C–C Coupling

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Catalysts for the Sonogashira Coupling—The Crownless Again Shall Be King

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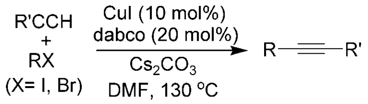
The Sonogashira reaction has emerged as the most widely used method for the synthesis of substituted alkynes. It is technically simple, efficient, high yielding, and tolerant towards a wide variety of functional groups:[1,2] properties that are typical of Pd-catalyzed cross-coupling reactions. Initially, the Sonogashira coupling involved palladium and copper complexes. However, recently, the repertoire of catalytically active metals in C(sp)–C(sp^2) coupling reactions has been extended significantly.

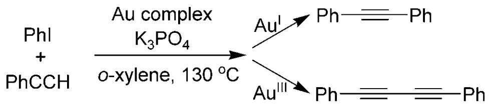
Traditionally, Pd or Pd/Cu salts have been used; however, the renaissance of copper in catalysis led to the development of efficient copper-only procedures in cross-coupling chemistry.[3] The Sonogashira coupling is remarkable in that it can be catalyzed by numerous metal complexes. Salts or nanoparticles of iron,[4] ruthenium,[5] cobalt,[6] nickel,[7] copper,[8] silver,[9] gold,[10] and indium[11] in combination with appropriate ligands are known to act as catalysts for C(sp)–C(sp^2) coupling. All of these reactions tend to be referred to as Sonogashira coupling, even though a more precise terminology may be appropriate.[12]

Copper catalysis is powerful in C–O, C–N, C–S, and some C–C bond-forming reactions.[3] Consequently, the copper-catalyzed Sonogashira reaction (or catalytic Stephens–Castro reaction) is the most potent of the Pd-free Sonogashira variants. Venkataraman and co-workers[13] reported efficient transformations of various aryl iodides with acetylenes in the presence of [Cu(phen)(PPh_3)Br] (phen = 1,10-phenanthroline). Copper nanoparticles prepared by the Reetz procedure were applied by Rothenberg and co-workers[14] and enabled quantitative conversion for all aryl iodides screened. Li et al. reported equally efficient reactions of aryl iodides and bromides with a simple Cu^I/dabco catalyst system (Scheme 1).[8] It is believed that the Cu-catalyzed coupling occurs through a Cu^I/Cu^{III} mechanistic pathway, as postulated by Miura and co-workers.[15]



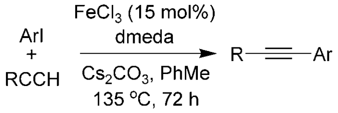
Scheme 1. Copper-catalyzed Sonogashira coupling. dabco = 1,4-diazabicyclo[2.2.2]octane, DMF = *N*,*N*-dimethylformamide.

Gold[16] is a fairly recent addition from the Corma research group to the arsenal of metals useful for C(sp)–C(sp^2) bond-forming reactions.[10] As shown by X-ray photoelectron spectroscopy, the deposition of gold on a CeO_2 support leads to a mixture of Au, Au^I, and Au^{III} species. This mixture catalyzes the cross-coupling of iodobenzene with phenylacetylene, albeit in modest yield. The next question was, which gold species, Au^0, Au^I, or Au^{III}, was the catalytically active species. Attempted cross-coupling reactions of nanoparticulate Au with the same coupling partners gave minute amounts of the cross-coupling product. Under the influence of Au^{III} salts, small amounts of the acetylene homocoupling product were formed. However, in the presence of the Au^I complex (20 mol %), the desired tolane was generated in 35–97 % yield (Scheme 2). It was thus concluded that the Au^I species is an active catalyst in Sonogashira-type cross-coupling reactions, whereas Au^{III} and colloidal Au are not.



Scheme 2. Gold-catalyzed Sonogashira coupling.

Another exciting variation of the Sonogashira coupling was developed very recently by Bolm and co-workers (Scheme 3).[4] The optimized catalyst system consists of $FeCl_3$/dmeda (*N*,*N'*-dimethylethylenediamine) and the base Cs_2CO_3 in toluene solvent. Various aryl iodides underwent Sonogashira coupling in good to excellent yields. Despite the use of a high-valent metal salt, a Hay-type homocoupling of



Scheme 3. Iron-catalyzed Sonogashira coupling.

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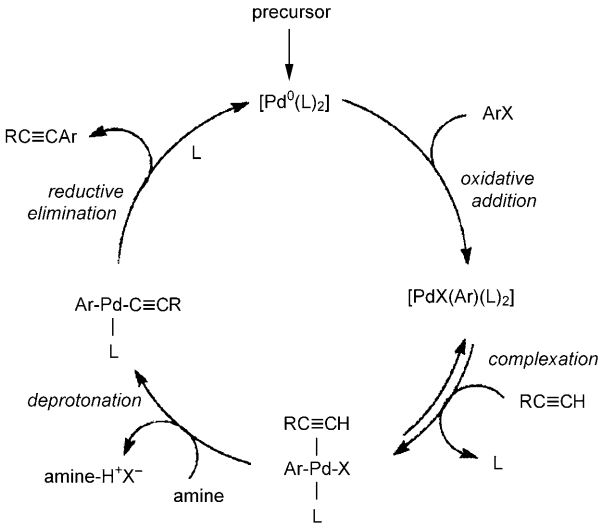
the aryl acetylenes was not observed. Interestingly, under the optimized conditions for $FeCl_3$-catalyzed O-arylation,[17] the Sonogashira product was not formed, whereas the conditions for N- and S-arylation[18,19] gave at least some product. The simplicity of the ligand in combination with the cheap and nontoxic iron salt offers enormous potential. Following the explosive growth of gold catalysis, iron seems to be the new rising star in catalytic chemistry.[20,21] It is an extraordinary development to have such a common metal performing tasks that were previously considered to be the domain of noble metals.



Scheme 4. Proposed mechanism for the Cu-free Sonogashira coupling.[22]

Several of the catalytically active metal centers reported to be active in Sonogashira-type reactions appear to fit into the established general mechanistic scheme for Pd-mediated cross-coupling reactions. Displayed in Scheme 4 is the copper-free mechanism reported by Jutand and co-workers.[22] The catalytic species simplifies to [Pd(L)] or $[Pd^0(L)(X)]^-$ for very bulky phosphine ligands L.[23] Accordingly, a low-valent metal undergoes oxidative addition by insertion into a $C(sp^2)-X$ bond. Coordination of the acetylene is then followed by formation of the acetylide, reductive elimination of the tolane product, and regeneration of the low-valent metal species. There are good arguments to support the belief that the reaction of the low-valent Pd complex and the aryl halide is the turnover-limiting step, which is normally categorized under the umbrella term oxidative addition.[24] Barrios-Landeros and Hartwig studied the oxidative addition of a bisphosphine–Pd^0 complex with various aryl halides ArX (X = Cl, Br, I). In their study, the rearrangement of the ligand sphere appeared to be the decisive step for aryl bromides and iodides, whereas the actual insertion of Pd^0 into the C–X bond was rate limiting in coupling reactions with aryl chlorides.[25] Plenio and co-workers determined numerous activation parameters for Pd/Cu-catalyzed Sonogashira coupling reactions with Ar–X (X = Cl, Br, I). The correlation of the HOMO energy of the various substituted aryl halides with the corresponding activation enthalpy $\Delta H^{\neq}$ revealed that the aryl halide is involved in the rate-limiting step. Extensive Hammett studies gave the best correlations for σ^{-}_{para} Hammett parameters and demonstrated the stabilization of a negatively charged transition state for the coupling reactions of all aryl halides.[26]

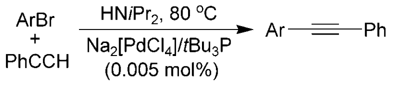
Amines, which are often used as a base and/or solvent in such reactions, were found by Jutand and co-workers to play multiple roles in copper-free Sonogashira reactions.[22] Depending on their coordinating ability, amines can interfere with the oxidative addition by an accelerating effect due to the formation of the more reactive [Pd^0L(amine)] complexes (not shown in Scheme 4). On the other hand, they can also substitute a single phosphine ligand in *trans*-$[PdI(Ph)(PPh_3)_2]$. Depending on the relative rates of the two substitution reactions (by the amine and by the alkyne), two different mechanisms can be operative.

The Pd-based catalytic cycle depicted in Scheme 4 appears reasonable for Ni and Cu complexes. For other metals, however, the situation is less clear. It was shown by Corma and co-workers that Au^I is active in the Sonogashira reaction.[10] From the point of view of the coordination chemistry of gold, an Au^I/Au^{III} pathway can not be excluded. On the other hand, the use of Au^{III} salts results in homocoupling of the acetylene to give the corresponding diphenylbutadiyne. The reduced gold species thus produced is not able to enter the catalytic cycle. With respect to Ag, it is hard to imagine silver shuttling between the Ag^I and Ag^{III} states, as Ag^{III} is a strong oxidant. Nonetheless, one should be cautious about excluding certain oxidation states. The debate about a Pd^{II}/Pd^{IV} cycle is not finished, even though a Pd^0/Pd^{II} redox pair now appears to be commonly accepted for such coupling reactions.[27]

A different scenario can be envisaged for the $FeCl_3$-catalyzed reactions reported by Bolm and co-workers. As the formation of the homocoupling product was not observed, a reductive pathway from Fe^{III} appears unlikely. An oxidative route is equally hard to imagine, as any oxidation state higher than Fe^{III} requires special stabilization. However, another scenario is conceivable, as it is known that Lewis acid additives can promote Sonogashira reactions. The first useful protocol for the Sonogashira coupling of aryl chlorides was reported by Eberhardt et al.[28] and relies on the addition of up to 100 mol % of $ZnCl_2$ to a Pd complex. In 2005, it was reported that $InCl_3$ is also able to catalyze Sonogashira-type coupling reactions.[11] $FeCl_3$, $ZnCl_2$, and $InCl_3$ are strong Lewis acids.

Nonetheless, behind all of these results lingers the nagging question as to whether the Sonogashira activity might have resulted from minute amounts of palladium impurities in certain reagents used for the cross-coupling reactions. The results described in initial reports of a transition-metal-free Sonogashira reaction[29,30] may need to be revised, as it was discovered that ultralow quantities of palladium in the 50 ppb range, the quantity of palladium contained in Na_2CO_3, were able to promote Suzuki cross-coupling reactions under microwave conditions.[31] With these potential obstacles in mind, Wang and Li checked the extent of palladium contamination of the reagents and solvent used in the AgI-catalyzed Sonogashira reaction by inductively coupled plasma mass spectrometry (ICPMS). Specifically, the Pd content in DMF (0.32 ppb), K_2CO_3 (9.15 ppb), PPh_3 (5.32 ppb), and AgI (2.64 ppb) was much lower than that found in Na_2CO_3. It was concluded that palladium impurities were not present in sufficient concentrations to effect the cross-coupling under thermal conditions.[9] Jin-Heng Li et al. also checked for residual Pd contamination in their copper-only transformations. Although CuI of 98 % purity is known to contain 6×10^{-5} mol Pd mmol^{-1}, the use of CuI of 99.999 % purity gave identical cross-coupling results.[8]

When traditional Pd- or Pd/Cu-based cross-coupling chemistry is compared with that of other metals, namely, copper and iron, the differences are striking. One example from the Pd camp may illustrate the extremely high efficiency of Sonogashira reactions with aryl bromides (Scheme 5): Only 0.005 mol % of the Pd–phosphine complex in HN*i*Pr_2 as the solvent enables the quantitative synthesis of a wide range of Sonogashira coupling products with turnover frequencies (TOFs) of 3000–10 000 h^{-1} at 80 °C.[32] This is clearly out of range for the other metals. Cu- and Fe-based systems currently require at least 10 mol % of the catalyst complex and reaction temperatures above 120 °C; moreover, large amounts of CsI waste are produced.[33] On the other hand, the simplicity, cheapness, and low toxicity of the metal sources ($FeCl_3$, CuI) and of the ligands provide a strong contrast to the oxidation-prone phosphine ligands preferred in Pd-mediated coupling chemistry.



Scheme 5. Palladium-catalyzed Sonogashira coupling.

It appears from the recent literature on applications of the Sonogashira coupling in organic synthesis that the community is hesitant to apply the new highly efficient Pd catalysts that have been developed. Still, a very significant proportion of Sonogashira coupling reactions are carried out with the classic catalysts ($[Pd(Cl)_2(PPh_3)_2]$ or $[Pd(PPh_3)_4]$) and aryl iodide substrates. Although a catalyst loading in the 1–5 mol % range may be required, with typical yields of around 75 %, the transformation relies on an established protocol. Copper-only procedures with aryl iodide substrates are already competitive with such Pd-catalyzed reactions, and iron-based procedures may soon be. From a practical point of view, the simplicity of the copper-only and iron catalytic systems is a strong argument in favor of their application in organic synthesis, whereas Pd-based Sonogashira catalysts are characterized by their outstanding efficiency.

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[33] To be fair: It took more than 30 years of research on Pd catalysts to reach the present levels of efficiency. With Cu and Fe, there is still plenty of room for improvement. Time will tell if the ligands will remain as simple as they are now.