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Nickel Complexes for Catalytic C–H Bond Functionalization

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The direct catalytic functionalization of traditionally unreactive C–H bonds is an atom-economic transformation that has become increasingly important and commonplace in synthetic applications. In general, 2nd and 3rd row transition metal complexes are used as catalysts in these reactions, whereas the less costly and more abundant 1st row metal complexes have limited utility. This Perspective article summarizes progress from our laboratory towards understanding the fundamental issues that complicate the use of Ni complexes for catalytic C–H bond functionalization, as well as approaches to overcoming these limitations. In practice it is found that Ni complexes can functionalize C–H bonds by processes that, to date, have not been observed with the heavier metals. An example is provided by the catalytic stannylation of C–H bonds with tributyllvinyltin, $Bu_3SnCH{=}CH_2$, which produces ethylene as a by-product.

1. Introduction

Over the last few decades the activation of C–H bonds at transition metal centres[1] has gone from an exotic stoichiometric reaction observed at only select transition metal complexes to a powerful step in catalytic transformations regularly employed by synthetic chemists.[2] The use of base metals such as Ni in catalytic transformations offers the benefits of low cost and improved sustainability;[3] however, the development of catalytic C-H bond functionalization reactions with 1st row metals faces many fundamental challenges.[4] Expensive and low-abundance noble metals such as Rh, Ir and Pt are more commonly utilized in C–H functionalization reactions, and for good reason. Catalytic transformations that require a C–H bond breaking step most typically occur via electrophilic activation or oxidative addition, as shown on the top of Figure 1, or a variant of these reactions.[5] Both these reactions are believed to initially involve the formation of a σ-adduct along the reaction pathway. The thermodynamic favourability of both the electrophilic and oxidative addition mechanisms depends on the formation of a strong M–C bond to offset the energy required to break a C–H bond. The metal-carbon bond strengths of 1st row transition metals are significantly lower than the heavier metals,[6] which results in a decreased thermodynamic driving force for these C–H bond cleavage reactions. The use of 1st row elements for reactions that functionalize C–H bonds requires a rethinking of how C–H functionalization can be accomplished, and possibly using or developing fundamentally different reaction types for the key C–H bond breaking step. An example is shown on the bottom of Figure 1, where the oxidative addition of a C–H bond is coupled to an insertion step.

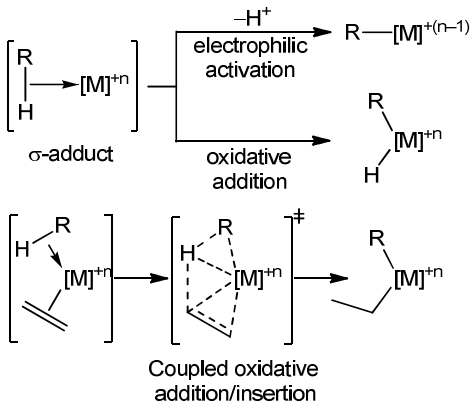
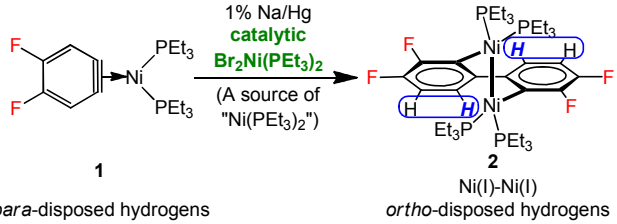


Figure 1. The common electrophilic and oxidative addition pathways to C–H bond activation, as well as a less common path where oxidative addition and insertion occur in one step.

Recent times have seen an increase in the use of first row transition metals such as Ni for C–H activation[7] and functionalization,[8] However, these examples still do not approach the scope of the C–H functionalization reactions catalysed by the heavier transition metals. This Perspective article outlines our attempts to better understand not only how the electronic and steric properties of Ni complexes can be tuned to facilitate C–H bond activation via similar pathways to the heavier metals, but also to identify new reaction types that facilitate the thermodynamically difficult C–H bond cleavage step.

Serendipitous Beginings: C–H bond isomerization in a Ni(I)-Ni(I) complex. Our initial observation of C–H activation by a Ni complex was in an esoteric biarylyl complex.[9] The synthesis of the benzyne complex **1**, first prepared by the Bennett group,[10] in the presence of a catalytic amount of the impurity $Br_2Ni(PEt_3)_2$ led to the dinuclear Ni(I) complex **2**, as shown in Scheme 1. A surprising aspect of the structure of **2** is that the hydrogen atoms on the aromatic rings are *ortho*-disposed, rather than *para*-disposed as they are in the precursor.



Scheme 1. Reversible cleavage of sp^2 carbon-hydrogen bonds in a dinuclear Ni(I)-Ni(I) complex.[9]

The "$Ni(PEt_3)_2$" source is believed to play the role of Lewis acid in this reaction, abstracting PEt_3 from the benzyne complex **1**, which then undergoes to C–C coupling to provide the dinuclear biarylyl Ni(I)-Ni(I) complex **2** via multiple reaction steps that involve C–H bond activation. At the time, there were few examples of Ni complexes activating aromatic C–H bonds. Although further mechanistic work provided detail into the mechanism of this reaction,[9a] the exact nature of the C–H bond cleavage step remains unclear.

The observation of the C–H bond isomerization in the conversion of **1** to **2** raised several questions: (1) Can Ni(0) complexes such as "$Ni(PEt_3)_2$" activate aromatic C–H bonds via oxidative addition?; (2) Could ligand design be utilized to design more reactive Ni(0) complexes?; (3) Do organometallic Ni complexes in uncommon oxidation states, such as the Ni(I) centres in **2**, participate in facile C–H bond activation via atypical mechanisms?

Thermodynamic and kinetic considerations.

To achieve the goal of using Ni complexes in C–H activation reactions, it is helpful to quantify the thermodynamic and kinetic barriers that must be overcome. In a 2004 study that influenced our approach to designing Ni catalysts for C–H functionalization, the decreased propensity of Ni(0) complexes to participate in C–H bond activation compared to its heavier congener Pt was quantified by DFT.[11] The oxidative addition of the C–H bonds of benzene to the hypothetical diphosphine supported Ni(0) moiety, $(H_2PCH_2CH_2PH_2)Ni$ was found to be disfavoured by +20.4 kcal·mol^{-1}, as shown in Figure 2. In comparison, the related Pt(0) complex $(Cy_2PCH_2CH_2PCy_2)Pt$ is experimentally known to undergo a thermodynamically favourable C–H bond oxidative addition with benzene.[12]

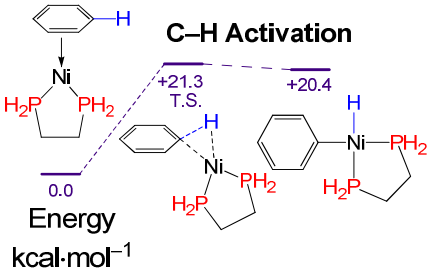


Figure 2. Calculated energies for the oxidative addition of C_6H_6 to $(H_2PCH_2CH_2PH_2)Ni$. Adapted from [11].

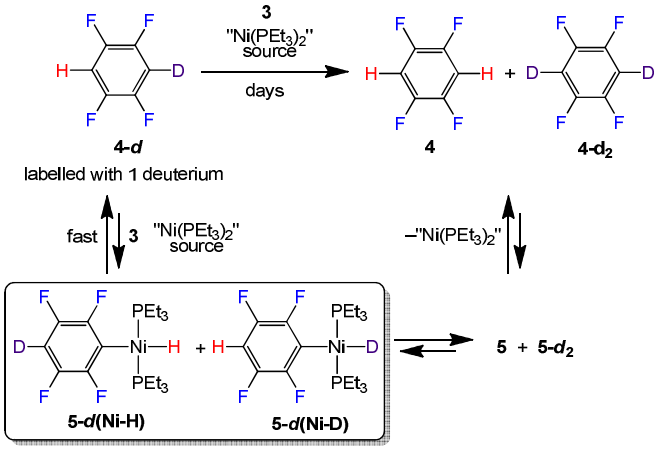
The same DFT study provides an interesting comparison of the propensity of Ni to undergo C–F bond activation versus C–H activation. Calculation predicts that the oxidative addition of $(H_2PCH_2CH_2PH_2)Ni$ to C_6F_6 is favoured by −19.7 kcal·mol^{-1}. The calculated activation barrier is 22.5 kcal·mol^{-1}. Real examples of Ni complexes, such as $(Et_3P)_4Ni$, that undergo C–F bond oxidative addition slowly at room temperature were reported first back in 1977.[13]

The unfavourable energy change associated with C–H oxidative addition of benzene to Ni(0) would seem to indicate that Ni would be incapable of this reaction. However, it should be noted that the activation barrier for the C–H activation shown in Figure 1 is only 21.3 kcal·mol^{-1}. This is actually less than that the activation barrier calculated for the concerted C–F bond oxidative addition of C_6F_6. The relatively low barrier to C–H activation suggested to us that Ni(0) should be capable of these reactions at room temperature, and faster than C–F bond activation! Our initial hypothesis was that coupling this facile C–H activation with other reactions that would functionalize the C–H bond and render the overall reaction thermodynamically favourable. Overall this would allow for catalytic C–H bond functionalization using Ni. The path to the discovery of suitable trapping reagents that would lead to synthetically versatile products of interest was not obvious. Moreover, the trapping reagent needed to not interfere with the already thermodynamically disadvantaged reactivity of Ni with C–H bonds.

2. Observing Ni(0) C-H Bond Oxidative Addition.

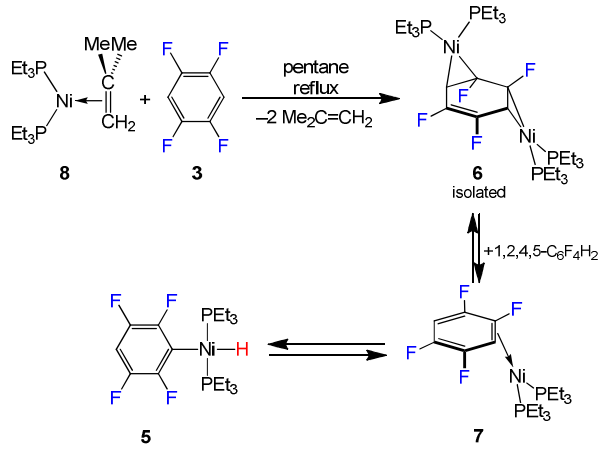
With the hypothesis that Ni(0) complexes were kinetically capable of C–H bond oxidative addition, we sought to find some experimental evidence for this reaction with highly reactive $(Et_3P)_2Ni$ sources. The direct reduction of $Br_2Ni(PEt_3)_2$ with Na/Hg in the absence of a trapping agent does not provide a stable "$Ni(PEt_3)_2$" moiety, but the phenanthrene and anthracene adducts $(Et_3P)_2Ni(\eta^2\text{-}C_{14}H_{10})$ (**3**) are stable as solids under an inert atmosphere.[14] Prior to trapping C–H activation products, it was desirable to design a reaction to show that the enthalpically uphill C–H bond oxidative addition reaction was actually occurring rapidly and reversibly at room temperature. The nickel-catalysed exchange of H/D labels in arenes was deemed a plausible test. Monodeuterated 1,2,4,5-C_6F_4HD (**4-*d***) was used to observe Ni(0) complex catalysed scrambling to provide $C_6F_4H_2$ (**4**) and $C_6F_4D_2$. (**4-d_2**). Scrambling did occur over days, but the ^1H ^{19}F and ^{31}P NMR spectra also unexpectedly provided evidence for

the rapid formation of small equilibrium amounts of the C–H and C–D activation products *trans*-$(Et_3P)_2NiH(C_6F_4D)$ **5-*d*(Ni-H)** and *trans*-$(Et_3P)_2NiD(C_6F_4H)$, **5-*d*(Ni-D)**, as shown in Scheme 2. The activation barrier for this C–H activation is sufficiently low that the **5-*d*** isomers were observed even when the reaction was performed at 243 K.



Scheme 2. Equilibrium C–H activation by nickel at room temperature.[14]

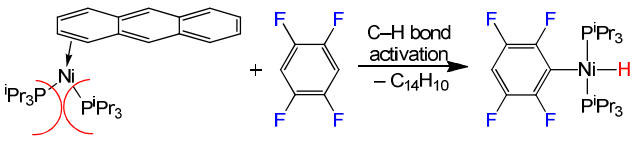
Hydride **5** could not be isolated, due to its being in equilibria with both the dinuclear adduct **6** and mononuclear adduct **7**; complex **6** proved isolable using the isobutene adduct $(Et_3P)_2Ni(\eta^2\text{-}H_2C{=}CMe_2)$ (**8**) as a $(Et_3P)_2Ni$ source, as shown in Scheme 3.[15] Similar dinuclear adducts of the formula $[(Et_3P)_2Ni]_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}C_6F_4H_2)$ with 1,2,3,5- and 1,2,3,4 tetrafluorobenzene were also isolated, and both were also found to exist in equilibria with their mononuclear adducts of formula $(Et_3P)_2Ni(\eta^2\text{-}C_6F_4H_2)$ in solutions with added tetrafluoroarene. The C–H activation analogue of **5**, $(Et_3P)_2NiH(C_6F_4H)$, was observed with 1,2,3,5-tetrafluorobenzene, but not with 1,2,3,4-tetrafluorobenzene; the latter does not contain C–H bonds with two adjacent *ortho*-F substituents. In solution, the mononuclear adducts and C–H oxidative products slowly convert to thermodynamic C–F activation products. Monitoring by low-temperature NMR spectroscopy also revealed kinetic C–H activation products even when $Ni(PEt_3)_2$ sources were reacted with substrates that undergo rapid room-temperature C–F bond activation, such as 2,3,5,6-tetrafluoropyridine.[16]



Scheme 3. Synthesis of isolable $[(Et_3P)_2Ni]_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}C_6F_4H_2)$ (**5**), and equilibria with the mononuclear adduct **7** and C–H activation product **5**.[15]

These reactions demonstrate the ability of Ni(0) to undergo C–H activation at sp^2-hybridized carbon, but it must be acknowledged that this substrate is thermodynamically activated towards C–H bond oxidative addition relative to benzene. DFT studies have shown *ortho*-F and *meta*-F substitution favour oxidative addition by 4.6 kcal·mol^{-1} and 1.2 kcal·mol^{-1}, respectively.[17] THHs for 1,2,4,5-tetrafluorobenzene, oxidative addition should be favoured by 11.6 kcal·mol^{-1} relative to benzene. Although substantial, the DFT calculations presented in Figure 2 suggest that benzene oxidative addition to Ni(0) is disfavoured by 20.4 kcal/mol; even with the activated substrate 1,2,4,5-tetrafluorobenzene oxidative addition should be uphill by 8.8 kcal/mol. This raises the issue of what the differences are between the model complex studied by DFT, $(H_2PCH_2CH_2PH_2)Ni$, and $(Et_3P)_2Ni$. Although one possible contributor is that Et_3P is a better donor, and thus favours the higher Ni(II) oxidation state, steric effects could play an equally important role. The steric relief in going from *cis*-disposed phosphines in the Ni(0)-arene adduct to *trans*-disposed phosphines in the C–H activation product could be used to provide additional thermodynamic impetus.

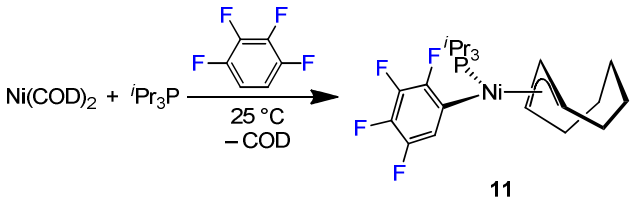
To test this hypothesis, the anthracene adduct of a bulkier phosphine, $(^iPr_3P)_2Ni(\eta^2\text{-}C_{14}H_{10})$ (**9**), was prepared. For complexes containing a *cis*-$(R_3P)_2Ni$ moiety, R = ^{i}Pr is among the bulkiest this fragment can be and maintain *cis*-trialkylphosphines. The Tolman cone angle of $^iPr_3P$ is 160°, whereas for Et_3P it is 132°.[18] The increased bulk of the $(^iPr_3P)_2Ni$ moiety in **9** does render C–H bond activation more favourable. The reaction of $(^iPr_3P)_2Ni(\eta^2\text{-}C_{14}H_{10})$ (**9**) with a number of fluorinated arenes that have hydrogens flanked by two ortho-F substituents gives isolable C–H bond activation products. For example, $(^iPr_3P)_2Ni(\eta^2\text{-}C_{14}H_{10})$ reacts with 1,2,4,5-tetrafluorobenzene (**4**) to give the C–H oxidative addition product *trans*-$(^iPr_3P)_2NiH(C_6F_4H)$ (**10**) as a stable solid, as shown in Scheme 4. The reaction is sufficiently thermodynamically downhill that heating to 50 °C is required to observe evidence of reductive elimination.[19]



Scheme 4. Relief of steric crowding in the cis-$(^iPr_3P)_2Ni$ moiety favours oxidative addition.[19]

Although both the $(^iPr_3P)_2Ni$ and $(Et_3P)_2Ni$ moieties demonstrate the ability to activate the strong C–H bonds with two *ortho*-F substituents, no substrates with hydrogens with a single ortho-F substituent underwent activation to give an observable nickel-hydride. Activation of C–H bonds next to a single ortho-F are presumably too thermodynamically uphill to observe via NMR, though given the room temperature activation of 1,2,4,5-tetrafluorobenzene, the activation of C–H bonds in substrates like 1,2,3,4-tetrafluorobenzene might be expected to be kinetically accessible. This appears to be demonstrated in the reaction of $Ni(COD)_2$, where COD =1,5-cyclooctadiene, as a Ni(0) source in the presence of $^iPr_3P$ and 1,2,3,4-tetrafluorobenzene to give **11**, as shown in Scheme 5.[19]

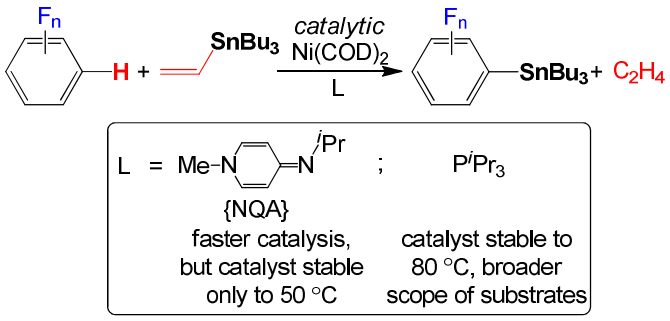
Compound **11** could arise from the C–H activation of 1,2,3,4-tetrafluorobenzene and the insertion of COD, followed by chain-walking to give the an allyl moiety. Although not catalytic, this reaction demonstrates how an observable C–H oxidative addition is not necessary to effect C–H activation with Ni. The exact mechanism of this C–H bond-breaking step is unclear; the hydride from oxidative addition of the C–H bond could be an true intermediate, or the oxidative addition and insertion reaction could occur in one step, in what could be viewed as an oxidative addition coupled to a barrierless insertion. The coupling of an enthalpically disfavoured oxidative addition with a favoured insertion step could provide a pathway where the thermodynamically uphill oxidative addition does not need to be accessed for a net C–H activation process.



Scheme 5. Activation next to a single *ortho*-F substituent.[19]

3. Catalytic C–H Functionalization.

With evidence that Ni was capable of stoichiometric C–H activation, suitable reagents and reactions that would provide useful catalytic functionalization were sought. The reaction of fluorinated aromatics with $Bu_3SnCH{=}CH_2$ with a catalyst prepared from a Ni(0) precursor and neutral ancillary ligand gave C–H bond stannylation products with ethylene as a byproduct, as shown in Scheme 6.[20] Although C–H borylation has been studied in depth,[2i, 21] and even commercialized to provide reagents for Suzuki coupling reactions, to the best of our knowledge C–H bond stannylation had not been previously demonstrated, despite the utility of Stille coupling in synthesis.[22] Similarly, the use of a vinyl moiety that eliminates as ethylene in the catalytic pathway is unusual for C–H bond activation, but critical to the activity of Ni as a catalyst in this reaction.



Scheme 6. Catalytic C–H bond stannylation, where the H functionalized has to at least one *ortho*-F substituent.[20]

Ligand choice significantly affects both the activity and scope of this reaction. The {NQA} ancillary ligand shown in Scheme 6 allowed for the catalytic functionalization of aromatic C–H bonds with two ortho-F substituents under milder conditions than the bulky phosphine $^{i}Pr_3P$. For example, C_6F_5H can be converted to $C_6F_5SnBu_3$ with a 1 % catalyst loading within minutes at room temperature, with the rapid release of ethylene gas visible immediately. The same reaction with $^{i}Pr_3P$ as the ancillary ligand requires heating above room temperature to achieve reasonable reaction rates. For less activated substrates, such as those with a single *ortho*-F substituent, the {NQA} ligand is ineffective below 50 °C, and Ni metal precipitates at higher temperatures. Although the $^{i}Pr_3P$ ancillary ligand supported catalysts are less active than the {NQA} ligands at low temperatures, they have the advantage of surviving temperatures up to 80 °C, which allows the functionalization of a broader scope of fluorinated aromatics, which includes aromatic hydrogens adjacent to a single ortho-F substituent. Examples of substrates which are readily converted to a monostannylated product are shown in Figure 3.

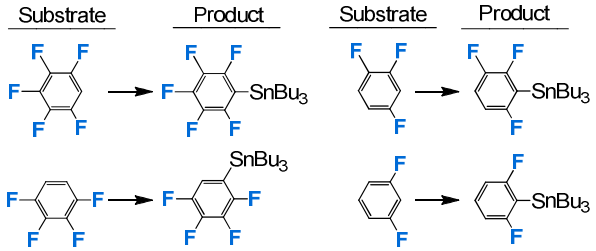


Figure 3. Substrates and products that undergo selective monostannylation.

Although the catalytic C–H bond stannylation of a variety of fluorinated aromatics occurs with excellent and predictable selectivity, compounds with multiple sites of similar activity are not deactivated by stannylation, for example 1,2,4,5-tetrafluorobenzene reacts to produce both the mono- and distannylated products when a 1:1 ratio of fluorinated arene and $Bu_3SnCH{=}CH_2$ are used. Monostannlyated products are easily obtained using an excess of fluorinated arene, and di- and tristannlyated products can also be made by adding an appropriate stoichiometry of $Bu_3SnCH{=}CH_2$. Examples of accessible products are shown in Figure 4.

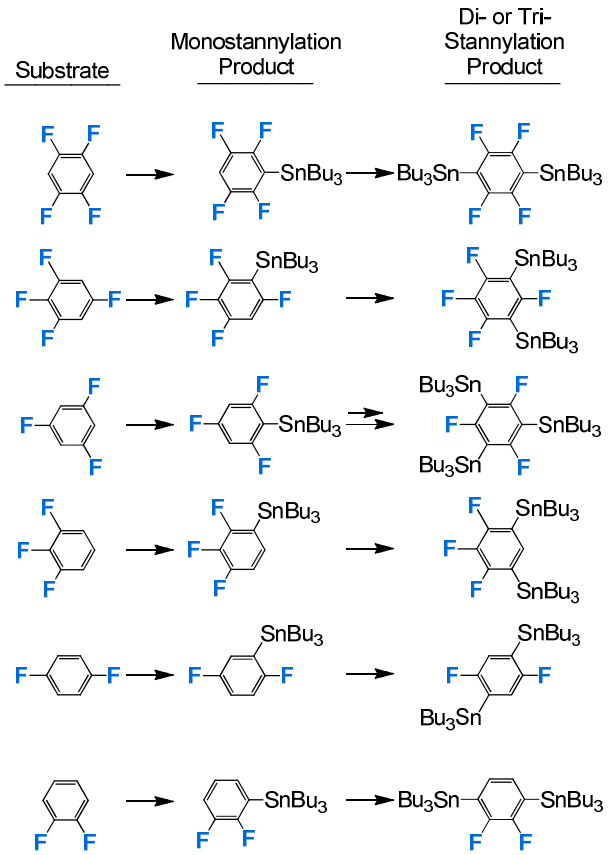
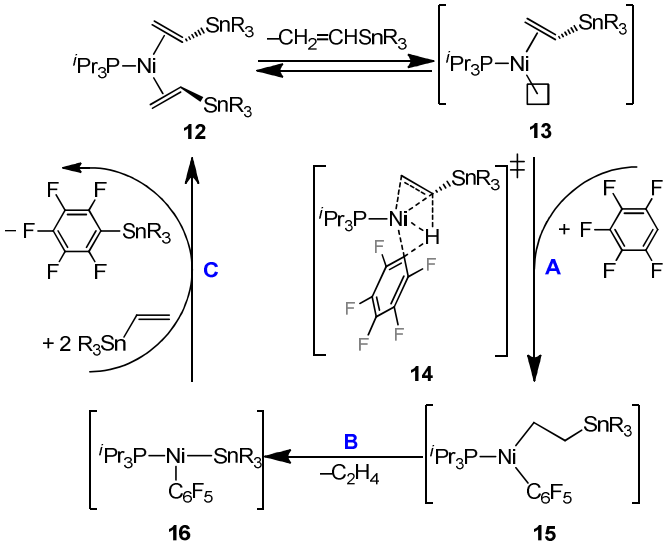


Figure 4. Substrates and products that can be converted selectively to monostannylated products using excess arene, or di- or tristannylated products using two or three equivalents of $Bu_3SnCH{=}CH_2$.

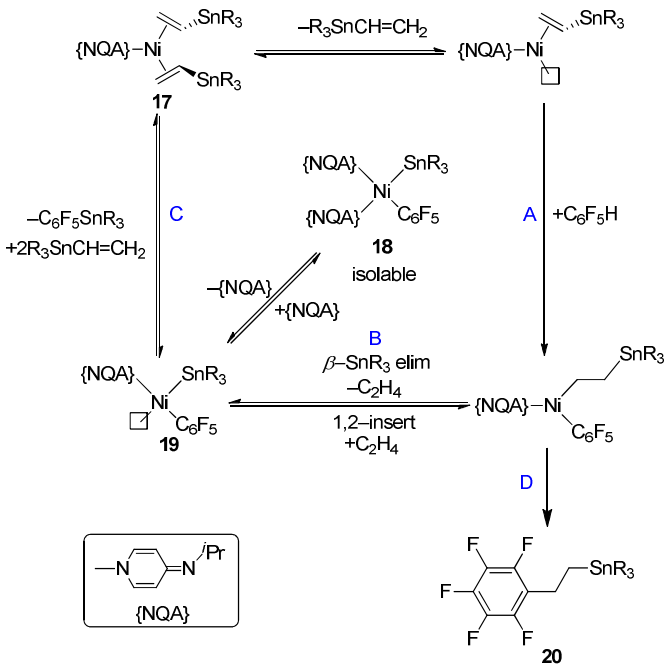
Catalytic Stannylation Mechanism. Mechanistic studies have been performed to better understand how improved catalysts could be designed for stannylation, as well as for the possible design of other carbon-heteroatom forming C–H functionalization reactions. The mechanism for C–H stannylation appears unique compared to other C–H functionalization reactions.

The proposed mechanistic pathway for the catalyst supported by the $^{i}Pr_3P$ ancillary ligand is shown in Scheme 7.[23] The resting state of the catalyst is the isolable and stable complexes ($^{i}Pr_3P$)Ni(η^2-$H_2C{=}CHSnR_3)_2$ (**12**), where R = Bu, though the complex where R = Ph is also active, and has been characterized by X-ray crystallography. After dissociation of $H_2C{=}CHSnR_3$ to give **13**, the nickel proceeds through the key C–H bond-breaking step, which is proposed to involve oxidative addition coupled with insertion, as shown step **A** with transition state **14**. Computational studies on the related Ni catalysed alkenylation of fluoroarene C-H bonds (alkyne hydroarylation) reported by Nakao[8k] support a similar C–H activation step, deemed ligand to ligand hydrogen transfer (LLHT).[24] Deuterium labelling studies support that a β-SnR_3 elimination occurs from **15** to provide **16**, as shown in step **B**, leaving a Ni(II) centre bearing SnR_3 and C_6F_5 groups that can undergo reductive elimination to give the C–H stannylation product $C_6F_5SnR_3$ and regenerate the Ni(0) catalyst, as shown in step **C**.



Scheme 7. Proposed mechanism of catalytic C–H bond stannylation supported by the ancillary ligand $^{i}Pr_3P$.[23]

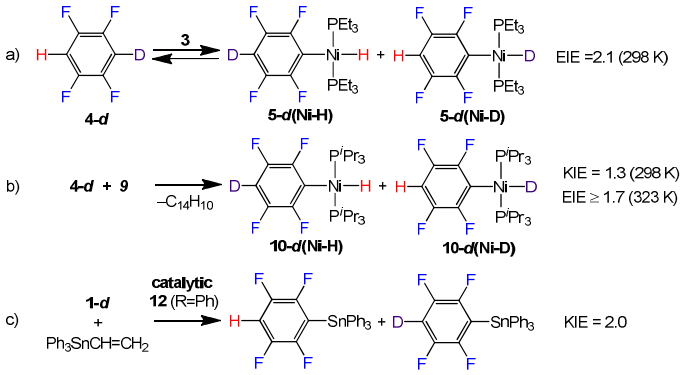
Mechanistic studies with {NQA} as the ancillary ligand[25] are suggestive of a similar mechanistic manifold as that shown in Scheme 7 for $^{i}Pr_3P$ supported stannylation, with the same main steps A, B, and C, but also with a few differences, as noted in Scheme 8. The resting state of the catalyst is condition dependent and includes both the Ni(0) complex {NQA}Ni(η^2-$H_2C{=}CHSnR_3)_2$ (**17**) and {NQA}$_2$Ni(C_6F_5)(SnR_3) (**18**) when R = Ph. In this catalytic cycle the last step is reversible, and complex **18** can alternatively be prepared via oxidative addition of $C_6F_5SnPh_3$ to Ni(COD)$_2$ in the presence of two equiv of {NQA}. In solution a rapid equilibrium with the single ancillary ligand bearing species {NQA}Ni(C_6F_5)(SnR_3) (**19**) occurs. The C–H bond alkylation (or alternately alkene hydroarylation) product $(C_6F_5)CH_2CH_2SnR_3$ (**20**) is also obtained in the product mixture via the reductive elimination pathway labelled **D** in Scheme 8. A recent report[26] using the IPr carbene ligand (IPr=1,3-bis[2,6-diisopropylphenyl]-1,3-dihydro-2H-imidazol-2-ylidene) showed that the scope of the alkene hydroarylation reaction mechanism that yields **20** can be extended to a variety of alkenes and even benzene, an unactivated arene, as the aromatic substrate, albeit with catalyst turnover numbers near one. A similar mechanistic pathway to that described here was proposed, with computational studies providing the relative energies and interconversions of the 3-coordinate Ni(II) intermediates. Our initial attempts[25] to use the IPr carbene as an ancillary ligand for the catalytic reaction shown in Scheme 8 yielded a nearly identical product mixture as observed with {NQA}.



Scheme 8. Proposed mechanism of catalytic C–H bond stannylation supported by the {NQA} ancillary ligand.[25]

Kinetic Isotope Effects for C–H Cleavage. The measurement of a kinetic isotope effects (KIE) provides otherwise difficult to glean insight into the transition state for the difficult C–H bond breaking step.[27] With the oxidative addition step in catalytic stannylation coupled to the insertion step, it is pertinent to consider whether these should be considered as entirely different reactions from either of the individual steps, which could steer complex design for catalytic C–H functionalization.

The C–H activation reaction of 1,2,4,5-C_6F_4HD (**4-*d***) with the $(Et_3P)_2Ni$ source **3** provides an equilibrium isotope effect (EIE) at 298 K of 2.1, as shown in Scheme 9a. This value is reflective of the slight thermodynamic preference for C–H bond activation caused by differences in the C–H bond and Ni–H bond zero point energies. In contrast, the kinetic isotope effect (KIE) observed for the stoichiometric reaction of the $(^iPr_3P)_2Ni$ source **9** with **4-*d*** was 1.3, as shown in Scheme 9b. This value is lower, and near 1, which is suggestive of an early rate determining step for this oxidative addition reaction, with very little C–H/D bond breaking. Given that the activation of 1,2,4,5-tetrafluorobenzene with $(Et_3P)_2Ni$ occurs even below room temperature, the transfer of the $(^iPr_3P)_2Ni$ could be rate limiting, with a very low energy barrier for oxidative addition compared to ring-whizzing; the latter is typically facile in related complexes. Heating at 50 °C for several hours shows that this C–H activation is reversible, and the ratio of C–H to C–D activation increased to 1.7 before competing conversion to **4** and **4-*d*$_2$** rendered it difficult to measure the EIE by ^{19}F NMR; the value of 1.7 is similar to the value of 2.1 anticipated from the related activation of **4-*d*** by **3**.



Scheme 9.

These stoichiometric KIE and EIE values provide a benchmark for what might be expected in catalytic reactions such as C–H stannylation. The stannylation of **4-*d*** with H_2C=CHSnPh_3 using catalytic $(^iPr_3P)Ni(\eta^2$-H_2C=CHSn$Ph_3)_2$ provided Ph_3Sn-2,3,5,6-C_6F_4D and Ph_3Sn-2,3,5,6-C_6F_4H with a KIE of 2.0, as shown in Scheme 9c. Although similar to the EIE observed in the reaction of 1,2,4,5-C_6F_4HD (**1-d**) with $(Et_3P)_2Ni$ sources, there is evidence from labelling studies that step **A** shown in Schemes 7 and 8 is not reversible with highly fluorinated substrates such as **1-d**.

The KIE values provide some insight into the differences between the stannylation reaction and the proposed mechanism for a related alkenylation reaction. In a computational study of the related Ni catalysed alkenylation of fluorinated aromatics it has been proposed that rather than considering this reaction an oxidative addition coupled with insertion it should be viewed as a ligand to ligand hydrogen transfer (LLHT).[24] As an experimental test for this mechanism, this paper predicts that an oxidative addition mechanism would give a predicted KIE of 2.57, whereas LLHT should give a kinetic isotope effect of 1.03 for alkenylation; the experimental value was found to be closer to the latter.[28] Although it is not clear that these values can be extended to other related reactions like this stannylation reaction it is notable that the catalytic stannylation reaction c) in Scheme 9 provides a value close to that suggested for oxidative addition, but the reaction in Scheme 9b provides a value closer to that postulated for LLHT in the related alkenylation reaction, despite the fact it is an oxidative addition; clearly the classification of a range of related reaction types based on the KIE is not yet feasible. More work is ultimately needed to understand the mechanistic implications of the KIEs for these reactions. Presumably the KIE is influenced by the nature of the ligand the H is being ultimately transferred to, the strength of the C–H bond being broken, and the electronic properties of the nickel centre; all these could affect whether the transition state would occur earlier or later along the reaction coordination for C–H bond breaking and making.

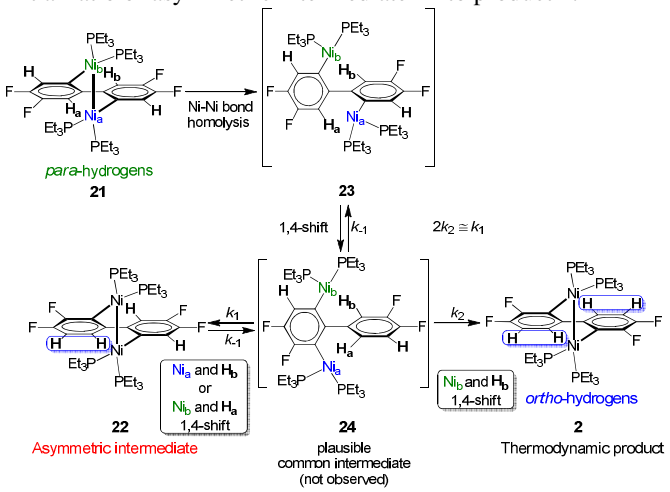
4. Alternate Ni Oxidation States for C–H Activation.

A limitation to using Ni(0) complexes for C–H bond activation is that although strong C–H bonds are readily activated, such as aromatic C–H bonds adjacent to a fluorine substituent, unactivated bonds are less reactive. For the catalytic stannylation shown in Scheme 6, this means that

catalyst **12** does not effectively stannylate unactivated arenes such as benzene. The least activated substrate to undergo Ni catalysed stannylation to date is monofluorobenzene, which undergoes only a few turnovers prior to catalyst deactivation.

The conversion of **1** to **2** shown in Scheme 1 suggests that it may be possible that alternative oxidation states such as Ni(I) might be able to facilitate C–H activation via novel mechanisms. The deliberate design of Ni(I) complexes capable of catalytic C–H bond functionalization is hampered by a poor understanding of what mechanisms are feasible.

Studies were performed to understand how the C–H groups go from *para*-disposed to *ortho*-disposed in **2** to determine if Ni(I) had a role in the activation of C–H bonds. Complex **21**, an isomer of **2** that has para-disposed H substituents, was prepared, and its isomerization was monitored. It was observed that the initial reaction mixture had an exactly 2:1 ratio of the asymmetric intermediate **22** to the final thermodynamic product **2**, as shown in Scheme 10. This can be explained by the mechanism shown, where Ni-Ni bond homolysis to give **23** is followed by a 1,4- shift of Ni_a and H_a to generate the unobserved high energy intermediate **24**, which has both Ni(I) centres on the same aromatic ring. Complex **24** can rearrange back to a biarylyl complex by four possible 1,4-shifts. A 1,4-shift of Ni_a and H_a regenerates the starting material **21**. Two possible 1,4-shifts, generate the asymmetric intermediate **22**. Only the 1,4-shift of Ni_b and H_b generates the thermodynamic product **2**. If it is assumed that these 1,4-shifts all have a similar activation barrier, this mechanism explains the 2:1 initial ratio of asymmetric intermediate **22** to product **2**.

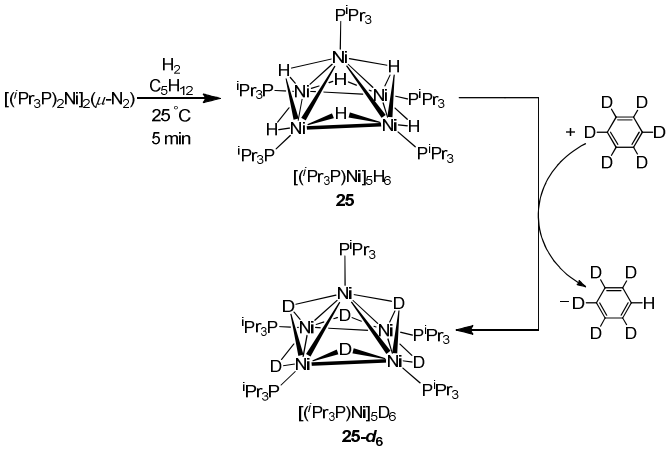


Scheme 10. Proposed mechanism for the C–H bond isomerization of **21**.[9]

Although the mechanism in Scheme 10 explains the initial product ratio, it does not provide much insight into the nature of the C–H bond breaking step. If this reaction simply involved concerted 1,4-shifts, where C–H bond breaking and making occurred simultaneously, it would be difficult to extend this result to design Ni complexes for catalytic C–H functionalization. A cleavage of the aromatic C–H bonds, rather than a concerted 1,4-shift would provide an intermediate that could be trapped and functionalized. A crossover experiment between **1** and **1-*d*$_2$**, where the benzyne moiety is doubly deuterated led to a statistical product distribution that included **2-*d*$_1$** and **2-*d*$_3$**. This showed that this unusual C–H bond activation did not occur via a concerted 1,4-shift, but rather must involve a true cleavage of the C–H bond. Attempts to isolate biarylyl complexes like **23** by increasing steric bulk have failed,[29] though recently we prepared a Ni(I) pentafluoropheyl complex, (^{i}Pr$_3$P)$_2$Ni(C$_6$F$_5$) that is stable to disproportionation[30]; Ni(I) complexes of this type are not improbable.

Cluster Reactivity with unactivated C–H bonds. In general mononuclear Ni(0) complexes are capable of activating the strongest C–H bonds, such as aromatic hydrogens activated by an *ortho*-F substituent. As discussed in the introduction, this is a result of the thermodynamic disadvantage Ni has relative to its heavier congeners when it comes to weaker Ni–C and Ni–H bond strengths. Alternate reaction pathways may be necessary to activate substrates with weaker C–H bonds, such as unactivated arenes like benzene, or sp^3 hybridized C–H bonds. An intriguing example of the C–H bond activation of benzene is provided by the pentanuclear cluster [(^{i}Pr$_3$P)Ni]$_5$H$_6$ (**25**) shown in Scheme 11.[31]

When dissolved in C$_6$D$_6$ this undergoes H/D-exchange over the course of a few hours to provide the deuterated complex [(^{i}Pr$_3$P)Ni]$_5$D$_6$ and C$_6$D$_5$H. Although the mechanism of the C–H bond breaking step is not yet clear, the cluster is electron-deficient and could undergo oxidation addition of the C–D bond to give the intermediate [(^{i}Pr$_3$P)Ni]$_5$H$_5$D(C$_6$D$_5$). Complex **22** also features a paramagnetic state that has slight thermal population at room-temperature. The involvement of this state in C–H activation is a distinct possibility. Further work is necessary to determine how this H/D exchange reaction might be tuned to result in C–H bond functionalization of unactivated C–H bonds.



Scheme 11. Synthesis of the cluster [(^{i}Pr$_3$P)Ni]$_5$H$_6$ and H/D exchange with C$_6$D$_6$.[31]

Conclusions

This Perspective summarizes our attempts to better understand the fundamental aspects of the reactivity of Ni complexes in C–H activation. At the current state of development it is clear that in some cases Ni can perform C–H bond activation and even catalytic functionalization, though often these processes rely on the use of activated substrates with strong polar C–H bonds. The stannylation of C–H bonds is a Ni catalysed transformation that has no reported analogue with other transition metal complexes, even though the heavier elements are typically more capable of C–H bond activation. The

mechanism of this reaction provides insight into how new C–H bond activation reactions could be designed. Equally intriguing is the prospect that Ni in less common oxidation states, such as Ni(I), and Ni clusters such as **25** can activate C–H bonds. This area of study is still in its infancy, and little is known about the C–H bond cleavage step in these reactions.

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Notes and references

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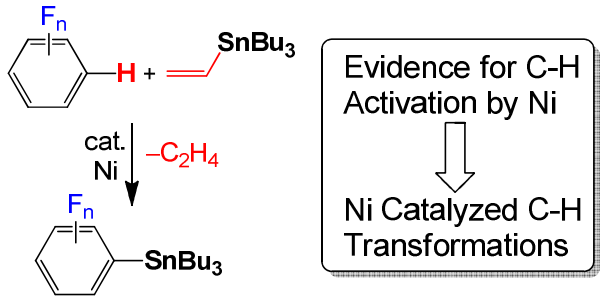
TOC Graphic



A search for fundamental understanding of how Ni complexes can be designed to undergo challenging C−H activation reactions provides an entry into unprecedented C−H functionalization reactions.