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Beyond the traditional roles of Ag in catalysis: the transmetalating ability of organosilver(I) species in Pd-catalysed reactions

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Silver salts are one of the most widely used additives in Pd-catalysed transformations. Apart from acting as halide scavenger and/or external oxidant, over the past decade it has been revealed that silver salts can play other roles such as C–H activation promoter or decarboxylating agent, generating organosilver(I) species. These nucleophiles can promote innovative transformations by reacting with Pd^{II} intermediates through a transmetalation step. This review article covers different Pd-catalysed C–C bond-forming reactions where silver complexes have been proposed to act as nucleophilic coupling partners. We will also provide relevant mechanistic features associated to these transformations.

1. Introduction

Without any doubt, silver salts are one of the most widely used additives in transition metal catalysis.¹ In most cases, it is proposed that these external additives act merely as halide scavengers² or oxidizing reagents.³ However, in the last few years, it has been unveiled that silver species can play other roles, generating efficient transmetalating agents. This has encouraged to explore this ability in one of the cornerstones in organic chemistry, Pd-catalysed C–C bond-forming reactions.⁴

The cooperation of two metal centres is well known in biological systems. Enzymes involving multiple metal centres represent an exceptional example of how the cooperativity of different metals can perform challenging transformations.⁵ However, it was not until the last decade when bimetallic systems, involving a transmetalation step that connects both metal centres, emerged as an attractive tool for the synthesis of a wide variety of C–C bonds.⁶

Typically, these reactions are performed between palladium and coinage metals.⁷ In this context, Pd/Ag bimetallic couples have demonstrated their extraordinary potential due to the efficiency of organosilver(I) intermediates as nucleophilic coupling partners. Although different catalytic cycles can be proposed depending on the nature of the starting materials, in Scheme 1 it is shown a general mechanistic picture for a Pd/Ag bimetallic process. The organosilver(I) species, generated through different routes described below, acts as a transmetalating agent to an organopalladium(II) intermediate. Subsequent reductive elimination releases the coupling product and the Pd⁰ catalyst.

Scheme 1: Simplified mechanism for synergistic Pd/Ag bimetallic processes.

The design and development of a productive Pd/Ag bimetallic system need to tackle different issues: (i) all the elementary steps involved in these transformations should be kinetically compatible; (ii) ligands, catalysts and reagents should not interfere with each other in order to avoid by-product formation and/or catalyst deactivation; and (iii) the transmetalation step should be faster than the decomposition of the resulting organosilver(I) complex.

This review covers the recent advances on the synergistic cooperation between Pd/Ag bimetallic couples for promoting the formation of C–C bonds in which organosilver(I) species act as nucleophilic shuttles (Scheme 2). We have classified the reactions into three categories depending of the role of the silver: 1) synthesis of perfluorinated derivatives based on Pd/Ag systems; 2) decarboxylative couplings; and 3) C–H functionalization reactions. Despite the importance of the Sonogashira cross-coupling reactions in this context, this specific transformation will not be

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discussed since it has been comprehensively covered over the past years.⁸ We will also gather some fundamental transmetalation studies, in order to point out the lack of mechanistic insights on this key step. Finally, we will give some hint on how we envision the field could move forward.

Scheme 2: Timeline representing the highlights for synergistic cooperation between Pd/Ag couples in the last decade.

2. Synthesis of organofluorine derivatives based on palladium and silver systems.

Perfluoroalkyl groups, CF₂H and CF₃, are prevalent motifs in pharmaceuticals, agrochemicals and materials due to its unique capability to change physical, chemical and biological properties of organic molecules.⁹ Thus, over the past years, the scientific community has directed its efforts towards the development of rapid and efficient strategies to install these privileged functional groups onto organic scaffolds.¹⁰ In this context, well-defined organometallic silver derivatives have demonstrated their great ability as transmetalating reagents in Pd-catalysed cross-coupling reactions. In the following examples of bimetallic processes, the silver derivatives only act as transmetalating shuttle.

2.1. Palladium-catalysed silver-catalysed/mediated difluoromethylation reactions

In 2014, Shen et al. reported for the first time the combination of aryl bromides or iodides and (difluoromethyl)trimethylsilane for the synthesis of difluoromethylated arenes using catalytic amounts of palladium and silver.¹¹ This methodology turned to be widely compatible with different functional groups and it was applied in the late-stage difluoromethylation of target molecules in medicinal chemistry such as nature hormone estrone or antioxidant vitamin E. Indeed, the authors were able to expand the scope of the organic electrophile to chloride and triflate using a combination of Buchwald's precatalyst and XPhos as ligand (Scheme 3).¹² This new procedure can be applied in the introduction of the difluoromethyl group in different agrochemical and drugs compounds that present an aryl chloride moiety.

Scheme 3: Difluoromethylation of aryl halides developed by Shen.

The authors pointed out that the development of the whole catalytic procedure was based on the isolation of the Pd^{II} and Ag^I intermediates, using them to test the feasibility of each elementary step in the catalytic cycle (Scheme 4). The experimental data suggest that the key step in this process is the transmetalation that connects the palladium and silver catalytic cycles.

Scheme 4: Proposed mechanism for the difluoromethylation of aryl halides.

In 2015, the same group extended this methodology to palladium-catalysed silver-mediated difluoromethylation of di-, tri-, or tetra-substituted vinyl bromides, triflates, tosylates and nonaflates.¹³ In all these examples, stoichiometric amounts of SIPrAgCF₂H were necessary to hamper the activation of the allylic C–F bond in basic conditions (Scheme 5). It should be mentioned that the authors observed the retention of the olefin geometry, when using *cis*-aryl-substituted alkenyl bromides as starting materials indicating that the reaction does not go through radical intermediates.

Scheme 5: Difluoromethylation of alkenyl bromides.

Interestingly, the difluoromethylation of vinyl triflates, nonaflates and tosylates has to be carried out using two equivalents of a salt such as potassium bromide to generate more stable [(dppe)Pd(alkenyl)(Br)] species that facilitates the transmetalation, the crucial step that interconnects both metals (Scheme 6).

Scheme 6: Difluoromethylation of alkenyl triflates, nonaflates and tosylates.

Aiming at extending the scope of this technology beyond other interesting substrates, the same group described in 2017 the palladium-catalysed silver-mediated difluoromethylation of heteroaryl halides (Scheme 7).¹⁴ The fine tuning of the reaction conditions respect to the first described methodology (Scheme 3) was again designed based on the isolation of the key intermediates and studying independently the elementary steps in both cycles. This protocol is compatible with numerous heteroaryl moieties such as pyridine, quinoline, thiophene, furan or indole, when using heteroaryl bromides. In the case of other halides such as iodide or chloride the scope was more limited and only activated chlorides (*ortho*-position to the heteroatom) gave the corresponding difluoromethylated molecules in good yields.

Scheme 7: General schematic for the difluoromethylation of heteroaryl halides.

2.2. Palladium-catalysed silver-mediated trifluoromethylation reactions

Pd^{0/II}-catalysed aryl trifluoromethylation processes remain a largely unresolved challenge for academic and industrial chemists.¹⁵ It is widely accepted that the reductive elimination step is the only problem associated with these processes. However, in 2006 Grushin and co-workers unravelled the usually overlooked challenge related to the transmetalation step, using Xantphos as ligand: mismatched transmetalations between aryl-palladium(II) complexes and/or ligand displacement by commercially available CF₃ nucleophiles (Scheme 8).^{15a,d} In order to overcome these limitations, the Pérez-Temprano group has recently shown that well-defined trifluoromethylsilver(I) complexes including a unique silver(I) ate-type complex, (Cs)[Ag(CF₃)₂], outperform commercially available nucleophilic trifluoromethyl sources as CF₃ shuttles to palladium(II) systems.^{15j} The authors described the rational design of an one-pot formation of PhCF₃ using PhI as starting material, under stoichiometric and catalytic conditions, based on the fundamental knowledge acquired using a Pd^{II} model system and the further translation to a productive one using Xantphos as ligand on the palladium (see Section 5.2). This work is a proof-of-concept of the crucial role of the nucleophile in the success or failure of the coupling process.

Scheme 8: a) Unproductive pathways in Pd^{0/II}-catalysed trifluoromethylation reactions; b) Use of "AgCF₃" complexes in a productive system in comparison with commercially available sources and development of a stoichiometric and catalytic protocol.

3. Pd/Ag-catalysed Decarboxylative coupling reactions

One of the most interesting reactivity patterns based on the cooperative behaviour of Pd/Ag bimetallic systems is based on decarboxylative coupling reactions. They enable the use of inexpensive and commercially available carboxylic acid derivatives as raw materials. In these systems, the silver species can play multiple roles: (i) promoter of the CO₂ extrusion from the carboxylic acid derivative, (ii) shuttle of the nucleophilic moiety to the palladium metal centre and, in some cases, (iii) also acts as external oxidant.

In this section, we have classified the different selected processes in two main categories: bimetallic Pd/Ag cross-coupling reactions and bimetallic Pd/Ag oxidative coupling reactions.

3.1 Bimetallic Pd/Ag cross-coupling reactions

In 2006, Gooßen proposed a new approach to form C–C bonds from stable, cheap and abundant pre-nucleophiles: benzoic acids.¹⁶ This so-called decarboxylative cross-coupling was inspired by enzymatic decarboxylation processes performed by living organisms. Originally, this methodology was developed using Pd/Cu bimetallic couples to promote the reaction between *ortho*-nitro-substituted benzoic acids and aryl bromides (Scheme 9a). One year later, Gooßen mentioned, for the first time, the use of silver salts as decarboxylating agents in this type of reactions, however

they observed less than 50% yield of the desired product (Scheme 9b).¹⁷ Concurrently, Wagner et al. described the use of super stoichiometric amounts of silver salts in Pd-catalysed processes to decarboxylate both electro-deficient and electro-rich benzoic acids.¹⁸ Interestingly, in 2010, Gooßen and co-workers described the formation of biaryls using aryl triflates as electrophiles and carboxylate salts as pre-nucleophiles, in the presence, for the first time, of catalytic amounts of palladium and silver.¹⁹ As it is shown in Scheme 9b, this work proceeded under milder conditions, more than 40 °C below, compared to the analogous copper version previously reported.

Scheme 9: a) First Pd/Cu-catalysed decarboxylative C_{sp}²-C_{sp}² coupling reaction; b) Pd/Ag bimetallic systems in decarboxylative C_{sp}²-C_{sp}² coupling reactions.

The proposed mechanism involves a transmetalation step from the arylsilver(I) species, generated in situ through the CO₂ extrusion by silver carbonate, to a [L_nPdArX] formed by oxidative addition of ArX to [Pd⁰L_n] (Scheme 10). The resulting biaryl palladium(II) complex undergoes reductive elimination, affording the cross-coupling product along with the Pd⁰ catalyst. In view of the complex mechanistic picture, Gooßen and co-workers emphasized the necessity of a perfect match between all the elementary steps involved in both catalytic cycles.

Scheme 10: Proposed mechanism for the palladium/silver-catalysed decarboxylative synthesis of biaryls.

More recently, Wu et al. disclosed a methodology to create Csp³–Csp² bonds between 2-picolinic acid derivatives and benzyl bromides highlighting the potential of Ag₂O as decarboxylative reagent (Scheme 11).²⁰ The coupling product is involved in a further transformation that allows to access 2-substituted double-benzylated pyridines.

Scheme 11: Palladium-catalysed silver-mediated decarboxylative synthesis in the one-pot double benzylation of 2-substituted pyridine.

3.2 Bimetallic Pd/Ag oxidative coupling reactions

Oxidative coupling reactions, which involve the reaction of two nucleophilic partners under oxidizing conditions, have become a greener alternative to traditional cross-coupling reactions.²¹ They offer multiple advantages such as the employment of more readily available starting materials and the minimization of by-product formation. We selected three types of transformations depending on the nature of coupling partner: alkenes, arenes or other carboxylic acid derivatives.

3.2.1 Palladium-catalysed silver-mediated decarboxylative Heck-type reaction

In 2002, Myers et al. disclosed the first example of Pd-catalysed decarboxylative Heck-type reactions between *ortho*-substituted benzoic acids and alkenes such as styrene, acrylates or cyclohexanone (Scheme 12a).²² In this seminal work, the authors proposed the necessity of the presence of silver salts due to its role as external oxidant. In contrast to the limited substrate scope for alkenes, electron rich and electron-withdrawing groups can decorate the *ortho*-substituted benzoic acid derivatives employed as starting materials. Additional mechanistic studies showed the capability of palladium species to promote the decarboxylation of electron-rich benzoic acids.²³ However, as Larrosa and Goossen pointed out, it is not possible to rule out the participation of silver in the decarboxylative event for electron-poor benzoic acids.²⁴ Indeed, in 2016, an interesting report by Jana group described a mechanistic divergence depending on the nature of the corresponding benzoic acid (Scheme 12b).²⁵ When using electron-poor scaffolds, the authors did not observe product formation in the silver-free system, providing a strong evidence of the participation of the silver salts not only as external oxidants but also as mediator of the decarboxylative process.

Scheme 12: a) Pd-catalysed decarboxylative Heck-type reaction of alkenes and benzoic acids; b) Mechanistic divergence depending on the nature of benzoic acid in Pd-catalysed decarboxylative Heck-type reaction.

The current mechanistic picture proposes the involvement of the silver salt in the decarboxylation process to afford the organosilver intermediate that participates in the transmetalation step to a [L₂Pd^{II}X₂] intermediate. The formed arylpalladium complex undergoes a migratory insertion followed by β-hydride elimination, releasing the desired product (Scheme 13). The [L₂Pd^{II}HX] intermediate undergoes a reductive elimination, regenerating the palladium(0) which is re-oxidised by silver. In this case, not only the silver salt plays a role as an external oxidant but also as decarboxylating agent and nucleophilic coupling partner.

Scheme 13: Proposed mechanism for the palladium-catalysed silver-mediated decarboxylative Heck-type reaction.

3.2.2 Pd-catalysed C–H activation and silver-promoted decarboxylation in the C–COOH/C–H coupling

In 2009, Glorius et al. published the first intramolecular example of the oxidative coupling between C–COOH and C–H moieties in which organosilver nucleophile was proposed as transmetalating agent after the decarboxylative event (Scheme 14a).²⁶ Although an analogous intermolecular version of this transformation was previously described by Crabtree, using microwave irradiation, the potential role of the silver was not explicitly mentioned.²⁷ Larrosa subsequently described the intermolecular synthesis of C–3 arylated indoles via a C–H activation-decarboxylation process.²⁸ While the silver salt mediates

the decarboxylation process, the palladium catalyst performs the C–H activation step to afford the corresponding Pd^{II} intermediate involved in the transmetalation step with the arylsilver(I) species (Scheme 14b). As in the previous shown examples, subsequent reductive elimination releases the organic product.

Scheme 14: a) Pd-catalysed intramolecular decarboxylative C–H arylation of 2-phenoxybenzoic acids; b) Direct C–3 arylation of indoles by C–COOH/C–H coupling.

Since these initial studies, different bimetallic Pd/Ag oxidative cross-couplings have been reported using indoles, benzoxazoles, thiazoles or perfluoroarenes as starting materials (Scheme 15).²⁹ When using perfluoroarenes, experimental studies proposed that the rate determining step is the electrophilic C–H palladation, in contrast with previous examples where the decarboxylation was assigned as the most energetically-demanding step.³⁰ It should be mentioned that the role of the silver in the C–H activation event cannot be discarded as we will discuss later.

Scheme 15: Scope of C–H moieties compatible with C–COOH/C–H coupling.

3.2.3 Palladium-catalysed silver-mediated decarboxylation reaction in the C–COOH/C–COOH coupling

In 2010, Larrosa and co-workers described an elegant alternative to C–COOH/C–H couplings based on the use of two

carboxylic acid derivatives as pre-nucleophiles, which are decarboxylated by the silver salt and, then, coupled by the palladium catalyst after two consecutive transmetalations.³¹ The authors could access symmetric biaryls in good to excellent yields using aromatic acids bearing an *ortho* electron-withdrawing substituent or a α heteroatom (Scheme 16). Mechanistically, the authors found that the nature of the group in *ortho* can affect the product formation. They proposed that this is due to the competition between the transmetalation step and the undesired protodemetalation of the organosilver(I) species. This points out the importance of the efficiency of the group transfer between Pd and Ag metals for the outcome of the reaction.

Scheme 16: General schematic for the Pd-catalysed decarboxylative homocoupling of aromatic carboxylic acids.

In this vein, Deng et al. introduced and Su et al. developed the Pd/Ag oxidative cross-coupling of two different carboxylic acids (Scheme 17).³² In this asymmetric version, silver salts should act as decarboxylating promoter, transmetalating agent and oxidant, and palladium catalyses the coupling of both nucleophiles. This represents a remarkable platform to couple two pre-nucleophiles with different electronic properties from cheap and not activated functionalities.

Scheme 17: General schematic for the Pd-catalysed decarboxylative heterocoupling between aryl carboxylic acids.

As it is shown in Scheme 18, the palladium catalyst is a mere vehicle for the coupling of the two decarboxylated moieties. Interestingly, all the processes must be kinetically compatible since homocoupling and/or protodecarboxylative product are not the main observed products.

Scheme 18: Proposed mechanism for the Pd-catalysed decarboxylative heterocoupling between aryl carboxylic acids.

3.3 Advances in the silver-promoted decarboxylation step

Due to the well-established knowledge on the palladium cycle, we want to provide a perspective on the known information of the behaviour of the silver in the decarboxylation event that would enable a rational improvement of these systems.

The ability of silver salt to promote decarboxylation processes was disclosed in the 70s by Chodowska-Palicka and Nisson but limited to electron-poor moieties (Scheme 19).³³

Scheme 19: First example of the silver-protodecarboxylation reaction.

In 2007, Wagner and co-workers provided some hints of the potential of silver salts to play a role in the decarboxylation of electron-rich carboxylic acids during the synthesis of biaryls via decarboxylative Pd-catalysed cross-coupling reactions.¹⁸ However, it was not until 2009, when Larrosa demonstrated that silver salts can catalysed not only the activation of C-COOH for electron-poor but also electron-rich substituents in the benzoic acids by studying the protodecarboxylation reaction.³⁴ In addition, they reported the lowest temperature for this transformation till date.

In this context, Gooßen provided a comprehensive study on the performance of different silver and copper sources in this reaction (Scheme 20).³⁵ Interestingly, the silver-catalysed protodecarboxylation requires lower reaction temperatures and shorter reaction times that similar copper systems. This study showed that the use of bidentate nitrogen ligands does not

improve the performance of the silver(I) species in contrast to the copper system.

Scheme 20: Comparative study of Cu- and Ag-catalysed protodecarboxylation of carboxylic acids.

Initially, all the methodologies were limited to the use of *ortho*-substituted benzoic acids, being unclear its crucial influence during the CO₂ extrusion step. In this regard, in 2011, Su and Lin reported a detailed computational study on this “*ortho*-effect” where they proposed that it favours the reactivity of the starting material due to the inherent steric repulsions with the carboxylic acid moiety.³⁶ They also observed a weak stabilization of the transition state, especially when using NO₂ groups, due to the coordination to the silver metal centre (Scheme 21). Subsequent computational and experimental study by Larrosa and Campanera showed that the decarboxylative event is not only affected by the steric destabilization of the organic substrate but also by an electronic contribution.³⁷ They highlighted an extra stabilization by the electron-withdrawing *ortho*-substituent during the decarboxylation process when a negative charge is generated on the ipso carbon. Moreover, they confirm the importance of the interaction of certain group, such as NO₂, with the metal centre during the decarboxylation that contributes to a larger decrease in the energetic barriers (Scheme 21).

Ortho effect studies

Scheme 21: Comparative pictures of the insights into the *ortho*-substituent effect on the Ag-catalysed decarboxylation of benzoic acids.

Recently, Hoover et al. has reported an elegant predictive model for silver-mediated decarboxylations using isolable and well-defined silver benzoates (Scheme 22).³⁸ On the one hand, they confirmed that *N,N* chelating ligands do not have a relevant role in

the decarboxylative reactions, as Gooßen had proposed in his previous work. On the other hand, they found a strong correlation between Swain-Lupton-Hammett field effect parameter (F) and the reaction rate. This dependence allows an easy prediction of the reaction outcome, opening the door for the rational design of silver-decarboxylative cross-coupling reactions and expand the scope to non-*ortho*-substituted aromatic carboxylic acid derivatives.

Scheme 22: Protodecarboxylation reaction of silver benzoate complex uses for the predictive model.

4. Pd-catalysed Ag-mediated C–H coupling reactions

In the past few years, different research groups have demonstrated the crucial role of silver species in the C–H activation step in Pd-catalysed reactions.³⁹ As shown in the previous sections, the resulting arylsilver(I) intermediate transmetalates efficiently its aryl moiety to a palladium intermediate in which the reductive elimination takes place leading to the target molecule.

In 2016, a pioneering work by Larrosa et al. revealed the efficient C(sp²)–H activation of electron-deficient arenes, by an in situ generated phosphine-ligated silver species [(PPh₃)Ag(OCOAd)], in the Pd-catalysed arylation of Cr(CO)₃-complexed fluorobenzene (Scheme 23).⁴⁰ Mechanistic studies including H/D exchange, KIE and kinetic studies suggested that the rate-determining step of the whole process is the Ag-mediated C–H activation of the Cr(CO)₃-complexed fluorobenzene. However, when the authors only considered the Pd^{0/II} catalytic cycle, they proposed as the rate-limiting step the transmetalation from the arylsilver(I) complex to the Pd^{II} species. They performed stoichiometric experiments between the *trans*-[(PPh₃)₂Pd(OCOAd)(*p*-C₆H₄OMe)] complex, a presumably palladium resting state of the catalytic cycle, and the arene–Cr complex under different reaction conditions affording the coupling product in 72% yield in the presence of AgOCOAd, PPh₃ and an iodoarene. This is an indirect proof of the group exchange from the in situ generated [(PPh₃)AgAr] to a Pd^{II} complex.

Scheme 23: a) Pd-catalysed Ag(I)-mediated C–H arylation of electron-deficient arenes; b) Role of the additives in the stoichiometric reaction.

More recently, the same research group described a skilful piece of work in which the Pd/Ag ratio led to a switch in regioselectivity in the coupling of benzo[*b*]thiophenes and aryl iodides, being the selectivity determined by the efficiency of the C–H activation and transmetalation step (Scheme 24).⁴¹ This methodology is compatible with multiple functional groups on both starting materials and it is susceptible to be scale up. Different mechanistic information was gathered to support a cooperative bimetallic process including competition experiments and kinetic studies as well as H/D exchange and KIE experiments. The singular regioselective swap is associated to the multiple roles of the silver salts, acting not only as a halide scavenger in the C-3 arylation of benzo[*b*]thiophenes but also as C–H activation promoter and transmetalating agent in the C-2 arylation of benzo[*b*]thiophenes. Indeed, it was suggested that the lower C2:C3 selectivity observed when using *ortho*-substituted aryl iodides could be attributed to the more challenging transmetalation step, favouring the formation of the non-desired product.

Scheme 24: a) Regioselectivity of the reaction depending on the Pd and Ag catalyst loadings; b) General schematic for the direct α-arylation of benzo[*b*]thiophenes.

A common mechanistic picture for both transformations has been represented in Scheme 25.

Scheme 25: Proposed catalytic cycles for Pd-catalysed Ag(I)-mediated C-H arylation.

In 2016, Sanford and co-workers reported the Pd^{II}-catalysed oxidative dimerization of 2-alkylthiophenes where it was demonstrated the role of silver in the C-H activation of alkylthiophenes (Scheme 26a).⁴² In this oxidative coupling system, silver plays multiple roles: C-H activation promoter, nucleophilic transmetalating agent and external oxidant to regenerate the active Pd^{II} catalyst. Mechanistic studies demonstrated the capability of AgOPiv to activate the 5-position of substituted thiophenes derivatives through H/D exchange reactions, obtaining the corresponding deuterated molecules in 50-60% yield in the absence of palladium (Scheme 26b). Indeed, in the same work, the authors observed for the first time, by ¹⁹F NMR spectroscopy, the stoichiometric in situ formation of AgC₆F₅ via C-H activation of C₆F₅H using AgOPiv. It is worth mentioning that the nature of the silver salt plays a crucial role in the outcome of the C-H activation step. When using silver salts such as AgX (X = PF₆, BF₄ or OTf) or different metal pivalates MOPiv (M = Cs, Na or NMe₄) only traces of Pd^{II}-(C₆F₅)_n were observed (Scheme 26c). A concerted metalation-deprotonation (CMD) pathway for the C-H activation by dimeric Ag-Ag species was proposed based on DFT calculations.

Scheme 26: a) Pd-catalysed oxidative dimerization of 2-alkyl-thiophenes; b) H/D exchange reaction of 2-alkylthiophenes promoted by AgOPiv; c) Effect of additives on the reaction of Pd complexes and C₆F₅H.

The same year, Hartwig and co-workers reported the selective formation of Csp²-Csp³ bonds by palladium-catalysed silver-mediated allylation of monofluorobenzenes or non-fluorinated benzenes with allylic pivalates to form (*E*)-allylarenes (Scheme 27a).⁴³ This work is particularly interesting since the authors were able not only to isolate and fully characterise for the first time a phosphine-ligated aryl silver(I) complex which is considered a key intermediate in this transformation, but also to establish its participation in the catalytic system (Scheme 27b). All the mechanistic data including H/D scrambling, KIE, in situ ³¹P NMR and stoichiometric experiments are in accordance with a Pd/Ag synergic system where the arylsilver(I) complex is able to transmetalate an aryl group to a (π-allyl)palladium pivalate species. The formed (π-allyl)palladium aryl complex undergoes a reductive elimination to produce the allylation product.

Scheme 27: a) General schematic for Pd-catalysed Ag(I)-mediated direct allylation of aryl C-H bonds; b) Proposed catalytic cycle.

Recently, Luscombe et al. have applied, for the time, this type of methodology in material science.⁴⁴ The authors describe a dual catalytic Pd/Ag system in the direct arylation polymerization of poly(3-hexylthiophene) (P3HT), a prevalent polymer in the field of organic electronics (Scheme 28).⁴⁵ Interestingly, the use of this bimetallic Pd/Ag protocol, catalytic in both metals, led to the desired conjugated polymer with low dispersities and regioregularity values up to 96%. They attributed the observed low dispersity due to the C-H bond-cleavage promoted by the silver salt. To hamper the potential competition between Ag and Pd during this step, the authors added pyridine to inhibit the C-H activation by the palladium to promote an orthogonal catalytic reactivity.

Scheme 28: General schematic for the dual Pd-Ag catalytic system for the preparation of P3HT.

5. Mechanistic features regarding the transmetalation step

As shown above, silver species can play different roles in Pd-catalysed transformations, being their performance as transmetalating agents key for leading to a successful reaction in Pd/Ag bimetallic systems. Despite the promising advances in this research area, there is an important lack of fundamental understanding on how the corresponding organic moiety is transferred from Ag^{I} to Pd^{II} . Here, we collected the limited examples of stoichiometric reactions between well-defined AgR (R = aryl, CF_2H , CF_3) species and halide or pseudohalides complexes of Pd^{II} , relevant to catalytic processes.

5.1 Aryl moiety exchange

For organometallic synthetic purposes, palladium complexes bearing fluorinated-aryl groups have been prepared by the transmetalation reaction between dimeric bis(halide)-palladium complexes and anionic organosilver(I) species with different perfluoroaryl moieties (Scheme 29).⁴⁶ These reactions proceed smoothly presumably due to the insolubility of the formed silver salts. This elegant work disclosed the capability of silver(I) ate complexes as aryl shuttles to Pd^{II} metal centres.

Scheme 29: General schematic for the preparation of perfluoroaryl-Pd complexes.

Other example of the isolation of bis-(pentafluorophenyl)-palladium complexes using silver nucleophiles was described by Sanford and co-workers in the context of C–H functionalizations.⁴² In this aforementioned work, the authors demonstrated the feasible transfer of pentafluorophenyl groups from AgC_6F_5 , synthesised independently, to $[(\text{N}^{\wedge}\text{N})\text{Pd}(\text{OAc})_2]$, producing the bis-(pentafluorophenyl)-palladium complex in high yields (Scheme 30).

Scheme 30: Stoichiometric reaction between $[(\text{N}^{\wedge}\text{N})\text{Pd}(\text{OAc})_2]$ and AgC_6F_5 .

As we mentioned previously, in 2016, Hartwig and co-workers developed the synthesis of (*E*)-allylarenes by the synergistic

cooperation of Pd/Ag bimetallic systems.⁴³ In this work, they were able to isolate and fully characterise for the first time the proposed reactive Pd^{II} and Ag^{I} intermediates involved in the transmetalation step within the catalytic cycle (Scheme 31). They proved the intermediacy and competence of both metal complexes in the group exchange step by observing the allylation product under stoichiometric conditions.

Scheme 31: Stoichiometric reaction between isolated Pd^{II} and Ag^{I} intermediates involved in the transmetalation step.

5.2 Perfluoroalkyl moiety exchange

In the context of Pd-catalysed perfluoromethylation reactions, the transmetalation between silver and palladium complexes have been employed for boosting the rational design and development of these new protocols.

Before developing the catalytic versions, Shen and co-workers performed different stoichiometric experiments in order to prove the feasibility of the transmetalation step between $[\text{L}_n\text{PdArX}]$ and $\text{SiPrAgCF}_2\text{H}$ within the context of Pd-catalysed difluoromethylation processes (Scheme 32).^{11,14} These experiments provided a direct proof of the CF_2H transfer from the silver(I) nucleophile to the Pd^{II} complex regarding the bimetallic catalytic process.

Scheme 32: Stoichiometric reactions between Pd^{II} and $\text{SiPrAgCF}_2\text{H}$ in the context of difluoromethylation reactions.

In 2018, the Pérez-Temprano group explored the reactivity of novel, well-defined and isolable “ AgCF_3 ” complexes as CF_3 shuttles in Pd-catalysed trifluoromethylation cross-coupling reactions.^{15j} Initially, they used a model system to explore the reactivity of the trifluoromethylsilver(I) complexes and compare their performance versus commercially available nucleophilic sources. This study showed for the first time, not only that the silver nucleophiles outperformed the traditional trifluoromethyl sources but also that the reaction outcomes highly depends on the nature of silver trifluoromethyl complex (Table, Scheme 33). It is worth mentioning the great performance of $(\text{Cs})[\text{Ag}(\text{CF}_3)_2]$. Before this report, the existence of bis(trifluoromethyl)argentate species had been only

confirmed by NMR spectroscopy and its reactivity had been completely unexplored.⁴⁷ Indeed, the extraordinary transmetalating capability of this ate-type complex gave access to [(Xantphos)Pd(Ph)(CF₃)] from [(Xantphos)Pd(Ph)I] in one-pot for the first time, overcoming the challenges associated to the transmetalation step in this specific system. This result was crucial for developing the catalytic version described in section 2.2.

Scheme 33: a) Reactivity of different "CF₃" sources in the model system; b) Translation to a productive system.

6. Summary and outlook

Over the past decade, Pd/Ag bimetallic systems have emerged as a really promising tool in organic synthesis. These strategies allow the employment of readily available starting material such as carboxylic acid derivatives or arenes in decarboxylative processes or C–H functionalization reactions. Without any doubt, the most interesting feature of the synergistic cooperation of this bimetallic couple is the development of innovative reactivity patterns due to the multiple roles exhibited by silver. Despite the tremendous advance of this elegant and versatile approach, Pd/Ag-catalysed transformations are still at their infancy and present some significant synthetic limitations, such as (i) there is minimal precedent for Csp³–Csp² and Csp³–Csp³ bond-forming reactions or (ii) there are only sporadic examples of methodologies catalytic in both metals. However, from our point of view, the real gap to close is the lack of fundamental understanding of the transmetalation step involved in these reactions. An efficient group exchange from an organosilver(I) species to a Pd^{II} intermediate is crucial for the successful outcome of the process. Therefore, more mechanistic insights are needed not only to shed light into these transformations but also for improving these methodologies and allowing the translation to new protocols. Moreover, we are convinced that detailed studies will reveal overlooked transformations promoted by Ag(I) salts in other Pd/Ag functionalization reactions. We encourage the scientific

community to merge organic and organometallic approaches to bring this field to its ultimate capability.

Conflicts of interest

There are no conflicts to declare.

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