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The emergence of Pd-mediated reversible oxidative addition in cross coupling, carbohalogenation and carbonylation reactions

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Abstract

Exploiting the reversibility of chemical processes is a long-standing tactic of organic chemists and permeates most areas of the discipline. The notion that oxidative addition of Pd(0) to Ar–X bonds can be considered an irreversible process has been challenged periodically over the last 30 years. Recent examples of methodologies which harness the reversibility of oxidative addition reactions in catalytic processes have enabled access to challenging carbocyclic and heterocyclic scaffolds. This perspective article seeks to describe the development of these processes from the early proof-of-principle findings, and highlight key challenges which remain in this avenue of research. In particular, we draw attention to significant deficiencies that remain in the choice of suitable ligands and additives for these transformations. We conclude by describing how the concept of reversible oxidative addition has recently been harnessed in the development of novel carbonylation reactions.

Introduction

Palladium-catalysed C–C and C–X bond formation through cross-coupling reactions is ubiquitous in modern organic chemistry.[1] Systematic study of the underlying mechanisms which enable palladium to catalyse these bond-forming reactions has led to development of numerous novel transformations, and in turn, the synthesis of many novel compounds. Although the specifics differ in a few aspects for most cross-coupling reactions, many of these transformations invoke a generic Pd(0)/Pd(II) redox cycle (Figure 1, [a]). A catalytically inactive ligand-bound Pd(0) or Pd(II) pre-catalyst is typically added to the reaction which becomes activated *in situ*. The nature of the ligand bound to the palladium centre is generally critical in determining the outcome of a given transformation, as it is capable of modifying the steric and electronic environment of the Pd(0) centre, thereby modulating its activity. Judicious choice of ligand can therefore result in wide variance in Pd-reactivity. Each of the elementary steps of Pd-catalysed cross-coupling has been intensively studied experimentally and computationally, which has enabled the rational design of ligands to deliver exquisitely selective and high yielding transformations. A comprehensive review on this topic has been assembled by Lin.[1]

The historical development of palladium catalysis has been punctuated by a number of significant breakthrough insights into the mechanism, which have frequently challenged long-held beliefs and facilitated new reactivities.[2] A salient example is the development of reversible oxidative addition of aryl halides from Pd(II) complexes and its subsequent application to form useful, newly functionalised products. Prior to seminal work by Hartwig,[3-5] oxidative addition of Pd(0) to Ar–X bonds had been considered a mostly irreversible process, as examples of the microscopic reverse, reductive elimination to regenerate the starting aryl halide, were sparse in the literature.[6,7] Oxidative addition of Pd(0) to Ar–X bonds is highly exergonic[8] and it was believed that the reverse reaction was too thermodynamically disfavoured to easily occur. Hartwig showed in a series of stochiometric experiments that sterically encumbered ligands enabled reductive elimination of aryl halides.[3-5] The synthetic potential of this transformation was later realised in the work of Newman and Lautens, who developed a catalytic

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reversible oxidative addition reaction to afford 2-bromoindoles and related compounds.[9] Further probing of the catalytic reductive elimination process led to discovery of hitherto unknown reductive elimination of C(sp^3)–X species from Pd(II). These carbohalogenation reactions (typified by Figure 1, [b]) are simple domino transformations which involve (sometimes reversible) Pd(0) oxidative addition, cyclisation and termination through reductive elimination of an alkyl halide. Subsequent reports by Tong, Mazet and Lautens have significantly expanded the scope of these transformations beyond their initial disclosures and many challenging, densely functionalised carbocyclic and heterocyclic products have been successfully accessed. The delivery of viable catalytic strategies stemming from Hartwig's original work has clearly been a significant achievement but there remain many areas of potential development. Currently, the state of the art relies heavily on a few key ligand-catalyst combinations to successfully effect these transformations and the choice of halide precursor is generally limited to more expensive, and less sustainable, aryl bromides and iodides.

This perspective article will begin by introducing the pioneering work on reductive elimination by Hartwig and then demonstrate its influence on the development of catalytic reversible oxidative addition and carbohalogenation, in the context of difficult-to-access cyclic scaffolds. The development of novel catalytic strategies involving the reversibility of oxidative addition in carbonylation reactions by Morandi and Arndtsen will then be described. This perspective does not seek to provide an exhaustive account of all modern applications of reductive elimination of alkyl/aryl halides from Pd(II) complexes. Furthermore, the related process of reductive elimination of Ar–X from Pd(IV) complexes will also not be discussed here, as this process has been recently reviewed.[10]

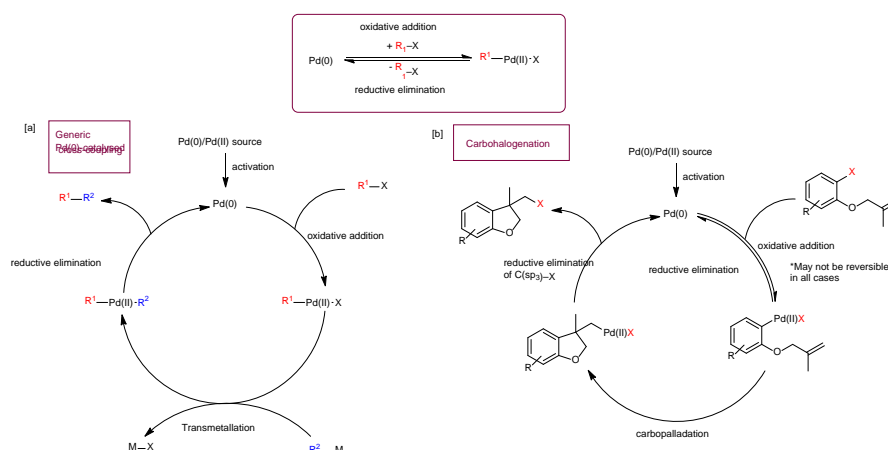
Figure 1 – **Applications of reductive elimination of ArPd(II)X to give Ar–X and Pd(0) discussed in this perspective.** [a] The catalytic cycle of a generic Pd(0)-catalysed cross-coupling reaction. [b] A typical example of a related process known as carbohalogenation, which also involves a critical reductive elimination of Ar-X. Ligands are omitted for clarity and R-Pd angles (which are likely to reflect three coordinate Pd-species) are depicted here arbitrarily.

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Reductive elimination of Ar–X from ArPd(II)X

As described in the introduction (*vide supra* Figure 1), an early step in many Pd(0)/Pd(II) catalytic cycles is oxidative addition of Pd(0) to Ar—X. The activation energy for oxidative addition increases in the order Ar—I < Ar—Br < Ar—Cl and in general proceeds more rapidly for electron rich Pd(0) species and electron deficient Ar—X species.[11] Oxidative addition is often the rate-determining step in a given catalytic cycle, particularly when unreactive Ar—Br or Ar—Cl species are employed.[12] As this step of the catalytic cycle is generally understood to be exothermic, it was considered practically irreversible. Consequently, the microscopic reverse of this transformation, reductive elimination of ArPd(II)X to give Pd(0) and Ar—X, is seldom observed. In order for catalytic reversible oxidative addition or carbohalogenation to be realised, both oxidative addition to and reductive elimination of Ar—X by Pd need to be achievable within the same catalytic cycle.

Prior to seminal work by Hartwig in 2001[5], isolated examples of reductive elimination to Ar—X had been disclosed by Ettorre[7] in 1969 (Figure 2, [a]) and Echavarren and Stille[6] in 1987 (Figure 2, [b]). Roy and Hartwig observed reductive elimination of Ar—X from dimers **A**, using stoichiometric Pd, upon treatment with tri-*tert*-butylphosphine, a sterically encumbered σ-donating ligand, at 70 $^{\circ}$C in benzene-d$_6$ (Figure 2, [c]).[5] Equilibrium constant (K_{eq}) data were obtained by initiating the reaction from either side of the equilibrium. These data indicated that reductive elimination from ArPd(II)Cl was considerably more favourable than from ArPd(II)Br or ArPd(II)I. Notably, aryl substituents lacking the *o*-methyl group eliminated to give the resulting aryl halides in lower yields, suggesting steric congestion may enhance the rate of reductive elimination. Based on the available data, the authors proposed that the dimer **A** dissociated irreversibly to give the three-coordinate, 14-electron complexes **B** (Figure 2 [d]) which underwent the reductive elimination.[4] It had been previously proposed that cross-coupling reactions with sterically demanding phosphine ligands occurred *via* similar intermediates[13,14] but this was the first time such species had been isolated for study. Interestingly, K_{eq} data for this transformation had indicated that reductive elimination to give Ar—Cl was more thermodynamically favoured than elimination of Ar—Br, which is at odds with observed kinetics for the transformation as Ar—Br eliminates *faster* than Ar—Cl (Figure 2, [d]). A subsequent ligand screen revealed that Q-Phos (**L5**) was also a viable ligand for this reductive elimination (Figure 2, [e]).[3] Other less sterically encumbered ligands were much less effective, highlighting the positive impact that steric congestion has on this process. Recent reports have described this reductive elimination chemistry in the context of aryl fluoride synthesis.[10] Work by Buchwald and co-workers has been extremely impactful, through their development of palladium-catalysed fluorination reactions.[15-19]
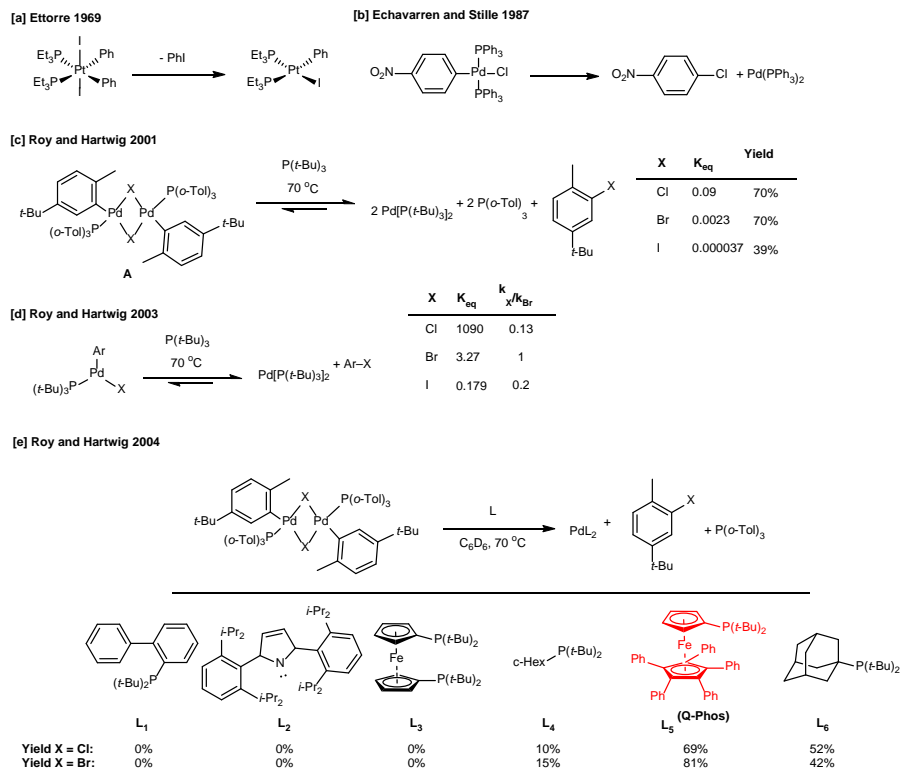
3

Figure 2 – Development of reductive elimination of Ar—X from ArXPd(II)L₂. [a] and [b] – Early examples of reductive elimination of Ar—X. [c] Hartwig's seminal study of reductive elimination of Pd(0) from Ar—X in dimeric Pd(II) complexes. [d] Confirmation of the intermediacy of a 14-electron monomeric species in the earlier reductive elimination reaction. [e] Study of the impact of various sterically encumbered phosphine ligands on the reductive elimination of Ar—X.

Catalytic reversible oxidative addition to Ar–X in cross-coupling reactions

The Pd(0)/Pd(II) catalytic cycle may be prematurely terminated if Pd initially undergoes oxidative addition at a non-productive site, or after the first turnover, effectively sequestering the catalyst, as the resulting Pd(II) complex is catalytically inactive (Figure 3, [a]). This represents a significant challenge in Pd-catalysed cyclic synthesis involving polyhalogenated substrates. When non-productive oxidative addition occurs, the addition of a suitable exogenous coupling partner, such as boronic acids[9,20-22], alkenes[23] or carbon monoxide[24] is necessary in order to achieve catalyst turnover by liberating Pd(0) (Figure 3, [a]). While this approach has been successfully applied to the synthesis of a number of complex heterocyclic products, it is manifestly unsuitable when the halogenated product is desired. Building on Hartwig's work on the reductive elimination of Ar—X from Pd(II), Newman and Lautens reported a catalytic application of this principle (Figure 3, [b]). Reversible oxidative addition facilitated the intramolecular cyclisation of a series 2-(2,2-dibromovinyl)anilines to the resulting 2-bromoindoles in 68-84% yields.[9] Notably, P(t-Bu)$_3$ was the only ligand, of those screened, found to furnish the indole product in useful yields. This observation is in accord with Roy and Hartwig's finding that sterically encumbered ligands induce reductive elimination of ArPd(II)X.[5] Notably, the halogen substituents on indoles **1** and **2** remain intact at the end of the reaction as a consequence of the reversibility of the oxidative addition, marking this approach as a powerful method for accessing polyhalogenated indoles. This methodology was further adapted to afford Heck-type product **4** (Figure 3, [c]) and 2,6-dibromobenzofuran **6** (Figure 3, [d]).[9] Subsequent modification of the original 2-bromoindole cyclisation procedure facilitated the parallel introduction of a nitrile moiety, which could be further telescoped to afford 2-tetrazoloindoles in one pot (Figure 3, [e]).[25]

Other work in this area by Mazet and co-workers is especially noteworthy, as it employed sterically crowded chiral *P,N*-type ligand **10** to effect a highly stereoselective cyclisation, affording brominated indane **9** in 87% yield (99% *ee*) (Figure 3, [f]).[26] The use of a sterically encumbered ligand again ensures that the oxidative addition step is reversible and the bromide substituent is retained.

It is likely that earlier instances involve reversible oxidative addition, but they were not recognised as such at the time. One such example is that from Watanabe in 2000, in which hydrazone **11** underwent Pd-catalysed cyclisation to afford indolamine **12** in 46% using P(t-Bu)$_3$ as a ligand (Figure 3, [g]).[27] The lack of reactivity of **11** under similar conditions in the presence of other ligands potentially implicates reversible oxidative addition as a key mechanistic feature of this reaction.
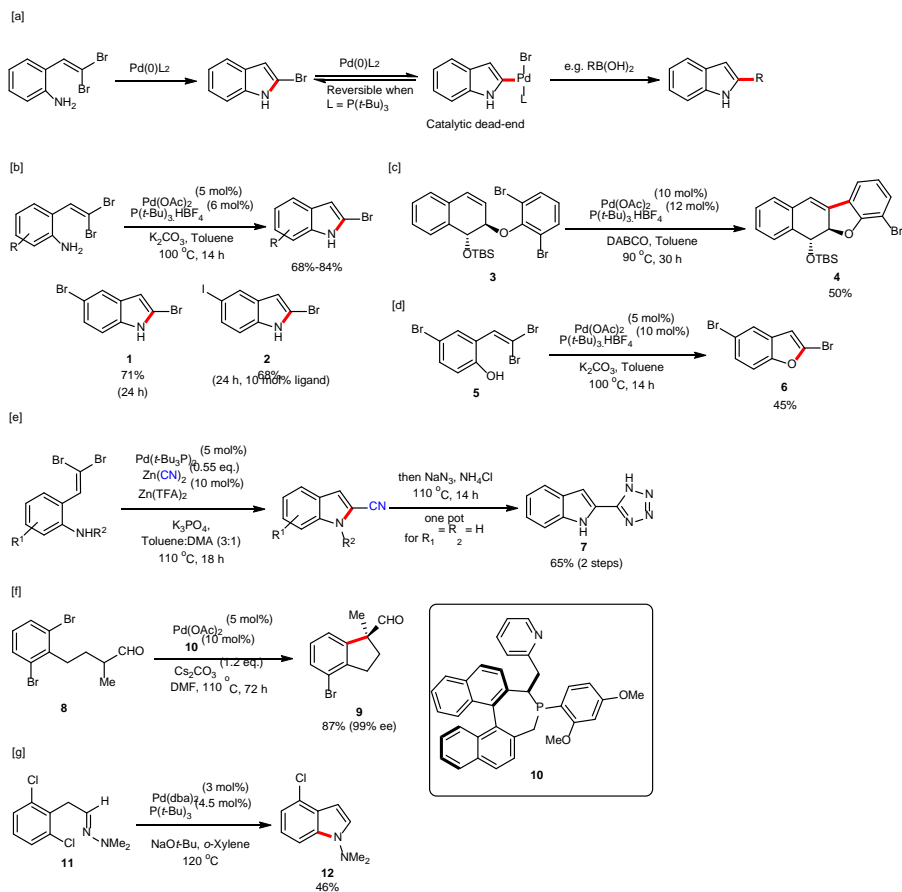
Figure 3 – Cyclisation reactions involving reversible oxidative addition. [a] Reversible oxidative addition in the context of Pd-catalysed indole synthesis. [b] Synthesis of 2-bromoindoles. [c] Synthesis of Heck-type product **4**. [d] Synthesis of benzofuran **6**. [e] Synthesis of 2-cyanoindoles. [f] Synthesis of indane **9** using *P,N*-ligand **10**. [g] Synthesis of indolamine **12**.

Carbohalogenation

The ArPd(II)X to Ar–X reductive elimination process has been applied in a conceptually different manner to the carbohalogenation process (Figure 4). The initial disclosure of this methodology by Newman and Lautens[28] involved treating alkene-tethered aryl iodides with Pd(Q-Phos)$_2$ at elevated temperatures, resulting in cyclisation to afford the halogenated products in good to excellent yields (Figure 4, [a]). Subsequent DFT studies shed light on the mechanism of this transformation.[29] Similar to a Heck-type process, the initial step of the mechanism involves oxidative addition of Pd(0) to the aryl iodide. A neopentyl Pd(II) species is then formed on carbopalladation of the olefin which, crucially, cannot undergo β-hydride elimination. A rate-limiting C(sp^3)–I reductive elimination gives the product and releases the active catalyst. Notably bulky ligands such as Q-Phos, P(t-Bu)$_3$ and PhP(t-Bu)$_2$ were essential to achieve conversion to the desired product, which is a hallmark of this type of reductive elimination process and is consistent with Hartwig's earlier findings (*vide supra*).[3]

A comparable reaction involving tandem Pd-catalysed halogen exchange with potassium iodide was subsequently developed by Lautens and co-workers to avoid recourse to aryl iodide starting materials (Figure 4, [b]).[30] The use of aryl bromide precursors significantly increases the usefulness of this approach as they are widely available and typically cheaper. The authors have further extended their methodology to facilitate domino processes in which multiple rings were formed simultaneously, typified by the high yielding synthesis of lactams **13** and **14** from the corresponding aryl bromide or iodide (Figure 4, [c]).[30]

Lautens later employed a highly diastereoselective variation of the above transformation to access a range of isochromans (Figure 4, [d]) and chromans (Figure 4, [e]).[31] As these classes of compound are ubiquitous in natural products and medicinal chemistry, a high yielding general approach to their synthesis is highly desirable. This report was especially noteworthy as nitrogen-containing heteroaryl compounds were shown to undergo the carboiodination process for the first time (*vide infra*). Additionally, di-iodochroman **15** could be prepared by adopting this strategy. Again this example showcases the power of reversible oxidative addition by allowing the Pd to be released from the non-productive C–I site. Triethylamine was a necessary additive to the reaction, as during optimisation it was found to dramatically increase yield (at the expense of reaction rate) although the provenance of this effect is unclear.

It was later shown that indenes could be prepared through a domino approach from *o*-isoprenyl iodobenzenes and internal alkynes involving reversible oxidative addition to C(sp^2)—I (Figure 4, [f]).[32] Further work on the intramolecular carboiodination reaction established that various classes of di-iodinated substrates were amenable to this approach (Figure 4, [g]).[33] Through the reversibility of the oxidative addition step in these cases, the iodide distal to the reaction site remains intact in the product. The authors were also successful in developing a challenging orthogonal intramolecular carboiodination/ intermolecular Heck reaction sequence (Figure 4, [h]). The reaction was found to be completely chemoselective as no undesired intermolecular Heck product was obtained. *In situ* ^{1}H NMR analysis confirmed that both the carboiodination and the Heck sequences were occurring simultaneously and not sequentially, providing indirect evidence of the ability of the catalyst to interact reversibly with both Ar—I bonds in the substrate.

Interestingly, Tong and co-workers have shown that less bulky ligands such as dppf (1,1'-Bis(diphenylphosphino)ferrocene) could also act as a viable ligand for the carbohalogenation process (Figure 4, [i]).[34] Notably, when (*S*)-BINAP was used as a ligand, tetrahydropyridine **16** was formed with 56% *ee*, albeit in only 10% yield. Further work by Tong's group employed similar cyclisation reactions to afford halogenated γ-lactams[35] and dihydropyrroles[36], although these processes fall outside the scope of this perspective.

Further extending the scope of these transformations, t vinyl halides were prepared through reversible oxidative addition by Lautens (Figure 4, [j]).[37] The combination of Q-Phos as ligand, in addition to the presence of a bulky R^2 substituent on the substrate, again proved critical in successfully delivering the product. It is believed that the combined steric effects enabled the key reductive elimination. This result is also in accord with Hartwig's original 2001 findings on reductive elimination, which demonstrated that encumbered substrates underwent reductive elimination more readily than less sterically congested analogues (*vide supra*).[5] Both *cis-* and *trans*-addition products were formed in this reaction. It was observed that the *cis*-addition products isomerised to the *trans*-addition products in the presence of the catalyst at elevated temperatures. The authors postulated that this occurs as both the oxidative addition and reductive elimination events in the mechanism are reversible. Notably this is among the few examples of aryl chloride precursors acting as viable substrates for this type of reductive elimination process.

Excellent diastereoselectivity is a salient feature of many of the examples of carbohalogenation reactions. The diastereoselectivity arises due to steric interactions between the substrate and ligand during the product determining step of the reaction. In one example, enantioenriched *N*-allyl carboxamides, underwent cyclisation reactions to furnish to the corresponding benzo-fused *γ*-lactams in good to excellent yields with high levels of stereocontrol (Figure 4, [k]).[38] A formal asymmetric synthesis of the natural product (+)–corynoline was achieved from lactam **17** adopting this approach (Figure 4, [l]). While a number of highly diastereoselective procedures have been developed, if reversible oxidative addition is to be widely employed in the synthesis of natural products, robust methods which can furnish targets in high enantiomeric excess must be identified. An ideal asymmetric transformation would involve a catalytic amount of chiral ligand. Tong had shown that using (*S*)-BINAP as a ligand induced some enantioselectivity, but the product yield was low in comparison to other, achiral, ligands (*vide supra*). Unfortunately, revisiting previously successful carbohalogenation reactions with a view to the asymmetric variant using chiral ligands has been met with only moderate success (Figure 4, [m] and [n]). For example, employing the chiral bidentate Josiphos ligand **SL-J002-1** in the cyclisation of ether **19** afforded the product **20** in 94% *ee*, albeit in a poor yield of 14%. By contrast, the reaction to furnish lactam **22** using Walphos ligand **SL-W001-1** proceeded in much higher yield, but with a significantly poorer enantiomeric excess of 40%. There is, therefore, a clear trade-off between levels of selectivity and reaction efficiency, which may be addressed in future by sophisticated ligand design.

With this in mind, the highly enantioselective carboiodination reactions recently reported by Li and Zhang[39] (Figure 4, [o]) and Cao, Xu and Xu[40] (Figure 4, [p]) represent significant advances in the field. By employing the XuPhos ligand, ***N*-Me-Xu3**, a highly enantioselective carboiodination of a range of olefin-tethered aryl iodides was realised by Li, Zhang and co-workers. ***N*-Me-Xu3** was identified in the course of an extensive ligand screen, which also revealed that chiral ligands such as **SL-J002-1** and **SL-W001-1** were ineffective, affording poor conversion to the product. A computational study conducted by the authors suggests that the enantioselectivity observed in this transformation, arises due to the energy difference between the two activation barriers of the stereo-determining alkene insertion step. In parallel, Cao, Xu and Xu disclosed a highly enantioselective Pd(0)-catalysed conversion of a range of 3-(2'-halophenyl)cyclobutanones to the corresponding indanones through a ring-opening carboiodination process.[40] During the optimisation of this transformation, it was found that TADDOL-derived phosphoramidites proved to be effective ligands for this transformation, furnishing the product in higher yields than achiral ligands such as Q-Phos or dppf.
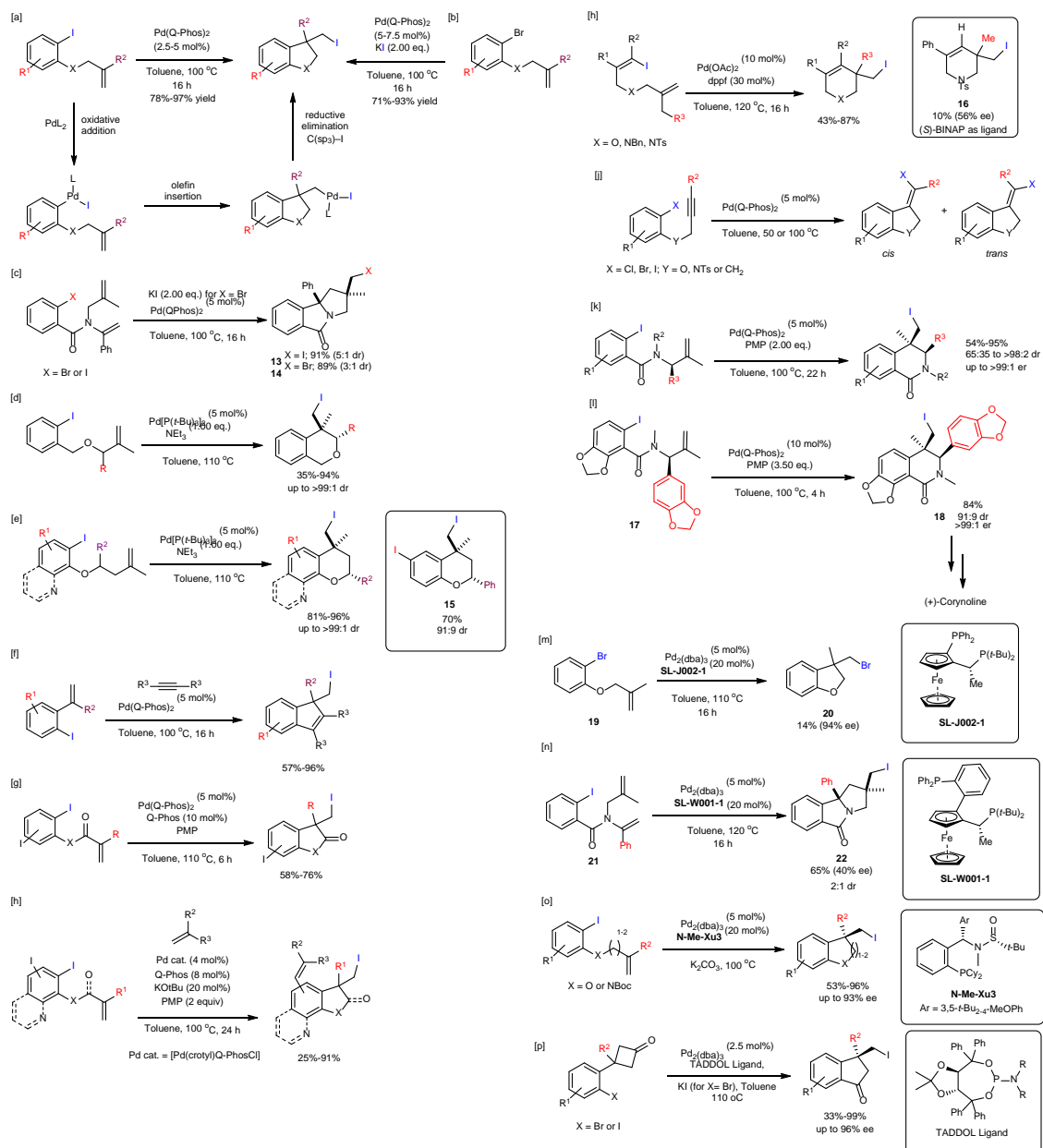
Figure 4 – **Intramolecular carbohalogenation facilitated by reductive elimination and reversible oxidative addition.** [a] and [b] Prototypical intramolecular carbohalogenation showing cooperative oxidative addition and reductive elimination. [c] Domino carbohalogenation to form polycyclic lactams **13** and **14**. [d] and [e] Synthesis of isochromans and chromans. [f] Synthesis of indenes. [g] and [h] Intramolecular carboiodination involving di-iodinated precursors. [i] Cyclisation of (*Z*)-1-iodo-1,6-dienes [j] Vinyl halide synthesis through intramolecular cyclisation of propargyl ethers [k] and [l] Stereospecific synthesis of gamma-lactams and application to the total synthesis of (+)-Corynoline. [m] and [n] Enantioselective carbohalogenations using Josiphos and Walphos ligands. [o] Enantioselective carboiodination using XuPhos ligands. [p] Enantioselective tandem ring-opening carboiodination using TADDOL ligands.

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Reversible carbonylation and decarbonylation

The ubiquity of the carbonyl moiety across all disciplines of chemistry has ensured sustained interest in the development of innovative methods for its incorporation into organic molecules. Palladium-catalysed carbonylation of aryl halides using carbon monoxide as a cheap and readily available C1 source is an attractive avenue for the preparation of carbonyl-containing compounds.[41] The reversibility of Pd(0)/Pd(II)-catalysed carbonylation reactions has been explored extensively by the groups of Arndtsen and Morandi.

Arndtsen and co-workers initially demonstrated that a range of aryl iodides[42], and later aryl bromides[43], underwent Pd-mediated carbonylation in the presence of a soluble chloride source, under a carbon monoxide atmosphere, affording a range of acid chlorides at elevated pressure and temperature (Figure 5, [a]). The use of Pd[P(t-Bu)$_3$]$_2$ as a pre-catalyst proved critical to the success of this transformation as an extended screen of phosphine ligands confirmed that no other ligand delivered the product in synthetically useful quantities. As acid chlorides readily undergo oxidative addition to Pd(0), reductive elimination to form an acid chloride is a highly disfavoured process and was hitherto relatively unknown. Extensive and elegant work has been reported by the Arndtsen group to elucidate the mechanism of this transformation across a number of publications.[42-44] It was initially thought that the P(t-Bu)$_3$ promoted this transformation by stabilising the formation of a coordinatively unsaturated T-shaped Pd-intermediate through an agostic interaction with one of the ligand C–H bonds. However, it was found that neither oxidative addition product **I** or **II** were able to generate the acid chloride in the absence of carbon monoxide (Figure 5, [b]). The acid chloride formed readily in the presence of carbon monoxide however, suggesting that carbon monoxide was involved in the reductive elimination step. It is likely that the steric strain induced upon carbon monoxide ligation to palladium leads to a favourable strain-relief mediated reductive elimination of the acid chloride.[44] On the basis of these observations, a catalytic cycle invoking intermediate **III** was proposed (Figure 5, [c]). Interestingly, the rate of acid chloride formation decreased rapidly as the reaction proceeded, as a consequence of the reversibility of the reductive elimination step. It was proposed that the elevated temperature and carbon monoxide pressure help to bias the equilibrium in favour of the product, thereby making the reductive elimination step viable near the end of the reaction.

The reverse reaction, oxidative addition of the acid chloride to Pd(0), can also be overcome by allowing the acid chloride to react further with an exogenous nucleophile. This enables the carbonylation reaction to take place under milder conditions, as the acid chloride is removed from the equilibrium mixture, thus driving the reaction to completion. For instance, aminocarbonylation to afford amides proceeds at room temperature and atmospheric pressure of carbon monoxide (Figure 5, [d]).[42] A diverse range of products including ketones[45], benzoxazoles[46], β-lactams[47], imidazoles[48] and pyrroles[49] have been prepared by varying the nature of the trapping nucleophile. Applying this methodology to isotopically-labelled carbon monoxide sources has also been demonstrated to afford [11]C-, [13]C- and ^{14}C-labelled carbonylation products. [50,51]

The reversibility of Pd(0) oxidative addition to acid chlorides has subsequently been exploited in a number of highly innovative protocols. Morandi and co-workers developed an isodesmic shuttle-catalysis reaction involving *in situ* HCl and CO transfer through Pd-catalysed decarbonylation of readily available butyryl chloride (Figure 5, [e]).[52] Transfer of the carbonyl group is achieved through ligand exchange after β-hydride elimination, which is rendered effectively irreversible due to the volatility of the by-product, propene (Figure 5, [f]). Although the substrate scope was limited with regard to alkenes, it proved to be more expansive with alkynes. In the same publication, the authors showed that the resulting acid chlorides could be converted *in situ* to various other products, such as esters, thioesters and amides, by treating them with nucleophiles in a one-pot fashion. The reverse process,

dehydrochlorocarbonylation of the acid chloride, was also harnessed using norbornene as an acceptor (Figure 5, [g]).

An interesting application of the reversibility of oxidative addition in this case is the development of functional group metathesis between aryl iodides and acid chlorides.[53] Generally, when a new functional group interconversion is developed, it takes advantage of the irreversibility of the desired transformation, thus ensuring that the product is formed in good yield. Generally, if the reverse reaction is required, a new synthetic strategy must be conceived. Systems amenable to functional group metathesis allow both the forward reaction and the reverse reaction to be carried out under similar conditions, exploiting subtle differences in the reactivity of the two functional groups. Morandi and co-workers observed the Pd-catalysed reversible exchange of iodide and acid chloride functionalities between aryl iodide and aroyl chlorides, leading to an equilibrium mixture of products.[54] The reversibility of the exchange was examined by control experiments in which the metathesis was initiated from both sides (Figure 5, [h]). Both reactions led to crude reaction mixtures of similar composition, confirming the reversibility of the exchange. Tuning the electronic and steric properties of the aryl iodide and the aroyl chloride allowed the equilibrium to be pushed forward and back (Figure 5, [i] and [j]). It was found that adding electron-rich aryl iodides or an excess of iodobenzene favoured the formation of the aroyl chloride and that adding electron-poor or ortho-substituted aroyl chlorides favoured the formation of aryl iodides. Interestingly, the phenyl groups on Xantphos were found to undergo exchange with the aryl groups of both the aryl iodide and the aroyl chloride. It was therefore postulated that Xantphos promotes the reaction through scrambling of the aryl groups on the aryl iodide and the aroyl chloride through reversible oxidative addition and carbonylation (Figure 5, [k]). The authors subsequently isolated one of the proposed phosphonium intermediates and showed that it was a competent catalyst in the reaction, supporting their mechanistic hypothesis. In parallel, Arndtsen and co-workers reported a similar Pd-catalysed metathesis reaction where ortho-substituted or electron-deficient aroyl chlorides were used as acid chloride donors for a range of aryl iodides acceptors (Figure 5, [l]).[55]
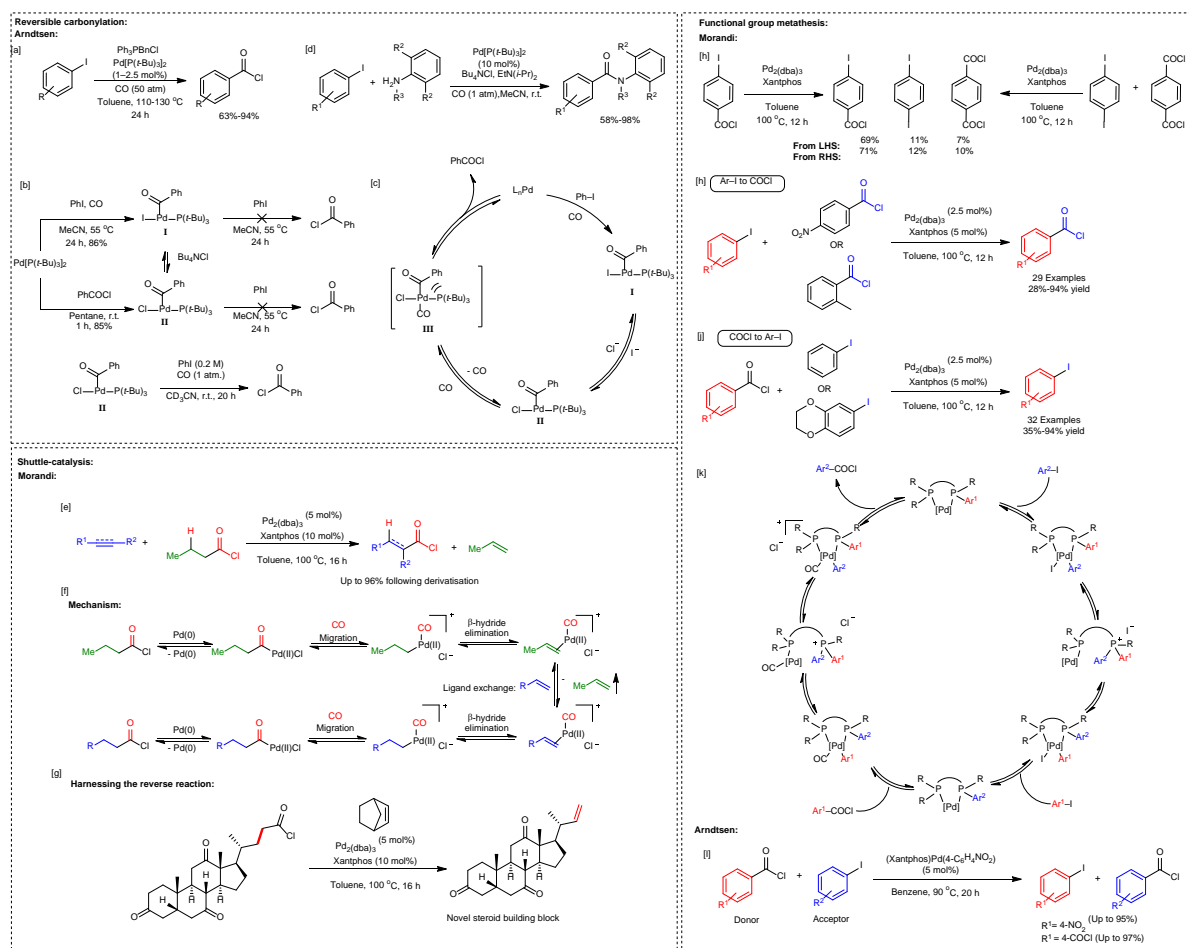
Figure 5 – Reversible oxidative addition in carbonylation/decarbonylation sequences. [a] Initial discovery of acid chloride synthesis through reversible carbonylation. [b] Mechanistic studies implicating CO in the reductive elimination step. [c] Proposed catalytic cycle. [d] Aminocarbonylation under mild conditions as an example of one pot functionalisation of the resulting acid chlorides. [e] Shuttle-catalysis developed by Morandi and co-workers. [f] Proposed mechanism involving ligand exchange and reversible oxidative addition. [g] Reverse reaction confirming alkenes can be regenerated from acid chlorides. [h] Exchange experiment showing Pd-mediated functional group metathesis, mediated by Xantphos. [i] and [j] Applied functional group metathesis in the synthesis of acid chlorides and aryl iodides. [k] Proposed catalytic cycle for functional group metathesis involving Xantphos-mediated aryl scrambling. [l] Related process reported in parallel by Arndtsen.

Outlook

It is anticipated that this perspective will help bring to the fore the concept of reversible oxidative addition to metal centres. Example processes such as Pd-mediated cross-coupling, carbohalogenation and carbonylation reactions are described herein, although the concept will, undoubtedly, be applied to a wide variety of transformations in the future. There are several literature reports of synthetic methodologies which rely on using exogenous coupling partners in order to avoid turnover limiting unproductive oxidative addition, which can now be re-evaluated. Additionally, there is a dearth of examples of coupling reactions which use multi-halogenated starting materials; a disparity which could be addressed. In order to ensure the broad applicability of this chemistry, a number of key limitations need to be overcome. A reliance on aryl bromides or iodides should be avoided, as they are more expensive than aryl chlorides and some other pseudohalides and functionalities.

It is also clear that more information is needed on the mechanism of these transformations. Further understanding of the role of additives and the role of the ligand is likely to lead to the development of highly robust processes. The identification of new ligand/pre-catalyst combinations is essential, given the very limited choice of suitable pre-catalyst/ligand combinations. The value of these reactions would further be enhanced if further asymmetric variants were to be established. It has been shown (*vide supra Figure 4)* that diastereoselective processes, exploiting chiral centres in the starting material, can lead to highly stereochemically enriched products. However, this can be problematic in the context of accessing all stereoisomers of a particular target. Consequently, the design of chiral ligands which retain the ability to effect reversible oxidative addition would be highly impactful. Complementary Nickel-catalysed carboiodination reactions have been recently reported which address some of these concerns.[56,57] These reactions are likely to proceed *via* different mechanisms to those invoked for the corresponding palladium-catalysed processes and thus will add significantly to the potential scope of these transformations. Recently reported enantioselective carboiodination reactions using TADDOL and XuPhos ligands are encouraging and the ability of these ligands to facilitate highly enantiomerically enriched products, in synthetically useful yields, is a significant advance. Although the current scope of enantioselective carbohalogenations is limited to two reports, it is possible that revisiting previously successful iterations of the reaction utilising similar ligand systems may further progress the state of the art.

Although exploitation of reversibility in carbonylation reactions has only been recently described, significant advances in this field have led to the development of highly innovative methodologies, which have been applied in the synthesis of complex building blocks, complementing the body of known work on the synthesis of aryl iodides and acid chlorides. Finally, the rapid emergence of the application of reversible oxidation yet again showcases how creative organic chemists can build on important proof-of-principle reactions in the inorganic and organometallic literature, to create synthetically useful processes.

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