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## Well-defined nickel and palladium precatalysts for cross-coupling

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### Abstract

Transition metal-catalysed cross-coupling is one of the most powerful synthetic methods and has led to vast improvements in the synthesis of pharmaceuticals, agrochemicals and precursors for materials chemistry. A major advance in cross-coupling over the past 20 years is the utilization of well-defined, bench-stable Pd and Ni precatalysts that do not require the addition of free ancillary ligand, which can hinder catalysis by occupying open coordination sites on the metal. The development of precatalysts has resulted in new reactions and expanded substrate scopes, enabling transformations under milder conditions and with lower catalyst loadings. This Review highlights recent advances in the development of Pd and Ni precatalysts for cross-coupling, and provides a critical comparison between the state of the art in Pd- and Ni-based systems.

Transition metal-catalysed cross-coupling is one of the most powerful synthetic methods and is used extensively in the preparation of active pharmaceutical ingredients, fine chemicals, and precursors for materials chemistry<sup>1–5</sup> (BOX 1). Typically, the most active cross-coupling catalysts are Pd complexes with sterically demanding, electron-rich phosphine or N-heterocyclic carbene (NHC) ancillary ligands. In fact, one of the major advances in cross-coupling over the past 20 years has been the development of specialized phosphine and NHC ligands, the complexes of which readily undergo the fundamental steps in catalysis such as oxidative addition and reductive elimination<sup>6–9</sup>. The use of these ligands has expanded the substrate scope of the reactions, as well as enabling the use of milder conditions and lower catalyst loadings. However, the monetary costs of these specialized ligands are often comparable to the Pd precursor, and as a consequence, the traditional route for generating the active species — addition of excess ligand to a Pd(0) precursor — becomes unattractive. Furthermore, in many cross-coupling reactions the optimal Pd to ligand ratio is 1:1, with the active species proposed to be monoligated Pd(0)<sup>10</sup>. As a result, it is now common to use well-defined Pd(ii) precatalysts containing one molar equivalent of ancillary ligand to facilitate cross-coupling reactions<sup>11</sup>.

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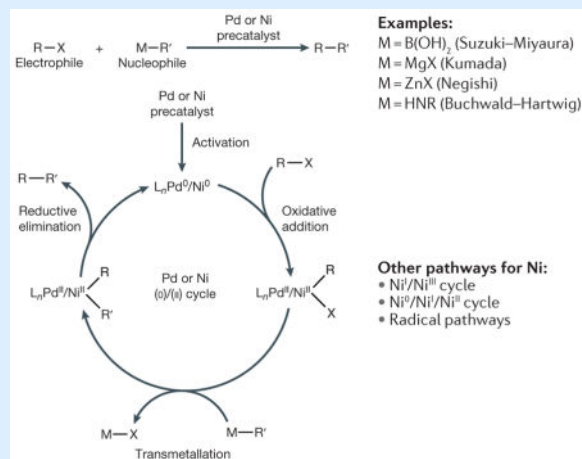
#### Competing interest statement

The authors declare no competing interests.

## Box 1

## A summary of Ni- and Pd-catalysed organic cross-coupling reactions

Ni- or Pd-catalysed coupling of an electrophile  $R-X$  with a nucleophile  $M-R'$  typically proceeds through oxidative addition, transmetalation and reductive elimination steps. Both Pd and Ni precatalysts have their advantages and disadvantages, and a 'universal' cross-coupling catalyst has yet to be identified.



Precatalyst	Advantages	Disadvantages
Pd	<ul style="list-style-type: none"> <li>• Low precatalyst loading (&lt;1 mol%)</li> <li>• Reactions proceed at room temperature</li> <li>• Reaction times &lt;1 h</li> <li>• High mechanistic understanding</li> </ul>	<ul style="list-style-type: none"> <li>• Low earth abundance</li> <li>• High cost</li> <li>• Specialized ancillary ligands can cost as much as the metal</li> </ul>
Ni	<ul style="list-style-type: none"> <li>• Low-cost Earth-abundant metal (~100 p.p.m.)</li> <li>• Can couple electrophiles that are not active with Pd precatalysts</li> <li>• Can undergo one-electron redox</li> </ul>	<ul style="list-style-type: none"> <li>• High precatalyst loadings</li> <li>• High reaction temperatures</li> <li>• Reaction times &gt;1 h</li> <li>• Low mechanistic understanding</li> <li>• One-electron redox can interfere with productive catalysis</li> </ul>

Although Pd-based precatalysts are currently the systems of choice for most cross-coupling reactions, there is growing interest in utilizing Ni-based systems, which represent potentially cheaper and more sustainable alternatives<sup>12–14</sup>. Alongside these intrinsic advantages, Ni catalysts are more efficient than Pd systems for certain cross-coupling reactions. For example, Ni catalysts show improved activity for some reactions involving heteroaryl substrates<sup>15</sup>, Suzuki–Miyaura and Buchwald–Hartwig couplings using aryl carbamates and carbonates<sup>16</sup>, and reactions that couple  $sp^3$ -hybridized atoms<sup>17–22</sup>. However, in comparison

to complexes of Pd, those of Ni are more likely to undergo one-electron redox processes, are not well understood mechanistically, and require higher loadings of catalyst and base (where required), as well as elevated reaction temperatures. Furthermore, the development of air- and moisture-stable Ni precatalysts is in its infancy, and general precatalysts that can be used for a wide range of cross-coupling reactions have yet to be discovered.

In this Review, we describe recent advances in the development of cross-coupling precatalysts incorporating either Pd or Ni, and consider the advantages and disadvantages of the different precatalyst classes (BOX 1). Our aim is not to provide a full 'catalogue' of precatalysts, but instead to explore the differences between major precatalyst classes and Pd and Ni systems. For brevity, only the most important examples are included, unless otherwise explained. Considering that Pd cross-coupling catalysis has been the subject of many useful reviews<sup>11,23–25</sup>, we pay particular attention to key developments since 2012. In the case of the more lightly studied topic of Ni catalysis, we provide a more comprehensive discussion. The individual sections are organized according to metal and the oxidation state of the precatalyst. Systems in which simple metal salts, such as NiCl<sub>2</sub> or PdCl<sub>2</sub> (or their solvated complexes), are used directly in catalysis in conjunction with added ligand are excluded, because in many cases the mixtures are intractable and teach us less than cases in which precatalysts are well defined.

There are relatively few cases in which precatalysts from different classes have been directly compared, and the optimal reaction conditions for one precatalyst are not always compatible with those used for another precatalyst. In the majority of cases, only one precatalyst class with an assortment of different ligands has been screened for a particular application. In this Review, we provide information about the different classes of precatalyst and the ligands that are compatible with them. We describe common applications of different precatalysts and compare their stability, but note that chemists are not in a position to prescribe the optimal catalyst for any given reaction. Although such a detailed comparison of the performance of different precatalysts for specific transformations would be of value to the community, in our opinion, more research is required before it is possible to make meaningful conclusions. To help guide such research, we conclude by discussing more general merits of Pd and Ni systems, and offer some future directions in precatalyst design.

## Pd-based precatalyst development since 2012

Pd is by far the most commonly used metal in catalysts for cross-coupling reactions<sup>4</sup>. This is in part due to its propensity to undergo two-electron processes, which are central to the proposed mechanism for cross-coupling reactions (BOX 1). Furthermore, Pd complexes are generally tolerant to a wide range of functional groups and, especially in the +ii oxidation state, are not sensitive to air and moisture. Nevertheless, there are problems associated with using Pd in cross-coupling reactions. In addition to its high cost relative to other metals, the toxicity of Pd means that rigorous and expensive purification is required before pharmaceuticals synthesized using cross-coupling can be administered<sup>26,27</sup>. Below we summarize the advancements in Pd precatalyst development from the past 5 years.

## Pd(II) precatalysts

**Palladacycle precatalysts**—Air- and moisture-stable Buchwald precatalysts (FIG. 1a), which feature a palladacycle, have been extensively used in cross-coupling reactions<sup>25</sup>. Comprehensive activation studies have shown that a Brønsted base is necessary to reduce the precatalysts to the active monoligated Pd(0) species, a process that requires deprotonation of the ligated amine, followed by reductive elimination of a nitrogen-containing heterocycle<sup>28</sup> (FIG. 1b). This is a facile process under the conditions generally used for cross-coupling. In conjunction with the dialkylbiarylphosphine ligands also developed by the Buchwald group, palladacycle-based precatalysts have now been used for nearly every type of cross-coupling. Recent notable applications of this system include facilitating state-of-the-art Suzuki–Miyaura<sup>29</sup>, Negishi<sup>30–33</sup> and aryl amination<sup>34–38</sup> reactions, as well as the cyanation<sup>39,40</sup> and hydroxylation<sup>41</sup> of aryl halides, the synthesis of methyl aryl ethers<sup>42</sup> and the aminocarbonylation of aryl bromides<sup>43</sup>. Buchwald precatalysts are now available commercially in preloaded capsules, which contain varying amounts and types of palladacycle, and are conveniently used in synthetic chemistry.

In addition to expanding the range of reactions catalysed by their precatalyst, the Buchwald group has also made key improvements to the precatalyst itself. In 2013, to make the precatalyst compatible with sterically bulky ancillary ligands, the chloro ligand in the 2nd generation system was replaced with a more weakly donating mesylato ligand to afford a 3rd generation system<sup>44</sup> (FIG. 1a). The ligated 3rd generation precatalysts are prepared from a dimeric  $\mu$ -mesylato precursor, which, in turn, is easily synthesized in one step from Pd(OAc)<sub>2</sub> and can be made on an industrial scale (FIG. 1c). The subsequent ligation reactions of the  $\mu$ -mesylato dimer can be performed *in situ*, such that this scaffold is amenable to catalytic screening in conjunction with a wide range of relevant phosphine ligands. Relative to a chloro ligand, mesylato is less coordinating and sterically demanding, allowing for bulky ligands, such as <sup>t</sup>BuXPhos, <sup>t</sup>BuBrettPhos and AdBrettPhos, to readily bind to the metal centre (FIG. 1d). By contrast, the chloro ligand in the 2nd generation systems makes them incompatible with these larger ligands<sup>45</sup>. Importantly, in addition to the expanded ligand scope, the catalytic activity of the mesylato palladacycles is comparable to that of the 2nd generation Buchwald palladacycles<sup>44,45</sup>. Although the mesylato precatalysts have been used extensively with phosphine ligands, there are no reports describing their activity when NHC ancillary ligands are present instead.

Recently, further modifications were made to 3rd generation Buchwald precatalysts to combat one of the major drawbacks to this system. The 2nd and 3rd generation precatalysts produce an equivalent of carbazole during activation to form the monoligated Pd(0) active species (FIG. 1b). The carbazole by-product poses both experimental and health concerns; it can participate in Buchwald–Hartwig reactions (thereby lowering expected yields) and is a suspected carcinogen<sup>46</sup>. To help eliminate the effects of this activation by-product, 4th generation palladacycle precatalysts were designed with either a –NHMe or –NHPh moiety in place of the traditional –NH<sub>2</sub> group<sup>47</sup>. The by-product produced from activation of these precatalysts is inert towards cross-coupling chemistry and does not pose any health risks.

**PEPPSI precatalysts**—Bench-stable Pyridine-Enhanced Precatalyst Preparation

Stabilization and Initiation (PEPPSI) precatalysts, developed by Organ and colleagues, are highly active but have largely been used only with NHC ancillary ligands<sup>23</sup> (FIG. 1e). Their conversion to active monoligated Pd(0) species involves double transmetalation of the precatalyst by the nucleophile used in cross-coupling, followed by reductive elimination and dissociation of pyridine to generate the active catalyst<sup>48</sup>. This generally occurs rapidly under the reaction conditions, but detailed studies of the rates of activation as a function of the nucleophile have not been performed. Recent work from the groups of Nolan and Organ has demonstrated that the PEPPSI scaffold can accommodate bulky ligands, such as IPr\* (REF. 49), IPent (REFS 50–52), IPent<sup>Cl</sup> (REFS 53–56) and IHept<sup>Cl</sup> (REFS 57,58), without any need to modify the precatalyst structure. Use of the PEPPSI framework with these newly designed NHC ligands has led to increased reactivity for the arylation of amines (using IPr\* (REF. 49) and IPent<sup>Cl</sup> (REFS 55,56)), as well as highly selective Negishi couplings with secondary alkylzinc reagents (using IPent<sup>Cl</sup> (REF. 53) and IHept<sup>Cl</sup> (REFS 57,58)). In fact, Negishi couplings with secondary alkylzinc nucleophiles using PEPPSI-IHept<sup>Cl</sup> exclusively gave the cross-coupled product with no rearrangement product observed<sup>58</sup>.

Recently, there have been two reports of small modifications to the PEPPSI precatalyst that have resulted in increased activity. For C–S bond formation reactions conducted in the presence of the IPent ancillary ligand, the efficiency of the precatalyst was improved by changing the 3-chloropyridine ligand commonly used in the PEPPSI scaffold<sup>51</sup> (FIG. 1f). Although an unsubstituted pyridine-ligated precatalyst yielded no product at 50 °C, a 2-methylpyridine-ligated analogue gave complete conversion. Using the same scaffold, Organ and co-workers<sup>50</sup> reported impressive results for the monoarylation of anilines using weak carbonate bases, achieving excellent yields using deactivated electrophiles. Additionally, by further understanding the activation mechanism, it has been shown that replacing the pyridine motif with morpholine allows for the room temperature coupling of thiols and aryl chlorides using IPent (REF. 52).

The PEPPSI precatalyst scaffold has also been used in heterogeneous catalysis<sup>59</sup>. By modifying the NHC ligand, a system related to PEPPSI-IPr could be supported on silica and used for continuous flow Negishi cross-coupling reactions. Not only could this system be used for room temperature transformations, but the catalyst, under batch conditions, could also be recycled up to five times while retaining high levels of activity. Under continuous flow conditions, the PEPPSI-IPr scaffold showed excellent activity over the course of 15 hours. These results demonstrate the versatility of this scaffold for both homogeneous and heterogeneous catalysis. In general, we suggest that there are significant opportunities to use well-defined precatalysts in flow chemistry, because most cross-coupling reactions performed under continuous flow currently use simple palladium salts, such as PdCl<sub>2</sub> and Pd(OAc)<sub>2</sub>, instead of state-of-the-art precatalysts<sup>60</sup>.

**$\eta^3$ -Allyl-type precatalysts**—There has been considerable improvement in precatalysts based on  $\eta^3$ -allyl ligands in the past 5 years. In a similar manner to the PEPPSI system, Nolan has demonstrated the efficacy of air- and moisture-stable  $\eta^3$ -allyl and  $\eta^3$ -cinnamyl precatalysts with bulky NHC ligands (FIG. 2a,b). Specifically, the [ $\eta^3$ -cinnamyl]Pd(L)Cl] scaffold (L = IPr\* (REFS 61–64) or IPr\*<sup>OMe</sup> (REFS 65,66)) has been incorporated into

several highly active catalysts for difficult cross-coupling reactions. Notably, tetra-*ortho*-substituted biaryls were synthesized using Suzuki–Miyaura reactions when the  $\eta^3$ -cinnamyl motif was used in conjunction with IPr\* (REF. 49). These challenging transformations could even be performed at room temperature at low catalyst loadings with aryl bromides and chlorides. The  $[(\eta^3\text{-cinnamyl})\text{Pd}(\text{IPr}^*)\text{Cl}]$  precatalyst was also found to be active for Buchwald–Hartwig reactions with secondary amines<sup>61</sup>, as well as for arylation of unactivated arylsulfoxides<sup>62</sup>. An interesting application of this precatalyst system is in the intramolecular  $\alpha$ -arylation of imines to form N-unprotected indoles from *o*-chloroarylimines, and this system proved superior to existing methodology in relation to catalyst loading, reaction scope, temperature and yield<sup>64</sup>. Switching the ancillary ligand from IPr\* to IPr\*<sup>OMe</sup> produces a precatalyst that is competent for several reactions, including Buchwald–Hartwig, Suzuki–Miyaura and Kumada couplings<sup>65</sup>, and the arylation of thiols<sup>66</sup>. The  $[(\eta^3\text{-cinnamyl})\text{Pd}(\text{NHC})\text{Cl}]$  scaffold has been shown to be compatible with even bulkier NHC ligands, such as INon, which results in active systems for the monoarylation of primary anilines<sup>67</sup>.

Although  $\eta^3$ -allyl-type precatalysts have proven effective when combined with NHCs, their particular utility comes from their compatibility with both NHC and phosphine ligands. The groups of Shaughnessy<sup>68</sup> and Colacot<sup>69</sup> have utilized the  $\eta^3$ -allyl motif to produce air-stable phosphine complexes that show excellent activity for various cross-coupling reactions. More recently, a team from Johnson Matthey led by Colacot<sup>70</sup> has synthesized precatalysts containing highly active Buchwald phosphines, including XPhos, RuPhos and BrettPhos. For the bulkier dialkylbiarylphosphines, the traditional chloro ligand was replaced with a weakly coordinating triflate ligand, allowing precatalysts with <sup>t</sup>BuXPhos, <sup>t</sup>BuBrettPhos and AdBrettPhos to be synthesized. These phosphine-ligated precatalysts were active for a range of cross-coupling reactions, including Buchwald–Hartwig, Suzuki–Miyaura and  $\alpha$ -arylation reactions<sup>70</sup>. Using these sterically demanding phosphine ligands curbed the formation of deleterious Pd(i) species such that the catalysts that formed were more active and longer lived.

In related chemistry from Yale, it was found that two processes govern the activation efficiency of precatalysts based on the  $\eta^3$ -allyl/ $\eta^3$ -cinnamyl moiety: the rate of reduction from Pd(ii) to the active monoligated Pd(0) species and the extent to which a detrimental dipalladium(i)  $\mu$ -allyl dimer is formed<sup>71,72</sup> (FIG. 2c). Through computational and experimental analysis, an activation mechanism for the reduction of NHC-supported  $\eta^3$ -allyl precatalysts to monoligated Pd(0) was determined under conditions relevant to the Suzuki–Miyaura reaction<sup>73</sup>. The proposed pathway involves initial coordination of the alcohol solvent, the deprotonation of which affords an alkoxo complex. A concerted hydride shift from the alkoxo to the allyl ligand affords the organic product with concomitant reduction of Pd. Although this mechanism is relevant to the Suzuki–Miyaura reaction, the pathway by which such precatalysts undergo activation is still unclear when other solvents and/or different ligands are used.

The mechanistic work on precatalysts featuring Pd ligated to  $\eta^3$ -allyl or  $\eta^3$ -cinnamyl was followed by the discovery that complexes bearing  $\eta^3$ -indenyl are more quickly reduced to their active Pd(0) species<sup>73</sup>. However, despite these increased activation rates, the  $[(\eta^3$ -



indenyl)Pd(IPr)Cl] precatalyst has a high propensity to convert to an inactive dipalladium(i)  $\mu$ -indenyl dimer during catalysis<sup>74</sup>. This problem was addressed by installing a *tert*-butyl substituent in the 1-position of the  $\eta^3$ -indenyl scaffold. The optimized [( $\eta^3$ -1-*t*-Bu-indenyl)Pd(IPr)Cl] precatalyst, which can be prepared on a large scale, is significantly more active than the state-of-the-art [( $\eta^3$ -cinnamyl)Pd(IPr)Cl] species for simple Suzuki–Miyaura reactions<sup>74</sup>.

Using this improved system, a range of bench-stable precatalysts of the formula [( $\eta^3$ -1-*t*-Bu-indenyl)Pd(L)Cl] were synthesized by ligand substitution reactions of the easily prepared dimeric precursor [( $\eta^3$ -1-*t*-Bu-indenyl)<sub>2</sub>Pd<sub>2</sub>( $\mu$ -Cl)<sub>2</sub>] (REF. 74). Both NHC and phosphine ligands, including sterically bulky systems, react with [( $\eta^3$ -1-*t*-Bu-indenyl)<sub>2</sub>Pd<sub>2</sub>( $\mu$ -Cl)<sub>2</sub>], and the precatalysts formed — either used *in situ* or after isolation — are readily amenable for ligand screening. So far it has been demonstrated that precatalysts based on [( $\eta^3$ -1-*t*-Bu-indenyl)Pd(L)Cl] are highly active for Suzuki–Miyaura reactions to form tetra-*ortho*-substituted biaryls using aryl chlorides, Buchwald–Hartwig reactions involving secondary amine substrates, Suzuki–Miyaura reactions with heteroaryl chlorides and boronic acids,  $\alpha$ -arylation reactions with aryl methyl ketones, and Suzuki–Miyaura couplings between alkyl trifluoroborate salts and aryl chlorides<sup>74</sup> (FIG. 2d). Furthermore, the first room temperature Suzuki–Miyaura couplings of aryl sulfamates facilitated by a Pd catalyst were recently described utilizing a strategy involving rapid ligand screening starting from dimeric [( $\eta^3$ -1-*t*-Bu-indenyl)<sub>2</sub>Pd<sub>2</sub>( $\mu$ -Cl)<sub>2</sub>] (REF. 75). These results were used to develop the first catalysts for Hiyama–Denmark reactions with aryl sulfamates, successfully pairing an electrophile that can be prefunctionalized before cross-coupling using directed C–H activation with less mutagenic arylsilanol nucleophiles<sup>75</sup>.

## Pd(I) precatalysts

**Bridging halide precatalysts**—The majority of the recent contributions describing Pd(i) precatalysts are from the Schoenebeck group. In 2012, they reported that the active species in catalysis using the popular [(P<sup>*t*</sup>Bu<sub>3</sub>)<sub>2</sub>Pd<sub>2</sub>( $\mu$ -Br)<sub>2</sub>] precatalyst is dependent on the specific catalytic conditions<sup>76</sup> (FIG. 3a). However, in all cases, Pd(0) complexes are still the catalytically active species. Surprisingly, disproportionation of the Pd(i) precatalyst into Pd(0) and Pd(ii) complexes was calculated to be unfavourable for activation, with the lowest energy pathway instead involving homolytic dissociation of the dimeric precatalyst, followed by reduction of the resulting monomeric Pd(i) complexes to the catalytically active species<sup>76</sup>. By contrast, a unique, non-cross-coupling application of [(P<sup>*t*</sup>Bu<sub>3</sub>)<sub>2</sub>Pd<sub>2</sub>( $\mu$ -Br)<sub>2</sub>], which is proposed to involve Pd(i) intermediates, is a halogen-exchange reaction that generates aryl bromides from aryl iodides<sup>77</sup>.

Much of the work performed on Pd(i) precatalysts in the past 3 years has involved the air-stable iodo analogue of [(P<sup>*t*</sup>Bu<sub>3</sub>)<sub>2</sub>Pd<sub>2</sub>( $\mu$ -Br)<sub>2</sub>] (REF. 78). Schoenebeck has demonstrated that although the bridging bromo species releases Pd(0) efficiently<sup>76</sup>, [(P<sup>*t*</sup>Bu<sub>3</sub>)<sub>2</sub>Pd<sub>2</sub>( $\mu$ -I)<sub>2</sub>] is more prone to react from the +i oxidation state<sup>77–80</sup> (FIG. 3). Two specific examples of this are the catalytic trifluorothioetherification<sup>80</sup> or trifluoromethylselenoetherification<sup>78</sup> of aryl iodides and bromides facilitated by [(P<sup>*t*</sup>Bu<sub>3</sub>)<sub>2</sub>Pd<sub>2</sub>( $\mu$ -I)<sub>2</sub>]. For each of these reactions, the nucleophile replaces the bridging iodo ligand, although the dimeric structure is proposed to

remain intact during catalysis (FIG. 3b,c). In these cases, the reactivity of the Pd(i) form may provide an orthogonal synthetic route to important functional groups (FIG. 3b). In complementary research, it was demonstrated that more basic nucleophiles ‘open’ the  $[(P^tBu_3)_2Pd_2(\mu-I)_2]$  dimer to generate LPd(0) (REF. 78). For example, using  $[(P^tBu_3)_2Pd_2(\mu-I)_2]$  as the precatalyst, Kumada reactions proceed very rapidly (<5 min) even at room temperature<sup>78</sup>. Despite the benefits and unique reactivity that  $[(P^tBu_3)_2Pd_2(\mu-Br)_2]$  and  $[(P^tBu_3)_2Pd_2(\mu-I)_2]$  offer, there are very few examples of related Pd(i) dimers with ancillary ligands other than  $P^tBu_3$ .

## Pd(0) precatalysts

**Bridging cyclooctadiene precatalysts**—Despite the consensus that the active catalytic species during cross-coupling reactions are typically Pd(0) complexes, examples of Pd(0) precatalysts are rare, largely owing to the inherent instability of Pd(0) species to air and moisture compared with Pd(ii) complexes<sup>10</sup>. Although early cross-coupling methodology called for the addition of excess ligand to a Pd(0) source, this has several drawbacks in terms of cost and catalytic efficiency. However, the discovery of stable Pd(0) precatalysts brings with it an obvious benefit, allowing one to eschew complicated activation processes.

In 2013, Buchwald and co-workers<sup>81</sup> reported that the use of preformed Pd(ii) precatalysts was detrimental to the fluorination of aryl triflates. Use of the bulky ligand AdBrettPhos in conjunction with  $[(\eta^3\text{-cinnamyl})_2Pd_2(\mu-Cl)_2]$  produced promising results, but it was discovered that chloride released during activation was preventing further improvement of this methodology. Similarly, a Pd(ii) palladacycle with AdBrettPhos failed to give better results owing to the acidic nature of the activation by-products. To address these issues, Buchwald and co-workers developed Pd(0) precatalysts of the general formula  $[(LPd)_n(COD)]$  (COD = 1,5-cyclooctadiene,  $n = 1$  or  $2$ ; FIG. 3d). To demonstrate the propensity of the precatalyst to convert to an active monoligated Pd(0) complex, it was shown that the AdBrettPhos-ligated precatalyst undergoes oxidative addition with 4-(*n*-butyl)phenyl triflate in 10 minutes at room temperature. Using this same precatalyst, nucleophilic fluorination can be achieved using aryl triflates, bromides and iodides<sup>82</sup>. Further optimization of the ancillary ligand has resulted in precatalysts that are able to perform room temperature fluorination using both aryl triflates and bromides<sup>83</sup>.

A potentially important application of the COD-ligated Pd(0) precatalysts is the cyanation of aryl halides<sup>84</sup>. Using a Buchwald Pd(ii) palladacycle precatalyst, temperatures of 100 °C and reaction times of 1 hour were required when XPhos was used as the ancillary ligand. However, when  $[(^tBuXPhosPd)_2(\mu-COD)]$  was used as the precatalyst, complete conversion could be achieved at room temperature in just 1 minute. This could enable the mild and rapid incorporation of <sup>11</sup>C — a radioactive isotope with a short half-life — into organic molecules for use in positron emission tomography.

The  $[(LPd)_n(\mu-COD)]$  precatalyst has several positive attributes, not least of which are its ability to ligate very sterically bulky phosphine ligands with proven catalytic capabilities, as well as simple activation that does not involve harmful by-products. One of the current drawbacks of this system is the difficulty in fully characterizing the precatalyst<sup>85</sup>. Owing to its low solubility in most organic solvents, NMR spectroscopy cannot be used to



characterize the system, regardless of the identity of the ancillary ligand. Currently, indirect evidence for the precatalyst structure is obtained by monitoring the reaction of  $[(LPd)_n(\mu-COD)]$ -type precatalysts with electrophiles and characterizing the products of these reactions. For example, reactions of  $[(LPd)_n(\mu-COD)]$  with 4-(*n*-butyl)phenyl bromide liberate COD along with  $\sigma$ -aryl Pd(ii) complexes of the type  $[(L)Pd(4-n\text{-butylphenyl})Br]$ , which can be fully characterized by NMR and X-ray crystallography. More recently, one example of this precatalyst system has been characterized by X-ray crystallography using the newly designed AlPhos ligand<sup>83</sup> (FIG. 3e). Another limitation of this precatalyst class is that it is not stable in solution<sup>81</sup>, which is problematic for using stock solutions for catalysis. The introduction of these Pd(0) precatalysts in paraffin wax capsules could offer a practical solution to this problem<sup>86</sup>.

## Ni-based precatalysts

As part of the current trend towards the replacement of precious metal catalysts with those based on earth-abundant metals<sup>87</sup>, there is significant interest in the development of Ni precatalysts as alternatives to Pd systems<sup>12–14</sup>. Furthermore, in comparison to the reactivity of its precious metal counterparts (such as Pd), Ni readily undergoes one-electron redox chemistry<sup>12,14,88</sup>. In this section, we summarize the use of Ni precatalysts in different oxidation states in cross-coupling reactions.

### Ni(II) precatalysts of the form $[L_nNiX_2]$

There are numerous examples of Ni(ii) precatalysts with two halo ligands (FIG. 4). One possible pathway by which these complexes are activated is transmetalation of both halo ligands by the nucleophile in cross-coupling. This is followed by reductive elimination of an organic by-product, although this process has not been studied. More commonly, these precatalysts are used with elemental reductants, such as Mn or Zn, which reduce Ni(ii) to Ni(0) (REF. 89). Unfortunately, these reductants reduce functional group tolerance. An advantage of precatalysts of the form  $[L_nNiX_2]$  is that they are generally stable in air and straightforward to synthesize through the ligation of Ni(ii) halide salts with ancillary ligands<sup>14,88</sup>. Furthermore, these systems are cost-effective, because they are usually derived from inexpensive ligands and base metal salts<sup>12,14</sup>. In general, triphenylphosphine (PPh<sub>3</sub>) and tricyclohexylphosphine (PCy<sub>3</sub>) are the most popular monodentate ligands, whereas bis(diphenylphosphino)alkanes and 1,1'-bis(diphenylphosphino)ferrocene (dppf) are the most common bidentate ligands. An additional weakness of such precatalysts is their low solubility, which can prevent reactions from being performed at ambient temperatures in non-polar solvents. Furthermore, there are few reports of these precatalysts being used in rapid ligand screening.

**$[(PPh_3)_2NiX_2]$** —In 1979, Wenkert *et al.*<sup>90</sup> reported that  $[(PPh_3)_2NiCl_2]$ , in combination with methyl- or phenylmagnesium bromide, catalysed both the arylation or alkylation of enol ethers and the arylation of aryl ethers. Subsequently, more than 20 years later, it was demonstrated that  $[(PPh_3)_2NiCl_2]$  catalyses Suzuki–Miyaura reactions with aryl halides in the presence of an excess of PPh<sub>3</sub> (REF. 91). These results were extended by Mizojiri *et al.*<sup>92,93</sup> who showed that non-classical electrophiles, including aryl mesylates, tosylates and

allyl carbonates, could be coupled with lithium arylborates under mild conditions with  $[(PPh_3)_2NiCl_2]$ . Recently, Percec and co-workers<sup>89,94</sup> demonstrated that  $[(PPh_3)_2NiCl_2]$  can effectively perform Suzuki–Miyaura reactions with both pseudohalides and phenol derivatives, such as sulfamates and carbamates, which can be used as directing groups in C–H functionalization reactions. Other non-classical electrophiles that can be used in coupling reactions with this precatalyst include 1,3-disubstituted secondary allylic carbonates in Suzuki–Miyaura reactions<sup>95</sup> and amides in Negishi reactions<sup>96</sup>. Although the dichloro is the most common, the dibromo congener  $[(PPh_3)_2NiBr_2]$  has also been used as a precatalyst and is competent for the homocoupling of aryl, alkyl and pyridyl halides in the presence of elemental Zn (REFS 97,98). Notably, 1,2-diphenylethane species can also be synthesized using this methodology through the homocoupling of benzyl chlorides and bromides<sup>97</sup>.

**$[(PCy_3)_2NiX_2]$** — $[(PCy_3)_2NiCl_2]$  is unique in its emergence as an almost universal dihalide precatalyst for the coupling of a wide array of electrophiles in Suzuki–Miyaura reactions. Along with traditional aryl halides, it can also couple heteroaryl halides<sup>99</sup>, as well as aryl mesylates<sup>99</sup>, carbamates<sup>99–103</sup>, carbonates<sup>100</sup>, sulfamates<sup>99,101</sup>, phosphates<sup>104</sup>, nitriles<sup>105</sup>, twisted amides<sup>106</sup> and pivalates<sup>99,100,107</sup> with boronic acids, boroxines or mixtures of both nucleophiles. In a particularly elegant demonstration of this chemistry, Garg and co-workers<sup>100</sup> synthesized the anti-inflammatory drug flurbiprofen by directed prefunctionalization of an aryl sulfamate before using the functionalized sulfamate as the electrophile in cross-coupling. Additionally,  $[(PCy_3)_2NiCl_2]$  can facilitate the Suzuki–Miyaura reaction of alkenyl acetates<sup>108</sup> and  $\alpha$ -pivaloxyl ketones<sup>109</sup>, indicating that this precatalyst is compatible with both alkenyl and aryl electrophiles.

Apart from Suzuki–Miyaura reactions,  $[(PCy_3)_2NiCl_2]$  has also been used in Kumada couplings. It can facilitate the reactions of methylmagnesium bromide or *p*-tolylmagnesium bromide with aryl ethers<sup>110</sup>, which are unusual electrophiles for Kumada reactions<sup>111</sup>. In related work, Jarvo and co-workers<sup>112</sup> also showed that  $[(PCy_3)_2NiCl_2]$  can mediate the stereospecific cyclization of secondary ethers in the presence of methylmagnesium iodide, despite the precatalyst being achiral. Other interesting reactions that are relevant to cross-coupling mediated by this precatalyst include the carboxylation of benzyl halides in the presence of elemental Zn (REF. 113) as well as the methylation of aromatic C–H bonds<sup>114</sup>.

**$[(dppf)NiX_2]$** —The bidentate, ferrocenyl-based ligand dppf is historically significant in Ni-catalysed cross-coupling reactions because it was one of the first to be successfully used in catalysis. In 1995, Percec *et al.*<sup>115</sup> described the coupling of aryl mesylates and sulfonates with arylboronic acids. The  $[(dppf)NiCl_2]$  precatalyst was proposed to be reduced to the putative catalytically active  $(dppf)Ni(0)$  species with elemental Zn. Around the same time, the Kobayashi group<sup>95</sup> described the coupling of 1,3-disubstituted secondary allylic carbonates with lithium aryl- and alkenylborates. Subsequently, in 1997, Miyaura and co-workers<sup>116</sup> reported the coupling of aryl chlorides and arylboronic acids with  $[(dppf)NiCl_2]$  that had been activated with butyllithium.

In the past 10 years, it has been demonstrated that  $[(dppf)NiCl_2]$  can activate benzylic ethers with alkylmagnesium bromides to generate alkylated naphthalene species<sup>117</sup>. Intriguingly, naphthalenes substituted with both methoxy groups and benzylic ethers could be

orthogonally coupled; use of  $[(PCy_3)_2NiCl_2]$  as the precatalyst led to the activation of the methoxy substituent, whereas the use of  $[(dppf)NiCl_2]$  as a precatalyst facilitated the activation of the benzylic group. Other C–O electrophiles that can be coupled using  $[(dppf)NiCl_2]$  are naphthyl pivalates in direct carboxylation reactions with  $CO_2$  using Mn as a stoichiometric reductant<sup>118</sup>.

**$[(dppp)NiX_2]$** —The precatalyst  $[(dppp)NiCl_2]$  (dppp = 1,3-bis(diphenylphosphino)propane) generates one of the most active systems for Suzuki–Miyaura reactions involving aryl chlorides and bromides<sup>119</sup>. It can successfully couple a wide array of substrates at only 1 mol% catalyst loading without the need for any exogenous ligands. This precatalyst has even been used to perform a Suzuki–Miyaura reaction in the synthesis of boscalid, a pesticide prepared on an industrial scale<sup>12</sup>. Similar to other Ni(ii) systems, phenolic derivatives, including aryl sulfonates<sup>120</sup>, tosylates<sup>120</sup>, mesylates<sup>120</sup> and sulfamates<sup>121</sup>, can be used as electrophiles in Suzuki–Miyaura reactions. The yields are similar to those using other systems but can be obtained using a significantly lower precatalyst loading (1–1.5 mol% compared with >5 mol%). Unique to this precatalyst is its ability to couple phenols through *in situ* derivatization using bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) in the same pot as boronic acids<sup>122</sup>. Borylations of heteroaryl bromides, chlorides, mesylates, tosylates, triflates and sulfamates using the boron reagent tetrahydroxydiboron are also possible using a remarkably low catalyst loading of only 1 mol%<sup>123</sup>. Finally, the first reports of Kumada couplings of aryl carbamate electrophiles were performed using  $[(dppp)NiCl_2]$  as the precatalyst<sup>124</sup>.

**$[(dppe)NiX_2]$** —The bidentate ligand 1,2-bis(diphenylphosphino)ethane (dppe) differs from dppp only in the length of the alkyl chain. Nevertheless,  $[(dppe)NiCl_2]$  often exhibits slightly better activity than its  $[(dppp)NiCl_2]$  analogue. In fact, Percec and co-workers<sup>125</sup> undertook a comparative ligand screen for Suzuki–Miyaura couplings of aryl chlorides, mesylates and tosylates, which indicated that  $[(dppe)NiCl_2]$  with an extra equivalent of dppe outcompeted the other supporting ligands examined, namely, 1,3-bis(diphenylphosphino)butane (dppb), dppf,  $PPh_3$  and  $PCy_3$ . In subsequent work, Percec<sup>126</sup> showed that  $[(dppe)NiCl_2]$  could catalyse the initial pinacolborylation or neopentylglycolboronation of aryl halides followed by cross-coupling of aryl halides with the generated boron nucleophiles. The  $[(dppe)NiCl_2]$  precatalyst has also been extensively used in Kumada couplings. Jarvo and co-workers reported the alkylation of secondary ethers<sup>127</sup> and the ring opening of oxygen-containing heterocycles with alkyl Grignard reagents<sup>128</sup>. The alkylation of allylic alcohols and ethers has also been reported with methylmagnesium iodide and  $[(dppe)NiCl_2]$  as a precatalyst<sup>129,130</sup>.

**$[(dtbbpy)NiX_2]$  and other nitrogen-containing analogues**—The precatalyst  $[(dtbbpy)NiBr_2]$  (dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) as well as chelates of other N-donor ligands have proven useful in coupling unusual substrates. For example,  $[(dtbbpy)NiBr_2]$  can be used to couple acyl-type electrophiles, which are readily available synthetically. Recently,  $[(dtbbpy)NiBr_2]$  was used by the group of Weix<sup>131</sup> to facilitate cross-electrophile couplings of aryl and alkyl halides in the presence of the organic reductant tetrakis(dimethylamino)ethane in non-amide solvents. Alternatively, the same group

demonstrated<sup>132</sup> that a non-photoredox- initiated decarboxylative coupling between aryl iodides and *N*-hydroxyphthalimide ester electrophiles could be catalysed by [(dtbbpy)NiBr<sub>2</sub>] over elemental Zn. The precedent for this chemistry lies, in part, in reports describing the electrochemical synthesis of ketones from alkyl and aryl electrophiles using [(bpy)NiBr<sub>2</sub>] or [(bpy)<sub>3</sub>Ni](BF<sub>4</sub>)<sub>2</sub> (bpy = 2,2'-bipyridine)<sup>133,134</sup>. These are highly unusual reactions, and there are few other precatalysts that can couple such electrophiles, notable exceptions being the coupling of twisted amides through [(PCy<sub>3</sub>)<sub>2</sub>NiCl<sub>2</sub>]-mediated C–N bond cleavage<sup>106</sup>, and the coupling of carboxylic anhydrides using [(PPh<sub>3</sub>)<sub>2</sub>Ni(1-naphthyl)Cl] (REF. 35). From these results it is evident that nitrogen-containing precatalysts are important in new reactions that can activate atypical electrophiles. However, there are still relatively few reported applications of well-defined precatalysts with N-donor ligands.

### Ni(II) precatalysts of the form [L<sub>n</sub>Ni(Ar)X]

Although extra steps are required to prepare  $\sigma$ -aryl complexes of the form [L<sub>n</sub>Ni(Ar)X] (REF. 136) (FIG. 5a), they are often preferred to dihalide precatalysts because they are generally bench-stable, are activated by milder nucleophiles, have greater solubility in many solvents and can be used for ligand screening<sup>137–140</sup>. Additionally, it has been demonstrated that this class of precatalyst is compatible with sterically bulky ligands that stabilize highly active cross-coupling catalysts, such as PAd-DalPhos (REF. 141), whereas most Ni precatalysts have only been used with more traditional monophosphines such as PPh<sub>3</sub> or PCy<sub>3</sub>. Activation of precatalysts of the type [L<sub>n</sub>Ni(Ar)X] generally involves transmetalation of the halo ligand with the nucleophile in cross-coupling followed by reductive elimination<sup>140,142,143</sup>. So far, there has been limited examination of the rates of the activation process under different reaction conditions, and detailed studies exploring this topic would assist in the optimization of reactions<sup>140</sup>.

**[L<sub>n</sub>Ni(1-naphthyl)X]**—It was demonstrated in 1973 that [(PCy<sub>3</sub>)<sub>2</sub>Ni(1-naphthyl)Cl] could be used as a precatalyst for the cyanation of aryl halides<sup>144</sup>. Despite this seminal work, there were relatively few additional reports describing the use of  $\sigma$ -aryl complexes as precatalysts for cross-coupling until the late 2000s. Since then, both the Yang and Percec laboratories have shown [(PCy<sub>3</sub>)<sub>2</sub>Ni(1-naphthyl)Cl] to be an efficient precatalyst for Suzuki–Miyaura reactions involving aryl halides<sup>145</sup>, tosylates<sup>145,146</sup>, sulfonates<sup>145</sup>, sulfamates<sup>94</sup> and mesylates<sup>94</sup>. In fact, [(PCy<sub>3</sub>)<sub>2</sub>Ni(1-naphthyl)Cl] is able to promote Suzuki–Miyaura coupling of aryl sulfamates with neopentylglycolboronates at room temperature<sup>147</sup>. Recently, [(PPh<sub>3</sub>)<sub>2</sub>Ni(1-naphthyl)Cl] has proven to be effective in Suzuki–Miyaura reactions that convert carboxylic anhydride electrophiles to diarylketones, highlighting the ability of this precatalyst to activate electrophiles that are harder to oxidatively add than aryl halides<sup>135</sup>. Additionally, [(PPh<sub>3</sub>)<sub>2</sub>Ni(1-naphthyl)Cl] is a precatalyst for Buchwald–Hartwig amination reactions involving aryl chlorides<sup>148</sup> and tosylates<sup>149</sup>.

**[L<sub>n</sub>Ni(*o*-tolyl)X]**—Known since 1999 to facilitate Suzuki–Miyaura reactions<sup>150</sup>, the [L<sub>n</sub>Ni(*o*-tolyl)X] scaffold has proven useful in several different cross-coupling reactions and is compatible with a range of ligands differing in both denticity and the type of donor atom. On many occasions this precatalyst leads to superior activity when compared directly with other Ni(0) and Ni(ii) precatalysts<sup>137,142,151</sup>, such that this *o*-tolyl scaffold is currently

considered one of the state-of-the-art Ni precatalysts for cross-coupling. For example, even low loadings of [(dppf)Ni(*o*-tolyl)Cl] enable coupling of heteroaryl chlorides and aryl sulfamates with boronic acids at ambient temperatures<sup>140,142</sup>. Additionally, when ligated with the bidentate phosphines PAd-DalPhos<sup>141</sup> or dppf<sup>137</sup>, this precatalyst system can mediate the Buchwald–Hartwig amination of heteroaryl halides and pseudohalides. In fact, [(PAd-DalPhos)Ni(*o*-tolyl)Cl] generates an active catalyst that allows the use of ammonia as the nucleophile in such reactions and is an example of the use of this precatalyst class with some of the most recently developed ligands for cross-coupling. The [L<sub>n</sub>Ni(*o*-tolyl)X] precatalyst class is also compatible with monophosphine ligands, with the benzylation of terminal alkenes being possible with the dicyclohexylphenylphosphine complex [(PCy<sub>2</sub>Ph)<sub>2</sub>Ni(*o*-tolyl)Cl]<sup>152</sup>. In related work, Cavell and co-workers<sup>150</sup> demonstrated this system to be compatible with NHC ligands as well, their coupling of aryl bromides and aryl boronic acids using [(tmly)Ni(*o*-tolyl)Cl] (tmly = 1,3,4,5-tetramethylimidazol-2-ylidene) being the first example of an NHC-ligated arylnickel complex in such reactions.

The nitrogen chelate complex [(TMEDA)Ni(*o*-tolyl)Cl] (TMEDA = *N,N,N',N'*-tetramethylethylenediamine), which was simultaneously reported by the groups of Doyle<sup>143</sup> and Monfette<sup>153</sup>, is of particular significance to rapid ligand screening. When mixed with ligands such as phosphines or NHCs, it generates active precatalysts for the Suzuki–Miyaura, Heck and Buchwald–Hartwig coupling reactions, as well as for cyclization and  $\alpha$ -arylation reactions. The high activity of the catalyst system allows for mild conditions to be used. This system is one of the first bench-stable Ni-based precatalysts suitable for ligand screening and compatible with a large range of ligands. However, one drawback is the potential for the free TMEDA to poison some catalytic reactions<sup>143</sup>.

### Ni(II) precatalysts of the form [L<sub>n</sub>Ni(allyl)X]

The first reports of allyl- and cyclopentadienyl (Cp)-based precatalysts in Ni-catalysed cross-coupling reactions (FIG. 5b) appeared much later than those describing Ni(ii) dihalide and  $\sigma$ -aryl precatalysts. Although allyl- and Cp-based precatalysts are bench-stable<sup>15,154,155</sup>, they are slightly more difficult to synthesize than dihalide or  $\sigma$ -aryl precatalysts. However, this class of precatalyst is significant because, like their  $\sigma$ -aryl counterparts, these species can be activated without the use of elemental reductants. Furthermore, in some cases they have been used in cross-coupling reactions that have not been performed with other types of Ni precatalyst. At the time of writing, their mechanism of activation is not well understood, yet their robustness and activity will no doubt motivate further work in this area<sup>15</sup>.

**[L<sub>n</sub>Ni(Cp)X]**—The utility of Ni precatalysts in coupling aryl sulfamates after directed *ortho*-metallation was described by the Snieckus group<sup>156</sup> in 2005. In this pioneering work, [(IMes)Ni(Cp)Cl] was used to form biaryls from phenyl sulfamates and arylmagnesium bromides. Since this report, several other classes of precatalyst have been used to facilitate this transformation. Furthermore, CpNi species bearing a range of NHCs were found by Nolan and colleagues<sup>157</sup> to promote thioaryl addition to alkynes. Nolan also described a CpNi complex of the bulky NHC IP<sub>r</sub>\*OMe that catalyses the Buchwald–Hartwig amination of aryl chlorides<sup>154</sup>.

**[L<sub>n</sub>Ni(allyl)X] and [L<sub>n</sub>Ni(cinnamyl)X]**—Precatalysts incorporating an allyl ligand have been used to facilitate interesting reactions somewhat outside the realm of standard cross-coupling chemistry. The Nolan group<sup>155</sup> reported the  $\eta^3$ -allyl complex [(allyl)Ni(IPr)Cl] to effect the conversion of aryl chlorides, bromides and iodides to amines and thioethers. Replacing the carbene ligand with IPr\*<sup>OMe</sup> allows for the carboxylation of organoborates, giving carboxylic acids upon acidic workup<sup>158</sup>. The use of the cinnamyl group as a supporting ligand in the precatalyst [(cinnamyl)Ni(dppf)Cl] resulted in a system that could perform Suzuki–Miyaura reactions between heteroaryl chlorides and heteroaryl boronic acids at catalyst loadings as low as 0.5 mol%<sup>15</sup>. When the cinnamyl complex is ligated by IPr\* or IPr\*<sup>OMe</sup> instead of dppf,  $\alpha$ -arylations are possible. Indeed, this precatalyst has been used to synthesize an intermediate en route to nafoxidine, which is a drug used to treat breast cancer<sup>159,160</sup>.

### Ni(I) precatalysts

Ni is considerably more likely than Pd to access odd-electron oxidation states. Consequently, although coupling reactions involving aryl substrates are thought to proceed via intermediates with the metal in the 0 and +ii oxidation states (similar to Pd), Ni(i) species are much more likely to form in catalysis as off-cycle species<sup>14,140</sup>. By contrast, for coupling reactions involving alkyl substrates, it is often probable that Ni(i) species are in fact in the catalytic cycle<sup>161</sup>, which partly explains the superior reactivity of Ni compared with that of Pd for these systems. Nevertheless, Ni(i) species capable of catalysing cross-coupling reactions with either aryl or alkyl substrates are of mechanistic interest. The relative paucity of Ni(i) precatalysts may soon change, especially given that the scope of reactions they catalyse is comparable to that of their Ni(0) and Ni(ii) analogues. As is the theme of this Review, the rational development of new Ni(i) precatalysts will rest on elucidating their activation pathways, which are presently not well understood.

Similar to Ni(ii) and Ni(0) precatalysts, Ni(i) precatalysts can promote both the Suzuki–Miyaura and Kumada couplings of aryl halides. Louie and co-workers<sup>162</sup> showed that the three-coordinate complex [(IMes)<sub>2</sub>NiBr] was a precatalyst for both reactions, and it has been demonstrated that [(dppf)NiCl] can perform Suzuki–Miyaura couplings with naphthyl chlorides<sup>142</sup> (FIG. 5c). Ni(i) species are also precatalysts for the coupling of alkyl substrates. The Vicic group<sup>161</sup> reported that [(terpyridine)Ni(CH<sub>3</sub>)] (terpyridine = 2,6-bis(2-pyridyl)pyridine) can facilitate the coupling of alkyl halide electrophiles and organozinc nucleophiles. Similarly, Doyle and co-workers<sup>163</sup> demonstrated [(bpp)NiCl] (bpp = 2,6-bis(*N*-pyrazolyl)pyridine) to be competent for coupling dialkyl ethers with aryl iodides in the presence of metallic Zn as a reductant and TMSCl (TMS = trimethylsilyl) as a Lewis acid. Considering the heightened attention towards the role of Ni(i) in cross-coupling, it is possible that more precatalysts in this oxidation state will be developed.

### Nickel(0) precatalysts

One of the major advantages of using Ni(0) precatalysts is that a reductant is not needed in their activation. Instead, a ligand simply needs to dissociate from the metal centre to open a coordination site. By far the most common Ni(0) precatalyst is [Ni(COD)<sub>2</sub>], which is typically mixed with the appropriate ligand to generate a more electron-rich complex *in situ*.



However,  $[\text{Ni}(\text{COD})_2]$  is relatively expensive, thermally unstable and air-sensitive<sup>13,136,153</sup>. With respect to the latter, it has recently been shown that  $[\text{Ni}(\text{COD})_2]$  can be encapsulated in paraffin capsules so that it can be used under aerobic conditions; the problems associated with its cost and thermal stability remain<sup>164</sup>. A large number of systems utilize  $[\text{Ni}(\text{COD})_2]$ , and this Review focuses on recent examples of preformed Ni(0) complexes with ancillary ligands that stabilize the catalytically active species. An advantage of these systems compared with  $[\text{Ni}(\text{COD})_2]$  is that in many cases excess free ligand, which can interfere in catalysis, is not required, although it should be noted that these systems are also generally air-sensitive.

**Ni(0) phosphine precatalysts**—Examples of preformed phosphine-ligated Ni(0) precatalysts are rare, with the most common method for accessing Ni(0) phosphines in catalysis involving combining  $[\text{Ni}(\text{COD})_2]$  and exogenous ligand to generate a precatalyst *in situ*. However, well-defined homoleptic and heteroleptic examples of Ni(0) precatalysts exist and have been used in Suzuki–Miyaura and Negishi cross-coupling reactions, as well as other C–C bond forming reactions. The Louie group<sup>165</sup> developed the homoleptic precatalyst  $[\text{Ni}(\text{Xantphos})_2]$  (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (FIG. 5d) for the Negishi coupling of naphthyl bromides and vinylzinc bromide. The related complex  $[\text{Ni}(\text{dppf})_2]$  can facilitate the Suzuki coupling of naphthyl halides under ambient conditions as well<sup>142</sup>. Monophosphine complexes are also useful, and  $[\text{Ni}(\text{PPh}_3)_4]$  is active for the inter- and intramolecular homocoupling of aryl and alkenyl halides to give cyclic biaryl products<sup>166</sup>. Heteroleptic examples of Ni(0) precatalysts include  $[(\text{dcype})\text{Ni}(\text{CO})_2]$  (dcype = 1,2-bis(dicyclohexylphosphino)ethane) for the decarbonylative C–H coupling of azoles and esters<sup>167</sup>, and  $[(\text{dppf})\text{Ni}(\eta^2\text{-C}_2\text{H}_4)]$  for the Suzuki–Miyaura coupling of naphthyl chloride<sup>142</sup>.

**Ni(0) NHC precatalysts**—In an analogous manner to phosphine-ligated Ni(0) precatalysts, the most common method for the generation of NHC-supported Ni(0) precatalysts is to add exogenous ligand to Ni(0) sources. Notable exceptions are NHC-ligated Ni(0) dimers from the group of Radius; such COD-bridged species are able to facilitate the Suzuki–Miyaura coupling of benzyl chloride electrophiles<sup>168</sup> or perfluorinated arene electrophiles<sup>169</sup>. Radius<sup>170</sup> has also reported the monomeric precatalyst  $[\text{Ni}(\text{IMes})_2]$  for the borylation of aryl fluorides. In terms of heteroleptic precatalysts, both the Buchwald–Hartwig amination of aryl tosylates<sup>171</sup> and the C–N coupling of indoles and carbazoles with aryl chlorides<sup>172</sup> can be mediated by the precatalyst  $[(\text{IPr})\text{Ni}(\eta^2\text{-styrene})_2]$ .

## Comparison of Pd and Ni precatalysts

For the vast majority of cross-coupling reactions enabled by both Pd and Ni precatalysts, a Pd-based system is likely to operate at lower catalyst loadings, milder temperatures, and require a lower number of equivalents of base and nucleophile, where appropriate. Although the superior activity of Pd catalysts can be partially attributed to inherent differences in reactivity between the two metals, historically there has been greater development of ancillary ligands and precatalysts for Pd than for Ni. This may be another reason for the greater activity of Pd systems described thus far. Currently, the best Pd precatalysts can be used for a wide range of cross-coupling reactions, are compatible with state-of-the-art

ligands, and have bench-stable and labile precursors, that can be used in conjunction with these ligands in efficient screening processes. Two minor challenges that still need to be addressed for Pd systems are the development of more systems that are compatible with both phosphine and NHC ligands, as well as the ligands of extreme steric bulk often required for challenging cross-coupling reactions.

In contrast to the well-trodden paths of Pd catalysis, there is room for considerable improvement in the development of Ni-based precatalysts. This is particularly important given that there are certain cross-coupling reactions in which Ni displays significantly better activity than Pd-based systems, and in many of them, such as those in which  $sp^3$ -hybridized C centres are coupled, precatalysts are rarely used at the moment. Additionally, many 'modern' cross-coupling reactions, such as photoredox-initiated processes and cross-electrophile reactions, are performed almost exclusively using Ni-based systems<sup>173–176</sup>. Despite the popularity of such methodology, to our knowledge, there has been no reported use of preformed Ni precatalysts for photoredox coupling reactions, with the limited examples mentioned in this Review being for cross-electrophile couplings. At this stage, it appears that bidentate N-donor ligands are optimal for these new types of cross-coupling reactions compared with phosphine and NHC ligands, which are preferred for standard cross-couplings. However, in comparison to phosphine- and NHC-ligated precatalysts, there is a lack of accessible systems containing suitable N-donor ligands, which prevents precatalyst development.

The rational development of nickel precatalysts is also slowed, in part, by the lack of bench-stable systems that are readily activated by mild reagents and that are also amenable for use in ligand screening. There are relatively few precatalysts compatible with the three classes of ligand commonly used in Ni-catalysed cross-coupling: NHCs, and neutral P- and N-donors. Finally, at this stage, the ambiguity over the role of metalloradicals in Ni-catalysed cross-coupling reactions complicates the rational design of Ni precatalysts, because the nature of the active species in catalysis is not always clear. For comparison, well-defined Pd precatalysts were designed after it was determined that a coordinatively unsaturated Pd(0) species is required for efficient catalysis. Thus, increased mechanistic understanding of Ni-catalysed cross-coupling is probably required before more efficient precatalysts can be developed.

## Conclusions and outlook

After almost 20 years of research, it is clear that well-defined precatalysts offer substantial benefits over other methods for generating the active species in cross-coupling reactions, such as mixing large amounts of free ligand with a Ni(0) or Pd(0) species. Therefore, it is surprising that the use of well-defined precatalysts is not more common, especially given the discovery of numerous bench-stable Pd systems that are commercially available, undergo facile activation and can be synthesized on a large scale. The future will probably see the development of Ni analogues of these Pd systems, which may see the use of the relatively expensive complex  $[\text{Ni}(\text{COD})_2]$  decline and lead to more efficient catalysts. Although it would be convenient if there was a universal precatalyst optimized for most reactions, in reality this is unlikely. Instead, we expect that, as is currently the case for Pd, researchers

will have a suite of precatalysts to select between, and different systems will be the most active depending on the exact nature of the cross-coupling reaction and the reaction conditions. In practice, a simple screen of precatalysts will determine the most active metal system, with a subsequent ligand screen using that precatalyst resulting in the optimal system for catalysis. Alternatively, the order of screening could be reversed, with different ligands being screened using a common precatalyst and then precatalysts screened using the optimal ligand. One of the keys for this strategy is that precatalysts need to be compatible with a wide array of ligands. Consequently, we anticipate that there will be continued growth in the discovery of new precatalysts in the next decade.

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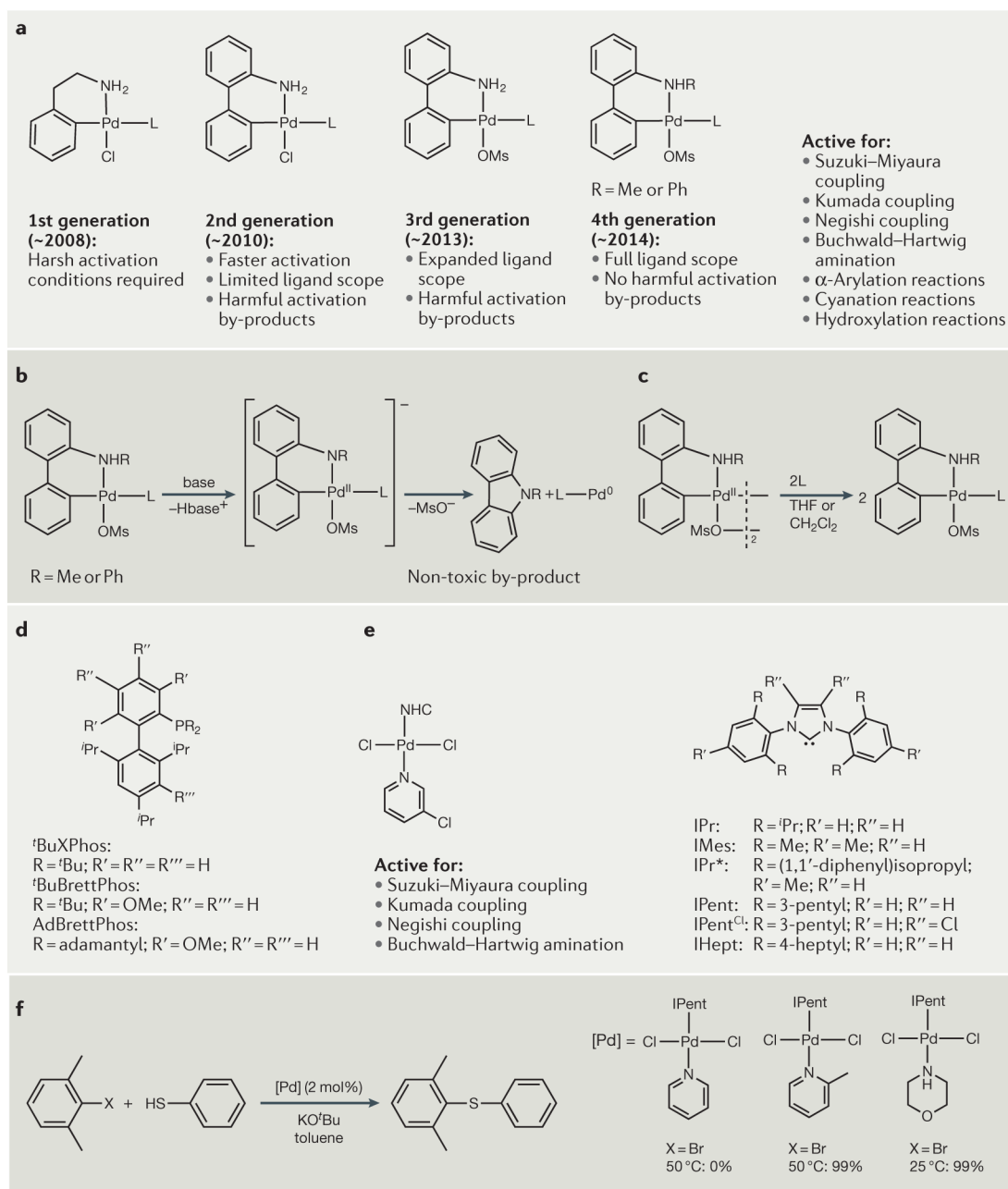
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**Figure 1. Recent developments in palladacycle and PEPPSI precatalysts**

**a** | The evolution of Buchwald palladacycle precatalysts from the 1st to the 4th generation. **b** | The activation of 4th generation Buchwald palladacycle precatalysts involves reductive elimination of a substituted carbazole and formation of an active Pd(0) species. **c** | Coordination of supporting ligands to dipalladium(ii) species affords Buchwald palladacycle precatalysts. **d** | Examples of sterically bulky phosphines typically incorporated into 3rd and 4th generation Buchwald palladacycle precatalysts. **e** | The Pyridine- Enhanced Precatalyst Preparation Stabilization and Initiation (PEPPSI) paradigm for Pd(ii) precatalysts developed



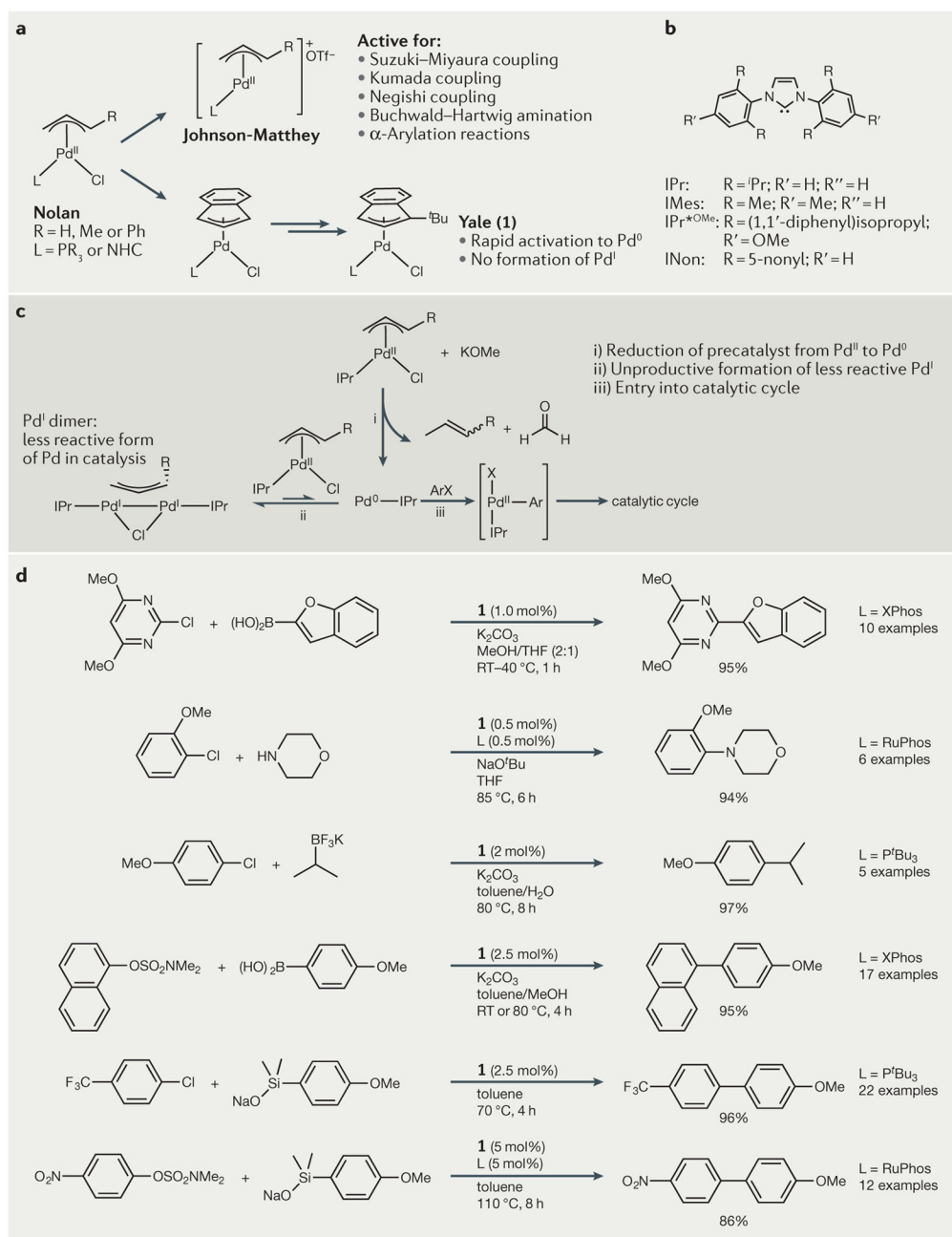
by Organ<sup>177</sup>. **f** | Examples of thioether formation mediated by Organ's PEPPSI-based precatalysts.

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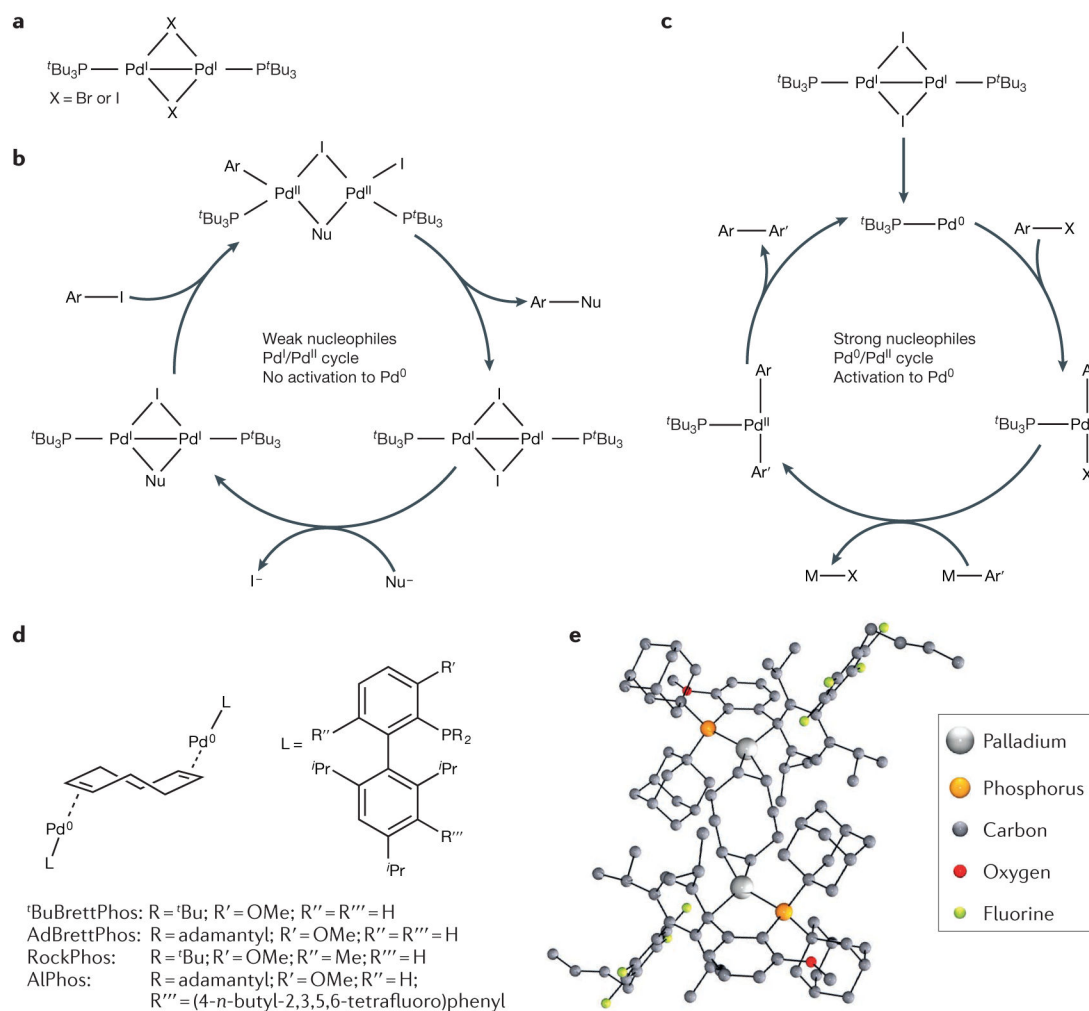
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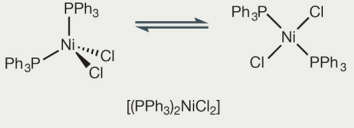
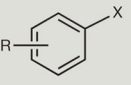
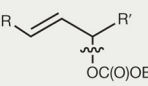
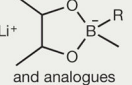
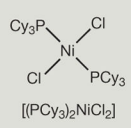
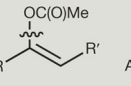
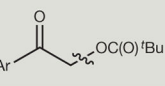
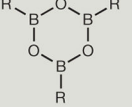
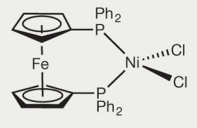
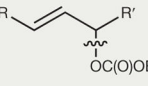
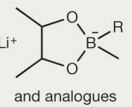
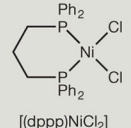
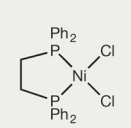
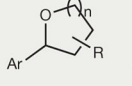
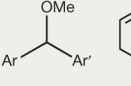

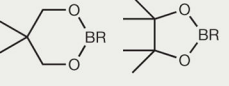
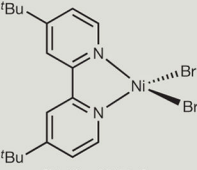
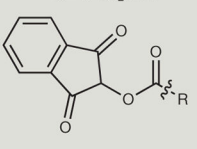
**Figure 2. A summary of recent improvements to  $\eta^3$ -allyl-type precatalysts**

**a** | Original allyl-type precatalyst from Nolan<sup>60</sup> and more efficient related precatalysts from Johnson Matthey and Yale. **b** | Selection of N-heterocyclic carbene (NHC) ligands that are compatible with allyl-type precatalysts. **c** | Pathway for the activation of allyl-type precatalysts, showing competition between unproductive Pd<sup>I</sup> dimer formation and entry into the catalytic cycle. **d** | Examples of cross-coupling reactions catalysed by Yale precatalysts.



**Figure 3. Proposed catalytic pathways for bridging halide Pd(I) pre-catalysts and structural evidence for new Pd(0) pre-catalysts**

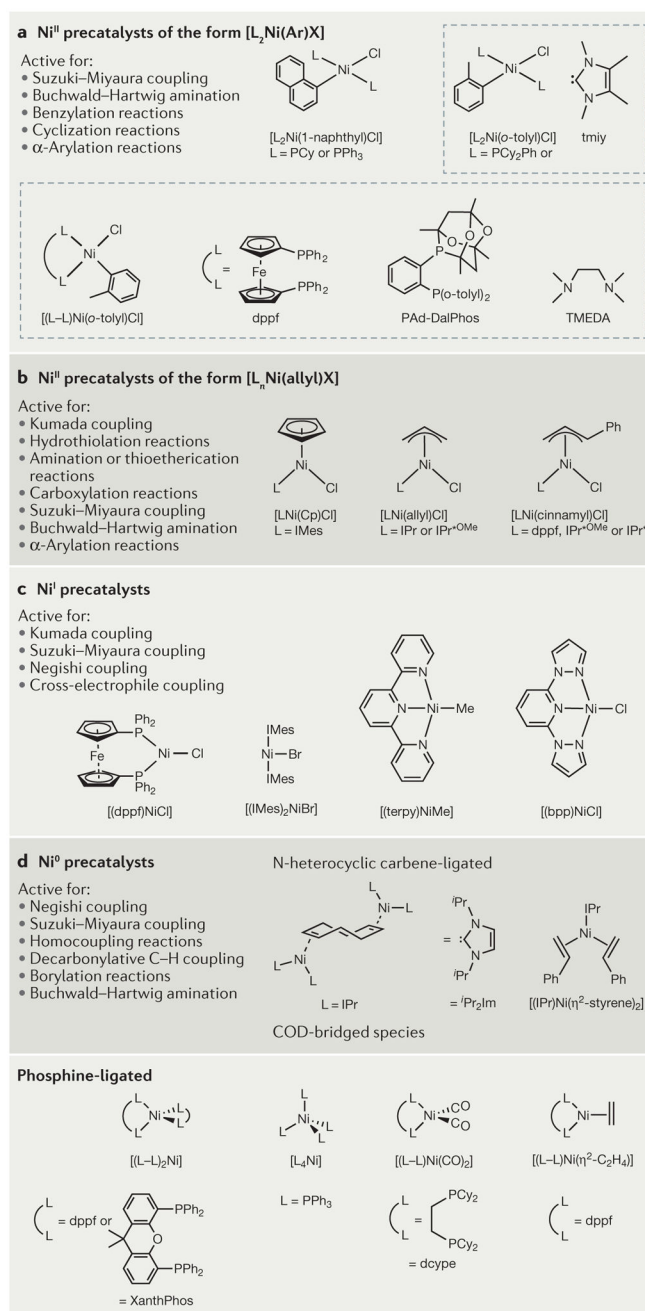
**a** | Structures of  $[(P^tBu_3)_2Pd_2(\mu-X)]$  ( $X = Br$  or  $I$ ) pre-catalysts. **b** | Catalytic cycle for cross-coupling reactions catalysed by  $[(P^tBu_3)_2Pd_2(\mu-I)]_2$  in the presence of weak nucleophiles. **c** | The catalytic cycle operative when strong nucleophiles are used. **d** | Generic representation of Buchwald Pd(0) pre-catalysts. **e** | X-ray crystal structure of  $[(AlPhos)_2Pd_2(\mu-COD)]$  (COD = 1,5-cyclooctadiene); the hydrogen atoms are omitted for clarity<sup>83</sup>.

Ni <sup>II</sup> precatalysts of the form [L <sub>n</sub> NiX <sub>2</sub> ]	Tolerated electrophiles	Tolerated nucleophiles
 <p>[(PPh<sub>3</sub>)<sub>2</sub>NiCl<sub>2</sub>]</p>	 <p>X = -OMe, -Cl, -Br, -OSO<sub>2</sub>Me, -OSO<sub>2</sub>(<i>p</i>-tolyl), -OSO<sub>2</sub>NMe<sub>2</sub>, -OC(O)NR<sub>2</sub>, -OC(O)<sup>t</sup>Bu, -OSO<sub>2</sub>CF<sub>3</sub> or</p> 	<p>ArMgBr, ArB(OH)<sub>2</sub>, ArZnCl, alkylZnBr, ZnAr<sub>2</sub></p>  <p>and analogues</p>
 <p>[(PCy<sub>3</sub>)<sub>2</sub>NiCl<sub>2</sub>]</p>	<p>X = -Cl, -Br, -I, -CN, -OP(O)(OR)<sub>2</sub>, -OSO<sub>2</sub>Me, -OSO<sub>2</sub>(<i>p</i>-tolyl), -OSO<sub>2</sub>NMe<sub>2</sub>, -OC(O)NEt<sub>2</sub>, -OC(O)<sup>t</sup>Bu, -OC(O)<sup>i</sup>Bu, -OSO<sub>2</sub>CF<sub>3</sub>, -C(O)(<i>N</i>-succinimidyl),</p>  	<p>ArB(OH)<sub>2</sub>, ArZnCl, ArMgBr, alkylZnBr, ZnAr<sub>2</sub> or</p> 
 <p>[(dppf)NiCl<sub>2</sub>]</p>	<p>X = -Cl, -OSO<sub>2</sub>CF<sub>3</sub>, -OSO<sub>2</sub>(<i>p</i>-C<sub>6</sub>H<sub>4</sub>F), -OSO<sub>2</sub>Me, -OSO<sub>2</sub>(<i>p</i>-tolyl), -OSO<sub>2</sub>NMe<sub>2</sub>, -CH<sub>2</sub>OMe, -OC(O)<sup>t</sup>Bu (+CO<sub>2</sub>) or</p> 	<p>ArB(OH)<sub>2</sub>, alkylZnBr, MnAr</p>  <p>and analogues</p>
 <p>[(dppp)NiCl<sub>2</sub>]</p>	<p>X = -Cl, -Br, -OSO<sub>2</sub>CF<sub>3</sub>, -OSO<sub>2</sub>Me, -OSO<sub>2</sub>(<i>p</i>-tolyl), -OSO<sub>2</sub>NMe<sub>2</sub>, -OH (+PyBroP) or -OC(O)NEt<sub>2</sub></p>	<p>ArB(OH)<sub>2</sub>, ArMgCl, ArMgBr or B<sub>2</sub>(OH)<sub>4</sub></p>
 <p>[(dppe)NiCl<sub>2</sub>]</p>	<p>X = Cl, Br, OSO<sub>2</sub>Me, OSO<sub>2</sub>(<i>p</i>-tolyl),</p>   	<p>ArB(OH)<sub>2</sub>, alkylMgBr, MeMgI</p> 
 <p>[(dtbbpy)NiBr<sub>2</sub>]</p>	<p>X = I, CH<sub>2</sub>Cl or</p> 	

**Figure 4.** Types of electrophiles and nucleophiles that can be coupled with Ni precatalysts of the form [L<sub>n</sub>NiX<sub>2</sub>]

Note that [(PPh<sub>3</sub>)<sub>2</sub>NiCl<sub>2</sub>] can exist in either square planar or tetrahedral isomeric forms.

Also, given that [(dtbbpy)NiBr<sub>2</sub>] (dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) is primarily used in cross-electrophile coupling, we do not give any nucleophiles for its reactions.



**Figure 5. Structures of common Ni precatalysts based on oxidation state and supporting ligands**  
**a** | Precatalysts of the form [L<sub>n</sub>Ni(Ar)X] can feature neutral C-, N- and P-donor ligands. **b** | The precatalysts [L<sub>n</sub>Ni(allyl)X] feature N-heterocyclic carbene (NHC) ligands and are active in a wide array of reactions. **c** | Common Ni(I) precatalysts are either three- or four-coordinate and feature one anionic ligand. **d** | Common Ni(0) precatalysts feature neutral, soft π-acceptor ligands.