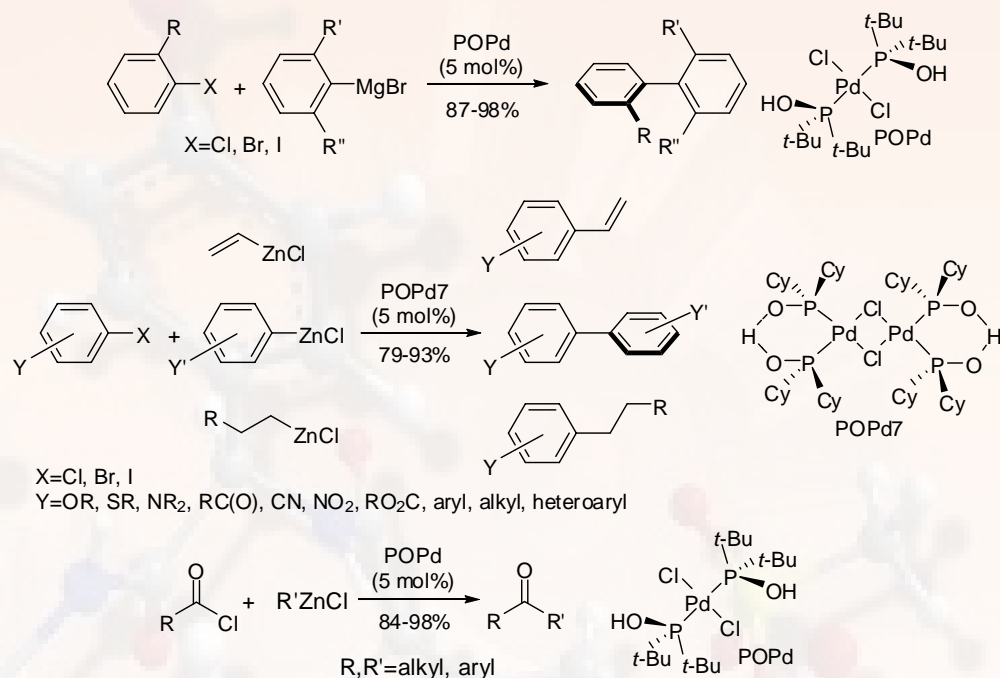
Entry	Aryl halide	Arylsiloxane	Product	Yield (%)
1				99
2				75
3				92
4				77
5				81
6				90
7				81
8				88
9				90
10				77

It is assumed that POPd1 undergoes reduction and deprotonolysis in the presence of a base, for example NaOH, to form a highly active anionic Pd(0) complex that readily undergoes oxidative addition to an aryl halide, Scheme 1. In addition, formation of a pentavalent silicate under basic aqueous conditions through nucleophilic attack of a hydroxide ion at the arylsiloxane increases the nucleophilicity of the aryl ring. Thus, sodium hydroxide fulfills two fundamental functions: activation of the catalyst for oxidative addition and activation of the arylsiloxane for the transmetalation step. The catalytic cycle is completed by reductive elimination which furnishes the desired biaryl and regenerates the palladium catalyst.



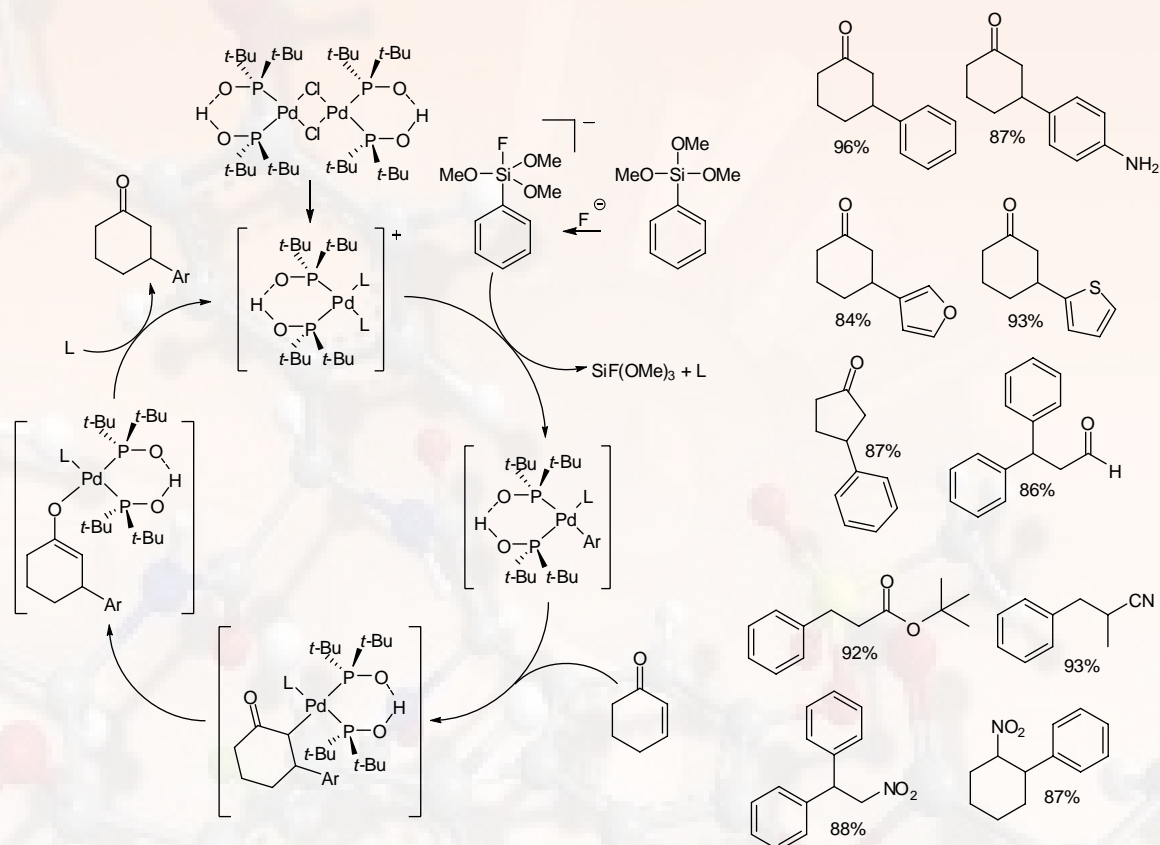
Scheme 1. Proposed catalytic cycle of the NaOH-promoted POPd1-catalyzed Hiyama cross-coupling reaction.

The coupling of aryl and acyl halides with aryl-, alkyl-, and vinylzinc reagents or Grignards has also been accomplished with selected palladium-phosphinous acids, Scheme 2.



Scheme 2. Scope of palladium-catalyzed couplings with organozinc and Grignard reagents.

We also successfully employed a palladium-phosphinous acid catalyst in microwave-assisted conjugate additions of arylsiloxanes to a wide range of α,β -unsaturated substrates in water. This reaction provides access to β -substituted ketones, aldehydes, esters, nitriles, and nitroalkanes which are obtained in high yields. Attractive features of the POPd1-catalyzed procedure are the broad application spectrum, tolerance of functional groups, short reaction times, and operational simplicity due to the stability of palladium-phosphinous acids to water and air. A proposed mechanism and some Michael addition products are given in Scheme 3.



Scheme 3. Proposed mechanism of the POPd1-catalyzed conjugate addition and selected products.

The remarkable versatility of palladium-phosphinuous acids has led us to the development of new synthetic methodologies. An example is the use of POPd as a reaction switch to control chemoselective nucleophilic arylation and single-step oxidative esterification of aldehydes in the presence of siloxanes. This convenient switching between two different reactions provides access to both secondary alcohols and esters using essentially the same starting material, reagent, additive, and solvent, Table 3. The POPd-catalyzed conversion of aldehydes to the corresponding methyl esters incorporates an oxidation and an esterification step into a single process under mild reaction conditions. While one-pot oxidative esterifications of aldehydes with hydrogen peroxide or oxone in alcoholic solution are known, few practical examples of transition metal-catalyzed processes can be found in the literature. Our method might become particularly useful for oxidation of aldehydes in multifunctional compounds when carboxylic acid intermediates need to be avoided or when sensitive electron-rich heteroatoms that do not tolerate commonly used oxidizing reagents are present. In the absence of POPd, we observed TBAF-promoted arylation of aldehydes towards secondary alcohols. This reaction affords high yields and shows superior functional group compatibility over Grignard additions.

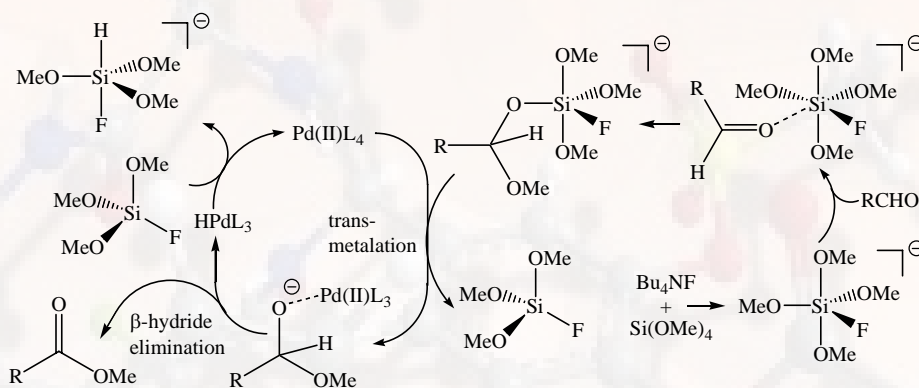
Table 3. TBAF-Promoted arylation and POPd-catalyzed oxidative esterification of aromatic aldehydes.

Entry	Aldehyde	1,2-Addition	Yield ^a (%)	Oxidative esterification	Yield ^a (%)
1			95		97
2			99		87
3			98		92
4			94		89
5			87		78
6			96		97
7			73		61
8			93		79
9			86		90
10			79		93
11			67		75 (77) ^a

^aOne gram scale.

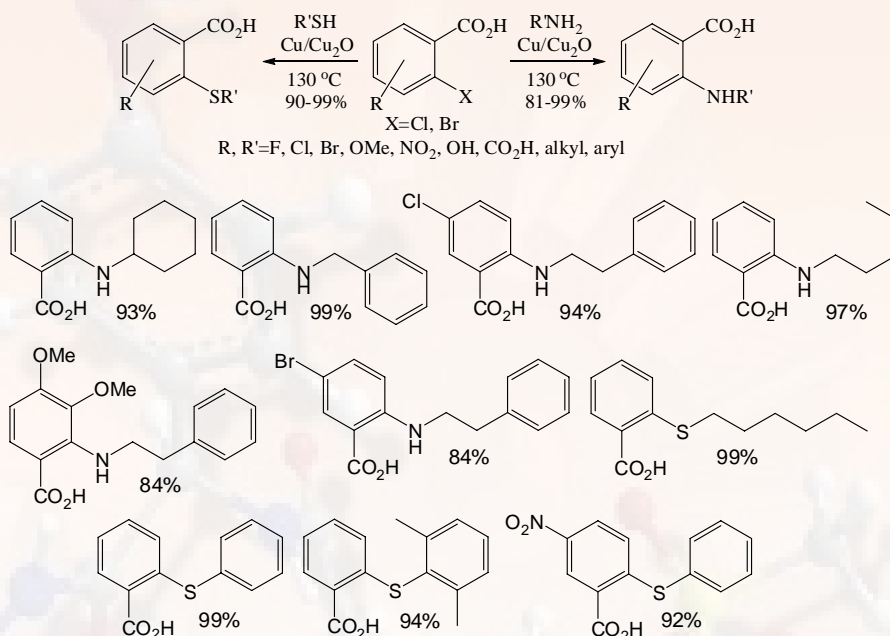
A proposed mechanism for the palladium-catalyzed one-pot esterification of aldehydes is shown in Scheme 4. POPd appears to be the catalytically active species and is regenerated at the end of the catalytic cycle. We have been able to recover POPd after

completion of the esterification of benzaldehyde and confirmed the structure by crystallographic analysis. Coordination of the aldehyde to the oxophilic pentavalent silicate generated *in situ* from TBAF and tetramethyl orthosilicate increases its electrophilicity and facilitates transfer of a methoxide group. Transmetalation from silicon to the palladium catalyst is then followed by β -hydride elimination and formation of the corresponding ester. The hydride might initially be bonded to the palladium catalyst but both proton and deuterium NMR studies with deuterated benzaldehyde showed that a siloxane functions as the hydride acceptor when acetonitrile is used as solvent. The siloxane thus fulfills three important functions: it generates a Lewis-acidic silicate that activates the aldehyde and it serves as both the methoxy group donor and the hydride acceptor.



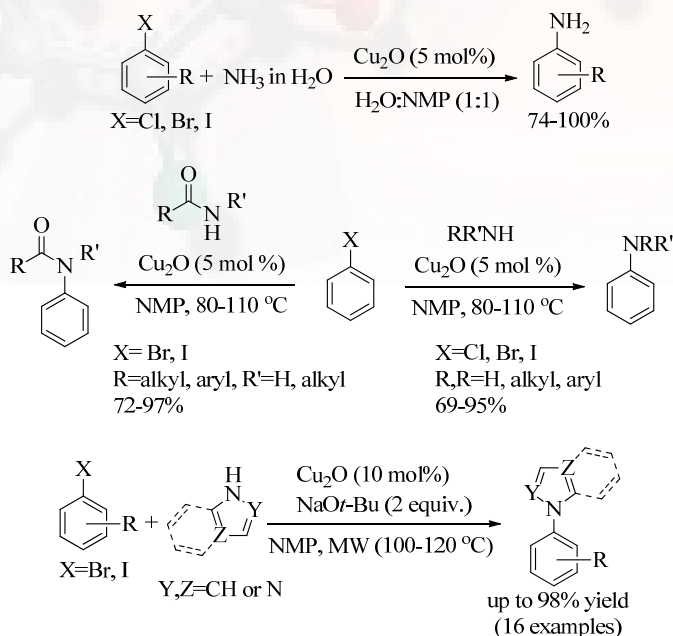
Scheme 4. Proposed Pd(II)-catalyzed oxidative esterification of aldehydes.

Our interest in transition metal catalysis is not limited to palladium complexes. We have developed a highly efficient Cu/Cu₂O-catalyzed C-N and C-S bond formation suitable to 2-halobenzoic acids and aliphatic and aromatic amines and thiols. This reaction tolerates a wide range of functional groups and provides a wide range of amines and sulfides in up to 99% yield. The remarkable regioselectivity, experimental simplicity, and the low cost of the catalytic system are attractive features of this procedure which may prove useful for the synthesis of pharmaceutically relevant anthranilic acids and benzoic acid-derived sulfides, Scheme 5.



Scheme 5. Copper-catalyzed C-N and C-S bond formation.

We have developed a Cu_2O -catalyzed amination of aryl halides with ammonia, amines and amides using *N*-methyl pyrrolidinone as solvent. The reaction also proceeds in aqueous solution and it eliminates the need for inert atmosphere, expensive catalysts and ligands, anhydrous solvents, and base or other additives, Scheme 6. This approach also allows coupling with heterocycles.



Scheme 6. Copper-catalyzed synthesis of anilines, anilides and *N*-substituted heterocycles.

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