

Understanding Reactions Between Nickel(0) and Substrates Relevant to Cross-Coupling Reactions

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Declaration

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

This thesis is dedicated to my mom and dad; Jayne and Paul. I could not have done this without you.

Acknowledgements

I am grateful to everyone who has been some part involved with my PhD project at some point or another. Including the many who I have met from around the globe at conferences, thanks for your helpful scientific discussions that have helped my research progress. Moving to Glasgow has been an amazing experience and it would have been very different if it was not for everyone's kindness and welcoming nature, so thank you.

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Finally, I would like to thank my family; Jayne (mom), Paul (dad) and Andy (brother). Without my parents, I would not be where I am today. They have always taught me I can be whatever I want to be and pushed me to do my best, all the way from primary school to now. Even if that sacrifices us living near each other... although they have had many free holidays to Glasgow over the last four years. I am grateful for you putting up with tears when I could not grasp chemistry at A level, but also for sharing tears of joy when I found out I got into university, secured my PhD place, and received an offer of my first postdoctoral position. My brother and I could not be more opposite and rarely see each other, but, when we do it's like we've never been apart. I love you all so much and cannot thank you enough for all the support and advice you have given me over the years, not just during my PhD but throughout my life.

Abstract

Nickel catalysis is a rapidly developing field within synthetic chemistry with the potential to replace palladium in several cross-coupling reactions. However, mechanistic insight with regards to nickel lags far behind, this work has shed light onto the mechanisms involved during the oxidative addition step in nickel-catalysis.

A kinetic study into the oxidative addition of alkyl halides to $[\text{Ni}(\text{COD})(\text{dppf})]$ was carried out. The active species $[\text{Ni}(\text{dppf})_2]$ (generate *in-situ*) undergoes halide abstraction with alkyl halides and radical recombination yields the oxidative addition products. Addition of excess dppf alongside $[\text{Ni}(\text{COD})(\text{dppf})]$, thus generating high concentrations of $[\text{Ni}(\text{dppf})_2]$, dramatically increased product formation in Kumada-Tamao-Corriu cross-couplings.

This reaction was not specific to $[\text{Ni}(\text{dppf})_2]$ and other three-coordinate nickel intermediates, $[\text{Ni}(\text{dppf})\text{L}]$, followed a similar mechanism. The effect of the identity of added ligand on rates of oxidative addition with alkyl halides was investigated using kinetic experiments and DFT calculations. The halide abstraction step was found to not always be irreversible and this can have a significant effect on the rate of reaction. Addition of any ligand free ligand used in this study improved the performance of $[\text{Ni}(\text{COD})(\text{dppf})]$ as a catalyst in Kumada-Tamao-Corriu cross-coupling of alkyl halides.

The reaction of both vinyl and aryl triflates with $[\text{Ni}(\text{COD})(\text{dppf})]$ was also investigated. Vinyl halides reacted faster than aryl triflates which is due to an initial displacement of COD to form the corresponding η^2 complex prior to oxidative addition. Reactions can proceed through either a 3-centred or 5-centred transition state for oxidative addition. Good conversion of both vinyl and aryl triflates was observed when employed as substrates in Kumada-Tamao-Corriu cross-couplings.

Finally, a study into the effect of ancillary ligands on oxidative addition of aryl halides to a $\text{Ni}^0\text{-dppf}$ species was conducted. A variety of ligands were studied and most showed slower reactivity when compared to COD, which is the most common ligand employed for $\text{Ni}^0\text{-dppf}$ species.

Peer-Reviewed Publications

1. Unexpected Nickel Complex Speciation Unlocks Alternative Pathways for the Reactions of Alkyl Halides with dppf-Nickel(0) - Megan E. Greaves, Thomas O. Ronson, Guy C. Lloyd-Jones, Feliu Maseras, Stephen Sproules, and David J. Nelson, *ACS Catal.* 2020, **10**, 10717–10725.
2. Reactions of nickel(0) with organochlorides, organobromides, and organoiodides: mechanisms and structure/reactivity relationships - Megan E. Greaves, Elliot L. B. Johnson Humphrey and David J. Nelson, *Catal. Sci. Technol.*, 2021, **11**, 2980.
3. The Effect of Added Ligands on the Reactions of [Ni(COD)(dppf)] with Alkyl Halides: Halide Abstraction May Be Reversible - Megan E. Greaves, Thomas O. Ronson, Feliu Maseras, and David J. Nelson, *Organometallics*, 2021, **40**, 1997 – 2007.

Abbreviations

acac	Acetylacetonate
bipy	2,2-Bipyridine
bimep	(P)-2,2'-bis(dimethylphosphino)-1,1'-biphenyl
BHT	2,6-Di- <i>tert</i> -butyl-4-methylphenol
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl group
EPR	Electron Paramagnetic Resonance
IR	Infrared
^{DMP} DAB	N,N'-Bis(2,6-dimethylphenyl)ethan-1,2-diimine
dba	Dibenzylideneacetone
DCD	Dewar-Chatt-Duncanson
DEM	Diethoxymethane
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
DIPHOS	1,2-Bis(diphenylphosphino)ethane
dipp	1,3-Bis(diisopropylphosphino)-propane
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
dmpe	1,2-bis(dimethylphosphino)ethane
DMSO	Dimethyl sulfoxide
dppb	1,1'-Bis(diphenylphosphino)butane
dppe	1,1'-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppm	1,1'-Bis(diphenylphosphino)methane

dppp	1,1'-Bis(diphenylphosphino)propane
DQ	Duroquinone
GC-FID	Gas chromatography-flame ionisation detection
GC-MS	Gas chromatography-mass spectrometry
HPLC	High-performance liquid chromatography
LiHMDS	Lithium bis(trimethylsilyl)amide
MA	Maleic anhydride
NHC	N-Heterocyclic Carbene
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
PhMe	Toluene
QPhos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
^{CF3} stb	Trans-4,4'-i- <i>tert</i> -butylstilbene
^{tBu} stb	Trans-4,4'-(trifluoromethyl)stilbene
TBAI	Tetrabutylammonium iodide
TEM	Transmission Electron Microscopy
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TEP	Tolman Electronic Parameter
THF	Tetrahydrofuran
Tol-BINAP	(<i>S</i>)-(-)-2,2'- <i>p</i> -tolyl-phosphino)-1,1'-binaphthyl
tpy	Terpyridine
UV-Vis	Ultraviolet-Visible

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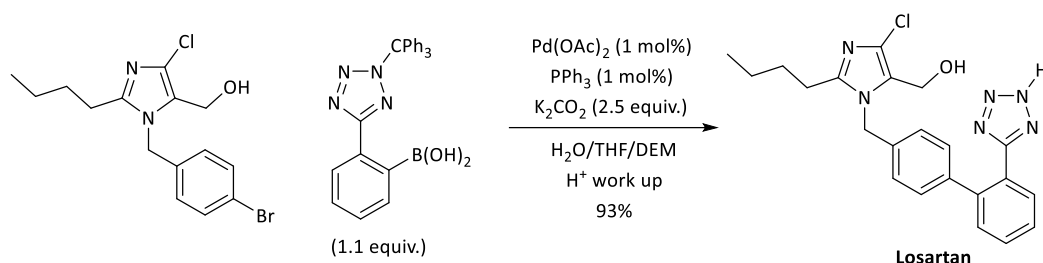
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Chapter 1 - Introduction

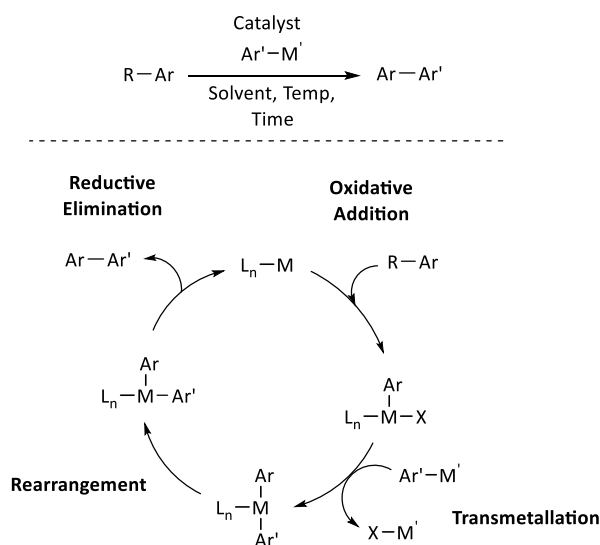
1.1. Cross-coupling Reactions

The first examples of cross-coupling reactions are from Kharasch in the 1940's. Several metal salts were employed as catalysts, including CoCl_2 , NiCl_2 , CrCl_2 , FeCl_3 and CuCl_2 , for the coupling of organic halides with Grignard reagents.¹⁻³ Since then, the scope of cross-coupling reactions and mechanistic understanding of these reactions has been dramatically improved. Cross-coupling reactions have since been scaled up for industrial use as a safe and robust method for accessing previously synthetically challenging molecules.⁴ To give one example, a new synthetic route to Losartan, used to treat high blood pressure, was developed by Merck in the 1990's, employing a Suzuki-Miyaura cross-coupling reaction (Scheme 1.1).^{5,6}



Scheme 1.1. Synthetic route to Losartan developed in 1994.⁶

The names of these cross-coupling reactions are indicative of the type of organometallic transmetalating reagent employed; Suzuki-Miyaura (boron species), Kumada-Corriu-Tamao (Grignard reagents, magnesium reagents), Negishi (zinc species), Stille (tin reagents).⁷ Although these reactions employ different transmetalating reagents, they typically contain broadly the same mechanistic steps within the catalytic cycle (Scheme 1.2): oxidative addition of an electrophile, a transmetalation step and finally reductive elimination to yield the coupled product.



Scheme 1.2. Typical catalytic cycle for a metal catalysed cross-coupling reactions involving an aryl halide and transmetalating reagent.

1.2. Nickel vs Palladium

1.2.1. Electronic Configuration

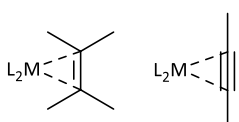
Although palladium and nickel occupy the same group (10) in the periodic table, they have very different electron configurations – Pd [Kr]4d¹⁰ and Ni [Ar]4s²3d⁸.⁸ These differences help explain the observed difference in reactivity; palladium is typically seen in the 0 and +2 oxidation states whereas nickel can occupy 0, +1, +2, +3 and +4 oxidation states. Due to the range of oxidation states it can occupy and the more nucleophilic nature of the nickel, it can carry out couplings with aryl chlorides more readily and will often require less sophisticated ligands than the corresponding palladium systems.⁸ The range of oxidation states means homolytic bond cleavage and radical chemistry is also prevalent in nickel catalysis.⁹

1.2.2. Ligands

Catalytic reactions often rely on ligand dissociation to generate active species *insitu*, therefore, the binding strength of ligands to metal centres is an important property to consider. These have been calculated and the trend for M⁰L₂ complexes was shown to be as follows; Pd-P (33.6 kcal mol⁻¹), Ni-P (39.7 kcal mol⁻¹) and Pt-P (45.5 kcal mol⁻¹). Lower bond energies were found for M^{II}L₂ complexes suggesting easier generation of vacant sites when

the metals occupy a +2 oxidation state.^{9,10} A unique property of nickel, compared to other group 10 metals, is the strong bonds formed to unsaturated compounds. Bonds to unsaturated compounds in nickel complexes range in strength from 34 – 47 kcal mol⁻¹ compared to Pd and Pt that only range from 16 – 23 kcal mol⁻¹ (Table 1.1).^{9,10} A similar study was carried out investigating the adsorption of ethene to group 10 metals. Pd and Pt were found to have similar adsorption energies (50 kcal mol⁻¹) whereas Ni had a much higher adsorption energy (68 kcal mol⁻¹), thought to be due to good overlap of the 3s orbitals of Ni and the antibonding orbitals in ethene.¹¹ This helps explain the stability of nickel complexes containing unsaturated molecules as ligands.^{12,13}

Table 1.1. Binding energies of alkene and alkynes to Ni, Pd and Pt.^{9,10}



Metal	ΔE (C=C) (kcal mol ⁻¹)	ΔE (C≡C) (kcal mol ⁻¹)
Ni	34.3	41.6
Pd	16.1	17.9
Pt	19.6	23.7

1.2.3. Cost

Palladium is considered as a precious metal due to its low natural abundance in the Earth's crust (mainly due to the extensive use in catalytic converters) and therefore has an inflated price when compared to other transition metals (Figure 1.1).^{14,15} PdCl₂ per mole has a cost of £10,781 compared to the analogous (anhydrous) NiCl₂ with a cost of £3,939, which presents an obvious benefit of replacing palladium catalysts with suitable nickel ones. It is noteworthy that the price of NiCl₂·6H₂O which is commonly used to make Ni^{II} pre-catalysts has an even lower cost of £927 per mole, a tenth of cost of the palladium precursor.¹⁶

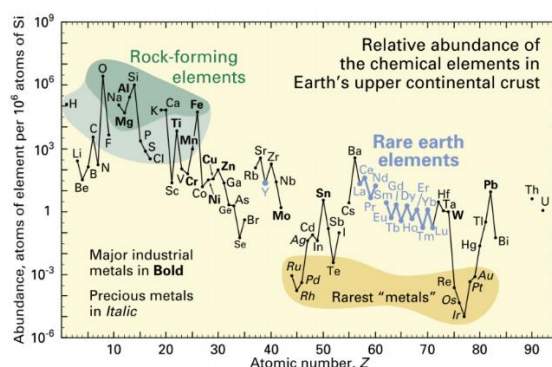


Figure 1.1. Abundance of the chemical elements in Earth's upper continental crust as a function of atomic number.¹⁴

1.2.4. Toxicity

A report published in 2016 reviewed toxicity data collected for a variety of different metals and salts (Ni, Cu, Fe, Pd, Pt, Rh, and Au). It was established that any absorbed nickel is likely to accumulate in the liver, kidney, and lungs. Occupational exposure is most likely through inhalation and was shown to induce lung tumours in exposed workers.¹⁷ In a case study, a 38-year old healthy (non-smoking) man died 13 days after exposure to nickel in a metal arc process, where nickel is sprayed onto a metal surface. A recreation of working conditions found that the worker would have inhaled approximately 1 g of nickel over a 90-minute period. This was sufficient for dense particles (up to 25 nm) to collect within lung tissue, as observed via Transmission Electron Microscopy (TEM) (Figure 1.2).¹⁸ Absorption of nickel through the skin is poor and only mild allergic reactions are the most common effect in humans.¹⁹

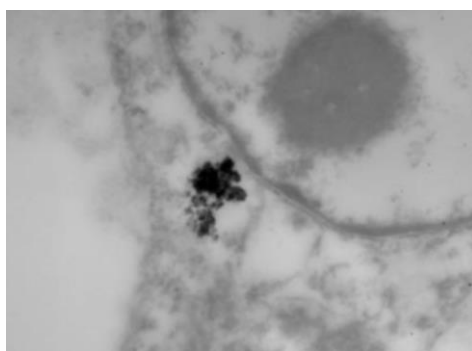


Figure 1.2. TEM of unstained section of lung showing electron dense nickel nanoparticles.¹⁸

Palladium was found to have the highest bioavailability in mussels when exposed to humic water (compared to Pt and Rh) and was found bound to many proteins.²⁰ Workers exposed to palladium in catalytic convertor manufacturing sites often suffer from occupational asthma provoked by exposure to chloroplatinates.^{17,21} However, retention of palladium in the body is low, especially when inhaled or ingested (the most common pathways into the body).

Cross-sensitisation is observed between nickel and palladium. A study by Kränke in 1995 found that Pd and Ni were the most frequently reacting sensitisers. Of all 10,000 patients, 5% reacted to PdCl₂ alone, whereas all other patients that experienced an allergic reaction also had a reaction to Ni₂SO₄. This indicated a shared protein-binding site between the two and they were able to mimic each other. A relationship between gender and sensitivity was also unearthed by Kanerva, where women were 10 times more likely to have an allergic reaction to the most popular sensitisers.^{17,22}

1.2.5. Robustness

When compared to palladium, nickel complexes are more sensitive to reaction conditions (solvents, temperature, base) and as such are more likely to undergo deactivation and lack robustness.²³ This robustness is evident with the pre-catalysts used in both palladium and nickel cross-couplings. A vast array of palladium precursors can be used to catalyse cross-coupling reactions, and even trace impurities are capable of turning over reactions.^{24,25} However, nickel systems require a more fine-tuned approach, where extensive ligand screens are often required to achieve any catalytic activity.⁹ This reliability on selective ligands can also be seen as an advantage, because it enables fine tuning of catalysts that enable only one transformation and limit off-cycle reactions. Although found to be more reactive than palladium in the case of aryl chlorides, the increased reactivity observed with nickel can be a disadvantage, where side-reactions can be difficult to predict and control.⁹ In a similar vein, the wider range of oxidation states accessible to nickel that can allow for useful radical chemistry can also lead to generation of several side products which are difficult to suppress.

1.4. Mechanisms of Palladium Catalysed Reactions

1.4.1. Oxidative Addition

Aryl Halides

In 1981, Fauvaraque investigated the kinetics of oxidative addition of $[\text{Pd}(\text{PPh}_3)_4]$ to aryl iodides.²⁶ As $[\text{Pd}(\text{PPh}_3)_4]$ in solution (in equilibrium with $[\text{Pd}(\text{PPh}_3)_3]$) is very pale yellow, UV-visible spectroscopy was unable to detect this and any intermediates when reacted with aryl iodides, and so electrochemistry was employed for kinetic analysis of this reaction. A solution of $[\text{Pd}(\text{PPh}_3)_4]$ and excess PPh_3 in THF (with added $[(n\text{-C}_4\text{H}_9)_4\text{N}][\text{ClO}_4]$ as the supporting electrolyte) under an argon atmosphere (up to 323 K) exhibits a reproducible oxidative wave at -0.47 V (vs AgClO_4/Ag electrode) that corresponds to $[\text{Pd}(\text{PPh}_3)_3]$, previously observed by Musco.^{26,27} Under pseudo-first order conditions (excess PPh_3), it was observed that oxidative addition of aryl iodides to $[\text{Pd}(\text{PPh}_3)_3]$ was first order with respect to Pd^0 and aryl iodide; the observed rate constant was also inversely proportional $[\text{PPh}_3]$.²⁶ Rate constants were obtained over 273 K to 323 K to obtain an Arrhenius plot; at 300 K, activation parameters (for oxidative addition) of $\Delta H^\ddagger = 18.4 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = 3.1 \text{ cal mol}^{-1} \text{ K}^{-1}$ were obtained.²⁶ Various *para*-substituted aryl iodides were reacted with $[\text{Pd}(\text{PPh}_3)_3]$ at 298 K, a Hammett plot was constructed and a ρ value of 2 was obtained (Figure 1.3). The positive ρ value indicates electron density transfer from the Pd^0 centre to the aromatic ring causing a build-up of negative charge on the aromatic ring in the transition state of oxidative addition, which is stabilised by electron-withdrawing substituents.²⁶

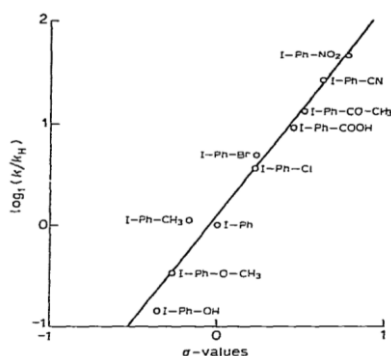
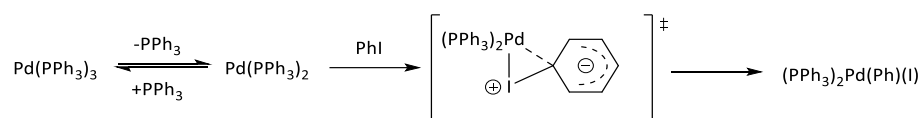


Figure 1.3. Hammett plot for oxidative addition of $[\text{Pd}(\text{PPh}_3)_3]$ to *para*-substituted aryl iodides at 298 K in the presence of 50 equivalents of PPh_3 .²⁶

Fauvaraque proposed a mechanism based on the kinetic observations; an initial dissociation of one PPh_3 to form a $[\text{Pd}(\text{PPh}_3)_2]$ active species for oxidative addition was proposed. This complex can accept a pair of electrons from the aryl iodide to form a three-centred type transition state and is similar in mechanism to nucleophilic aromatic substitution (Scheme 1.3).²⁶



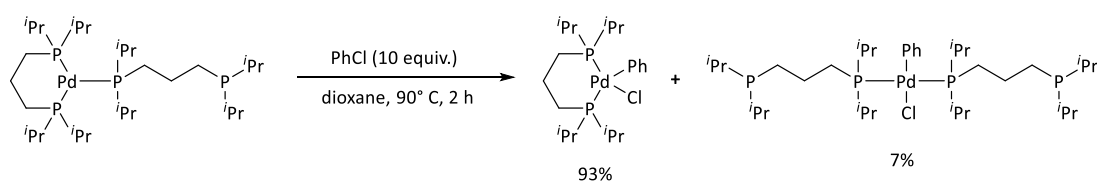
Scheme 1.3. Fauvaraque's proposed mechanism for the oxidative addition of $[\text{Pd}(\text{PPh}_3)_3]$ to aryl iodides.²⁶

In 1990, Amatore repeated kinetic experiments (oxidative addition of $[\text{Pd}(\text{PPh}_3)_4]$ to aryl iodides) by Fauvaraque in toluene, as opposed to THF.²⁸ The disappearance of a unique electrochemical oxidation wave attributed to Pd^0 was monitored over time in the presence of aryl iodides. The reaction was overall a second order process, and first-order with respect to both Pd^0 and aryl iodide.²⁸ When PPh_3 was added to kinetic experiments, the rate was found to be inversely proportional to the concentration of PPh_3 , which was expected as dissociation of PPh_3 is required for oxidative addition to occur (Scheme 1.3).^{26,28} Arrhenius plots over 293 K – 323 K gave linear correlations and provided the following activation parameters for oxidative addition; $\Delta H^\ddagger = 17.9 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = 1.7 \text{ cal mol}^{-1} \text{ K}^{-1}$.²⁸ Several different *para*-substituted aryl iodides were used as substrates and a Hammett plot was produced, with a linear correlation and ρ value of 2.3.²⁸ As the activation parameters and ρ value in the Hammett plot were almost identical to those observed by Fauvaraque in THF, it was concluded that the reaction mechanism was independent of the solvent used.²⁶ The mechanisms were concluded to be identical, suggesting no coordination of palladium intermediates to solvent molecules, that would hinder reactivity, over the course of the reaction.²⁸

The order of reaction rate for oxidative addition of $[\text{Pd}(\text{PPh}_3)_4]$ to aryl halides was found to be $\text{I} > \text{Br} > \text{Cl}$ as first reported in 1971 by Fitton and Rick, which is consistent with the breaking of the carbon-halogen bond being the rate determining step.²⁹ Although lacking in-depth kinetic studies, a three-centred transition state (as in Scheme 1.3) was predicted to

be the most likely pathway for oxidative addition.²⁹ To further probe the mechanism, *para*-substituted aryl chlorides were reacted with $[\text{Pd}(\text{PPh}_3)_4]$. Chlorobenzene or aryl chlorides bearing electron donating groups gave no reaction at high temperatures over long periods of time, whereas electron deficient aryl chlorides readily formed the oxidative addition product. This result was expected due to the ability of electron-withdrawing substituents to stabilise the charge on the aryl ring in the transition state.²⁹

Portnoy and Milstein pioneered the use of palladium catalysts to successfully carbonylate and formylate aryl chlorides in the late 1980's to give rise to numerous useful functionalised products.^{30,31} Monodentate phosphines were shown to be poor ligands for these transformations; dippp (1,3-bis(diisopropylphosphino)propane) was uniquely able to catalyse these reactions (of the bidentate phosphine ligands tested). This prompted an in-depth study into the mechanism of oxidative addition of chlorobenzene to $[\text{Pd}(\text{dippp})_2]$.³² The reaction between $[\text{Pd}(\text{dippp})_2]$ and chlorobenzene yielded three products in the ^{31}P NMR spectrum, and free dippp was present as one of the products. Also present were two doublets attributed to the *cis* oxidative addition product (93%), and a singlet associated with the *trans* oxidative addition product (7%) (Scheme 1.4).³² The reaction of the pure *cis* product with free ligand showed that the *cis* and *trans* isomers are in equilibrium with each other, and this equilibrium led to imperfect kinetic data. Despite this, the reaction was confirmed to be first order in chlorobenzene and Pd^0 , and inverse first order in dippp, thus supporting a transition state involving a $[\text{Pd}(\text{dippp})]$ 14-electron species.³²



Scheme 1.4. Products observed via NMR spectroscopy when an excess of chlorobenzene is reacted with $[\text{Pd}(\text{dippp})_2]$ in dioxane at 90 °C.³²

A similar transition state as proposed by Amatore was given as a plausible intermediate in the reaction of $[\text{Pd}(\text{dippp})_2]$ and chlorobenzene (Figure 1.4b).³² The bidentate dippp gives rise to a more nucleophilic Pd^0 centre with a bent P-Pd-P geometry, which is able to react rapidly with aryl chlorides. This, coupled with the ability of dippp to act as both a bidentate and

monodentate ligand, uniquely facilitates the catalytic reactions developed by Portnoy and Milstein.³² The intermediate proposed was also supported by Hammett plots constructed. The highly positive ρ value obtained (Figure 1.4a) suggests a significant build-up of negative charge in the transition state.³²

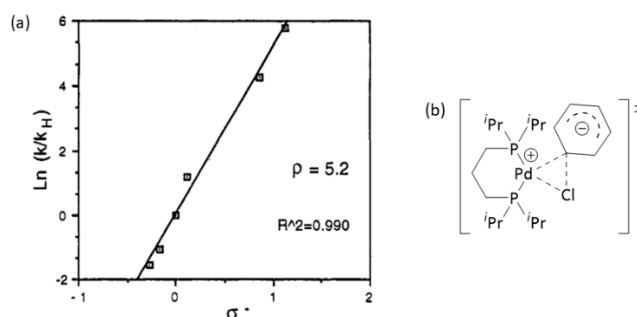
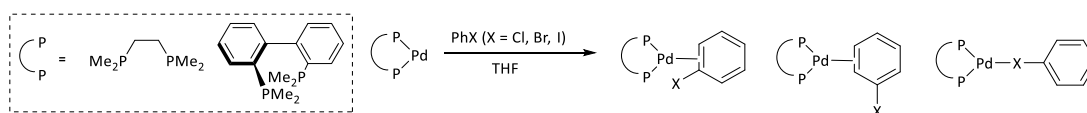


Figure 1.4. (a) Hammett correlation of the observed pseudo-first order rate constant vs σ^- .
(b) Transition state proposed by Portnoy and Milstein for the oxidative addition of [Pd(dipp)₂] to chlorobenzene.³²

In 2004, Ziegler used DFT calculations to investigate the oxidative addition of chloro-, bromo- and iodobenzene to Pd⁰L₂ complexes bearing bidentate phosphine ligands, where L was either dmpe (1,2-bis(dimethylphosphino)ethane) or dimep ((P)-2,2'-bis(dimethylphosphino)-1,1'-biphenyl).³³ DFT calculations were used to differentiate between concerted and S_NAr mechanisms; they also investigated the effects of solvation in THF on transition states. For oxidative addition, ligand dissociation from PdL₂ must first occur, and barriers for this ranged from 35 – 45 kcal mol⁻¹ for dmpe and dimep, both in the gas phase and solvated in THF (the COSMO continuum solvation model was used).³³ Solvation reduced the required energy for both ligands by 5 kcal mol⁻¹.³³ Once PdL has formed, aryl halides act as π -acceptor ligands to stabilise the Pd⁰ centre prior to oxidative addition. There are three different conformations for this binding: η^2 -coordination at the C_{ipso}-C_{ortho} bond, η^2 -coordination at the C_{ortho}-C_{meta} bond or binding directly through the halogen (Scheme 1.5), all of which were more stable when compared to unsaturated PdL.³³



Scheme 1.5. Possible coordination modes of the aryl halide to unsaturated PdL complex.³³

In all coordination modes (Scheme 1.5), a lengthening of the C-X bond was observed in the order $\text{Cl} < \text{Br} < \text{I}$.³³ The η^2 binding modes were energetically favoured over halide binding. The two η^2 -bound intermediates were of similar stability, however, in η^2 *Cipso-Cortho*, the C-X bond was more activated and more suitably orientated for oxidative addition, and this was the complex used for further computational study.³³ Notably, during this step dmpe formed a more stable complex than dimep, which compensated for the advantage dimep experienced during ligand dissociation; this made the dmpe and dimep complexes equally stable relative to PdL_2 .³³ From this η^2 *Cipso-Cortho* bound intermediate, oxidative addition is energetically favourable (-22 to $-31 \text{ kcal mol}^{-1}$) for both ligands and all halides, to form an almost perfectly square planar d^8 complex.³³ A concerted transition state (Figure 1.5) could not be located in solution, however, a dissociative transition state (Figure 1.5) with an elongated C-X bond was almost barrierless ($\text{Cl } 7.5 \text{ kcal mol}^{-1}$, $\text{Br } 3 \text{ kcal mol}^{-1}$, $\text{I } 1 \text{ kcal mol}^{-1}$) in THF.³³

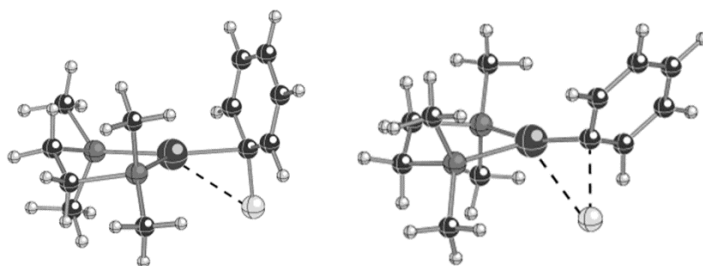
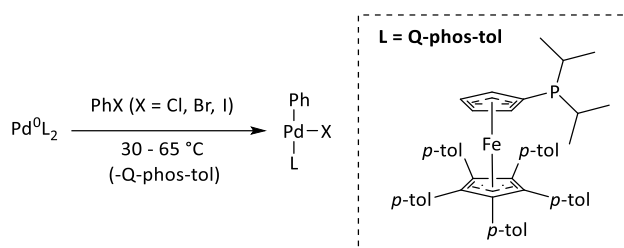


Figure 1.5. Transition states for oxidative addition of PhX to $[\text{Pd}(\text{dmpe})]$.³³

Ziegler concluded that in solution, dissociation of halide from the $\text{PdL } \eta^2$ coordinated complex was kinetically and thermodynamically facile and barrier free.³³ Initial coordination of the aryl halide to PdL was the most endothermic step and ligand dissociation was the rate-limiting step of the overall reaction.³³

Up until this point, no experimental mechanistic studies had been reported where oxidative addition of PhCl, PhBr and PhI to the same Pd^0 complex were studied, which prompted Hartwig to fill this gap in the literature in 2005.³⁴ The Pd^0 complex studied was

[Pd(Q-phos-tol)₂], where QPhos (1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene) is an extremely bulky and electron rich ligand that enables oxidative addition of aryl chlorides to be observed (Scheme 6).³⁴ These QPhos ligands were also found to form active species that are synthetically useful, and able to facilitate the arylation of esters, amides, cyanoesters and malonates.^{35,36} PhCl, PhBr and PhI were all found to oxidatively add and quantitative conversion to the corresponding Pd^{II} complexes, [Pd(Q-phos-tol)(Ph)(X)] (where X = I, Br and Cl), was observed *via* ³¹P NMR spectroscopy.³⁴



Scheme 1.6. Oxidative addition of aryl halides to [Pd(Q-phos-tol)₂] in neat aryl halide at various temperatures, monitored via ³¹P NMR spectroscopy.³⁴

The *k*_{obs} for oxidative addition of iodobenzene to the [Pd(Q-phos-tol)₂] complex was found to be first order in [PhI] and had no dependence on the concentration of free ligand (Figure 1.6), eliminating a pathway in which ligand dissociation was involved in the rate-determining step.³⁴

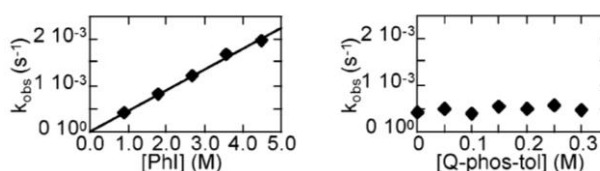
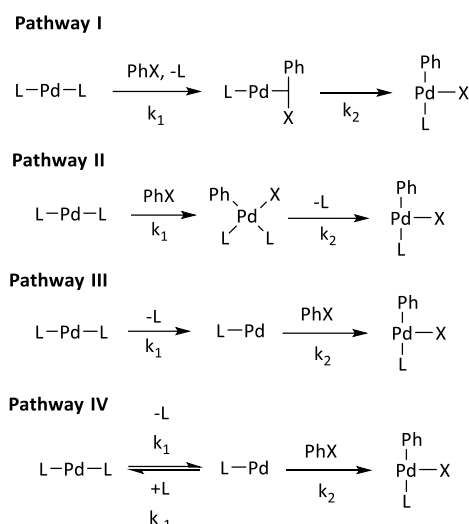


Figure 1.6. Plots of *k*_{obs} vs [PhI] and *k*_{obs} vs [Q-phos-tol] for the oxidative addition of PhI to [Pd(Q-phos-tol)₂].³⁴

There were two possible pathways that this kinetic data would support, I and II described here (Scheme 1.7).³⁴ In pathway I, PhI coordinates to the Pd⁰ centre displacing a ligand in one distinct step, followed by a subsequent fast irreversible oxidative addition step. In pathway II; oxidative addition occurs first and then dissociation of the ligand occurs afterwards in a second step. To distinguish between these possible mechanisms, reductive elimination of an

analogous Pd^{II} complex was studied. Reductive elimination was found to be independent of [L], meaning that coordination of substrate and ligand dissociation must occur in the same step (Pathway I, Scheme 1.7).³⁴ The rate expression for the oxidative addition of PhI to [Pd(Q-phos-tol)₂] is given in Equation 1.1.



Scheme 1.7. Possible pathways for oxidative addition of aryl halides to [Pd(Q-phos-tol)₂].³⁴

In contrast to PhI, k_{obs} for the oxidative addition of PhBr was found to be independent of the concentration of both PhBr and free Q-phos-tol.³⁴ This indicated that the rate-limiting step must be dissociation of ligand from the [Pd(Q-phos-tol)₂] complex (Pathway III, Scheme 1.7); this was experimentally confirmed by showing that the k_{obs} for oxidative addition was identical to the rate of dissociation of a Q-phos ligand from [Pd(Q-phos-tol)₂].³⁴ Due to difficulties in observing ligand dissociation with Q-phos-tol, Q-phos-CF₃ and Q-phos (Figure 1.7) were used as alternatives. Q-phos was added in excess to [Pd(Q-phos-CF₃)₂] and ligand exchange was observed *via* ³¹P NMR spectroscopy, to obtain a rate constant for ligand

dissociation.³⁴ This confirmed Pathway III was in operation for the reaction of PhBr with [Pd(Q-phos-tol)₂].

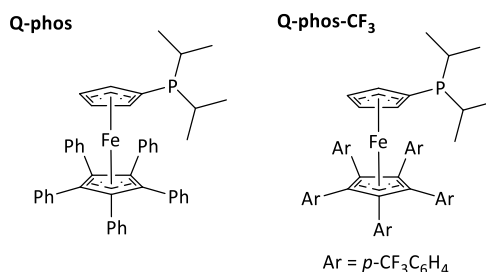


Figure 1.1.7. Q-phos and Q-phos-CF₃ ligands.³⁴

A third different mechanism was involved in the oxidative addition of PhCl. The observed rate constant was dependent on [PhCl] but inversely proportional to the [Q-phos-tol]. The k_{obs} value observed was identical to that observed for ligand dissociation from [Pd(Q-phos-tol)₂] and almost identical to k_{obs} for the oxidative addition of PhBr. This confirmed a mechanism very similar to that seen with PhBr whereby dissociation of Q-phos-tol was still rate-limiting. However, as the rate of this reaction was inversely proportional to ligand concentration, ligand dissociation must be reversible in the case of PhCl (Pathway IV, Scheme 1.7).³⁴ The rate expression helps explain why the pathways differ (Equations 1.1 – 1.3).³⁴

Equation 1.1. Rate expression for oxidation addition of PhI to [Pd(Q-phos-tol)₂] via pathway

I.³⁴

$$k_{obs} = k_1[PhX]$$

Equation 1.2. Rate expression for oxidation addition of PhBr to [Pd(Q-phos-tol)₂] via

pathway II.³⁴

$$k_{obs} = k_1$$

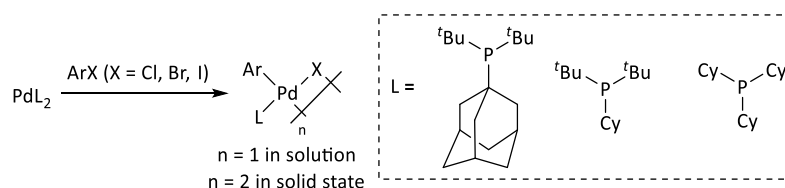
Equation 1.3. Rate expression for oxidation addition of PhCl to [Pd(Q-phos-tol)₂] via

pathway III.³⁴

$$k_{obs} = \frac{k_1 k_2 [PhX]}{k_{-1} [L] + k_2 [PhX]}$$

After identifying individual mechanistic pathways for the three different aryl halides, in 2009 Hartwig investigated the effect (on the mechanism) of changing ligands bound to

palladium.^{37,38} An extensive kinetic study looked at the oxidative addition of $[\text{PdL}_2]$ complexes, where L were trialkylphosphine ligands (Scheme 1.8). It was concluded that the nature of the aryl halide was more important than the steric bulk of the phosphine ligand bound to the Pd centre. Reactions with chloro-, bromo- and iodobenzene were all first order in aryl halide. With iodobenzene, no dependence on the concentration of added ligand was found, suggesting that oxidative addition occurred directly to PdL_2 .³⁸ However, reactions with chlorobenzene were found to have rates that were inversely proportional to added ligand, meaning that the dissociation of the ligand must occur before oxidative addition.³⁸ Bromobenzene was found to undergo oxidative addition *via* a combination of both pathways.³⁸ The reasoning behind these different mechanisms was given; it was suggested that this is due to the reactivity of the aryl halide (the BDE of the C-X bond). The more reactive iodobenzene can undergo reactions with PdL_2 while the less reactive chlorobenzene requires the more reactive unsaturated monoligated PdL species.³⁸

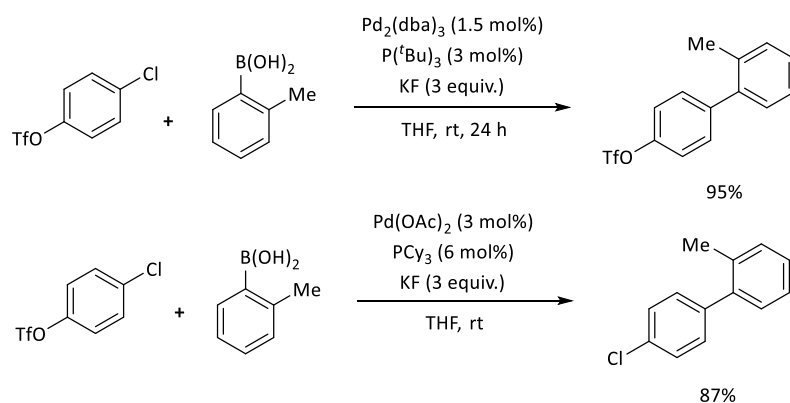


Scheme 1.8. Oxidative addition of aryl halides to $[\text{PdL}_2]$ complexes, where L is an alkyl phosphine ligand. Forming a dimeric species in the solid state that becomes monomeric in solution.³⁸

Fu and Schoenebeck later encountered systems (in different palladium catalysed reactions) where ligands did have a significant effect on the mechanism. Whilst investigating palladium catalysts for the Suzuki cross-coupling of arylboronic acids with aryl and vinyl halides, Fu focused on electron rich ligands as they had been shown to be necessary for the successful coupling of aryl chlorides under mild conditions.^{39–41} The cross-coupling of aryl chlorides and arylboronic acids was achieved using a $\text{Pd}_2(\text{dba})_3/\text{P}(\text{tBu})_3$ catalyst system, employing Cs_2CO_3 as the base (in 1,4-dioxane).⁴⁰ The ratio of Pd to $\text{P}(\text{tBu})_3$ was an important factor to consider when optimising these reactions. A 1:1 ratio produced a very active catalyst whereas a 1:2 ratio led to sluggish reactions.⁴¹ Studies by ^{31}P NMR spectroscopy revealed ratios from 1:1 to 1:1.5 ($\text{Pd}_2(\text{dba})_3:\text{P}(\text{tBu})_3$) showed only one species in solution, attributed to $[\text{Pd}(\text{P}(\text{tBu})_3)_2]$.⁴¹

Adding a further excess of phosphine ligand had no effect on the palladium species present, with only the bisphosphine complex and free ligand present in the ^{31}P NMR spectra. Although it was obvious that the bisphosphine complex was favoured, this was deemed not to be the active catalyst as a very slow reaction ensued when $[\text{Pd}(\text{P}^t\text{Bu}_3)_2]$ was used as a catalyst in the cross-coupling of 3-chloropyridine with *o*-tolylboronic acid. However, when excess $\text{Pd}_2(\text{dba})_3$ was added, a rate increase was observed, suggesting that the monophosphine complex $[\text{Pd}(\text{P}^t\text{Bu}_3)]$ was the active species in catalysis, confirmed later by Hartwig *via* kinetic studies.^{41,42}

Although successful in the cross-coupling of aryl chlorides, bromides and iodides, the $\text{Pd}_2(\text{dba})_3/\text{P}^t\text{Bu}_3$ catalyst system was unsuccessful when aryl triflates were used as substrates. The substitution of P^tBu_3 for PCy_3 (Cy = cyclohexyl) in the catalyst system fully converted 4-methoxyphenyl triflate and *o*-tolylboronic acid into the corresponding cross-coupled product at room temperature in only six hours.⁴¹ This observed reactivity was exploited to perform chemoselective Suzuki cross-couplings (Scheme 1.9); these allow the selective coupling of an aryl chloride in the presence of an aryl triflate, or *vice versa*, through choice of catalyst system.⁴¹ This is remarkable, particularly in the case of the selective oxidative addition of Cl over OTf, considering the order of reactivity decreases in the following order; $\text{I} > \text{OTf} > \text{Br} \gg \text{Cl}$.⁴³



Scheme 1.9. Chemoselective cross-coupling of 4-chlorophenyltriflate with *o*-tolylboronic acid using two different catalyst systems.⁴¹

In 2010, Schoenebeck and Houk investigated this chemoselectivity that was observed *via* computational experiments.⁴⁴ Oxidative insertion of $[\text{Pd}(\text{P}^t\text{Bu}_3)]$ into 4-chlorophenyltriflate

showed favoured insertion into the C-Cl bond (by 5.8 kcal mol⁻¹ vs insertion into C-OTf bond), as observed experimentally.⁴⁴ This confirmed Fu's suggestion that the monophosphine complex was the active species, when employing the Pd₂(dba)₃/P(^tBu)₃ catalyst system.

When using PCy₃ as the ligand, the monophosphine complex [Pd(PCy₃)] also favoured insertion into the C-Cl bond (by 3.6 kcal mol⁻¹ vs insertion into C-OTf bond), the opposite to what was observed experimentally.⁴⁴ It was actually the bisphosphine complex [Pd(PCy₃)₂] (rather than [Pd(PCy₃)]) that favoured the C-OTf bond over C-Cl (by 4.3 kcal mol⁻¹).⁴⁴

This suggests that when P(^tBu)₃ is employed, a monophosphine complex is catalytically active whilst when PCy₃ is used, a bisphosphine complex is the active species.⁴⁴ This is an excellent example of where slight changes in ligand properties (Table 1.2) can mean that different complexes act as the active species.^{45,46} It also highlights the importance of understanding the catalytic cycle, to enable the full optimisation of these catalytic systems. TEP (Tolman Electronic Parameter) is a measure of the electron donor properties of phosphine ligands and cone angle (°) quantifies the steric properties of a ligand, a more extensive discussion of these can be found in Section 3.2.2. (Ligand Properties).

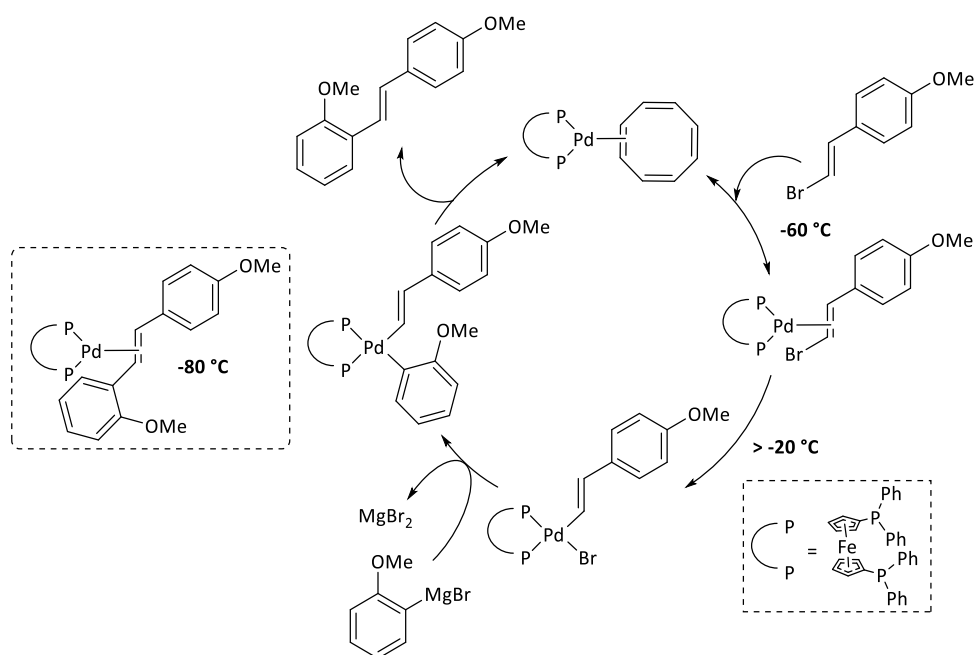
Table 1.2. TEP and cone angles for PCy₃ and P(^tBu)₃.^{45,46}

Ligand	TEP (cm ⁻¹)	Cone Angle (°)
PCy ₃	2056.4	170
P(^t Bu) ₃	2060.3	182

Vinyl Halides

With the mechanism of aryl halides (Cl, Br and I) now understood, attention turned to vinyl substrates and how they interact with Pd⁰. The successful cross-coupling of vinyl halides with Grignard reagents had been independently reported by both Corriu and Kumada in 1972.^{47,48} However, it was not until 1988 that Brown provided some insight into the mechanism of oxidative addition of vinyl halides to Pd⁰, the proposed catalytic cycle is shown in Scheme 1.10.⁴⁹ Brown focused on the oxidative addition of [Pd(dppf)(cyclo-octatetraene)], a synthetically useful catalyst, to 4-methoxy-β-bromostyrene and monitored the reaction *via* ³¹P NMR spectroscopy. In the presence of excess styrene at -40 °C (in THF), a reversible reaction between Pd(dppf)(cyclo-octatetraene) and the η² alkene complex was established.⁴⁹

This reversible binding of alkenes to Pd was also observed in the Heck arylation of methyl acrylate, a study also carried out by Brown.⁵⁰ When the reaction mixture was warmed above -20 °C, formal oxidative addition occurred to form the Pd^{II} oxidative addition complex. The species observed depended on the halide used; the use of 4-methoxy- β -chlorostyrene formed the corresponding η^2 alkene complex that was stable at 60 °C. However, when 4-methoxy- β -iodostyrene was used, no η^2 alkene complex intermediate was observed, only full conversion to the oxidative addition Pd^{II} complex.⁴⁹



Scheme 1.10. Brown's proposed mechanism from intermediates observed via ³¹P NMR spectroscopy in the reaction of 4-methoxy- β -bromostyrene with [Pd(dppf)(cyclo-octatetraene)] and transmetalation reagent *o*-methoxyphenylmagnesium bromide.⁴⁹

Addition of *o*-methoxyphenylmagnesium bromide at -80 °C, to the oxidative addition product, formed the new corresponding η^2 alkene complex observed via ³¹P NMR spectroscopy. This coupled product was readily displaced by cyclo-octatetraene to generate the desired coupled product and regenerate the Pd⁰ active species.⁴⁹ Notably, intermediates were only observed due to extreme low temperatures used.

Alkyl Halides

Suzuki, Negishi, Kumada and Stille couplings had been successfully optimised for the cross-coupling of alkyl halides. Interestingly, the vast majority of these reactions employed alkylphosphine ligands for these transformations in palladium catalysis.^{51–54} Whilst optimising the cross-coupling of boronic acids with unactivated alkyl bromides in 2002, Fu isolated crystals (suitable for X-ray crystallography) of the oxidative addition product formed from the reaction of $[\text{Pd}(\text{P}^t\text{Bu})_2\text{Me}]_2$ and 2-bromoethylbenzene (Figure 1.8).⁵⁵ The complex was remarkably stable as it did not undergo rapid β -hydride elimination as would be expected, thought to be due to the steric hinderance at the Pd centre. This complex is also a competent catalytic intermediate, as when reacted with *o*-tolylboronic acid and K^tOBu it gave the corresponding coupled product in 94% yield.⁵⁵

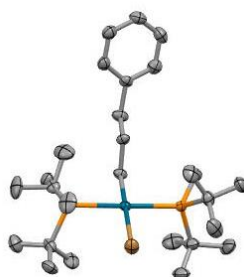
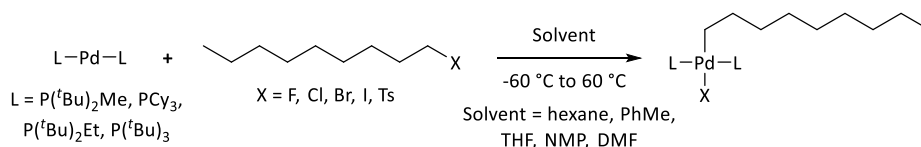


Figure 1.8. Crystal structure of the product from oxidative addition of $[\text{Pd}(\text{P}^t\text{Bu})_2\text{Me}]_2$ to 2-bromoethylbenzene.⁵⁵

Fu investigated the unique effects of these ligands and the factors that affected oxidative addition of alkyl halides to Pd^0 catalysts.⁵⁶ The oxidative addition reactions of *n*-nonyl halides were studied with a variety of PdL_2 complexes (with alkyl phosphine ligands) in different solvents to explore the mechanism (Scheme 1.11).



Scheme 1.11. Oxidative addition of nonyl-halides were studied to various complexes of Pd^0 and in different solvents, over a temperature range that depended on halides studied.⁵⁶

Activation parameters were obtained for the oxidative addition of *n*-nonyl bromide to $[\text{Pd}(\text{P}(\text{tBu})_2\text{Me})_2]$: $\Delta G^\ddagger = 20.8 \text{ kcal mol}^{-1}$ (at 293 K), $\Delta H^\ddagger = 2.4 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -63 \text{ kcal K}^{-1} \text{ mol}^{-1}$.¹ The large negative value obtained for $\Delta S^\ddagger$ was considered to be consistent with an $\text{S}_{\text{N}}2$ type mechanism.⁵⁶ Increasing the polarity of the solvent decreased the magnitude of the activation parameters obtained, by stabilising the cation formed, also supporting nucleophilic attack of PdL_2 at the R-X bond.⁵⁶ The addition of excess ligand to the oxidative addition reactions had no effect on the rate, meaning that oxidative addition occurred to the PdL_2 species. The trend observed for the *n*-nonyl halides/pseudo halide was as expected and found to be $\text{I} > \text{Br} > \text{OTs} > \text{Cl}$, while no reaction was observed with *n*-nonyl fluoride.⁵⁶

Steric hinderance had the biggest influence on the rate of oxidative addition, both with regards to the ligands and substrates used. Branching in the γ and β positions on the alkyl halide dramatically reduced the rate of reaction whereas no oxidative addition was observed when an α branched substrate was used (ruling out a radical mechanism).⁵⁶ Adducts of $\text{P}(\text{tBu})_2\text{Me}$ and PCy_3 were effective ligands for oxidative addition. However, the use of $\text{P}(\text{tBu})_2\text{Et}$ and P^tBu_3 exhibited no oxidative addition reaction, despite their similar cone angles to $\text{P}(\text{tBu})_2\text{Me}$.⁵⁶ Further study showed favoured conformations of $\text{P}(\text{tBu})_2\text{Et}$ and P^tBu_3 were found to impede access to the Pd centre, thus explaining the lack of oxidative addition reactivity observed.⁵⁶

Comparing Aryl, Vinyl and Alkyl Halides

DFT calculations were used in 2006 by Lin to investigate the ease of oxidative addition of $\text{Pd}(\text{PH}_3)_2$ to aryl, vinyl and alkyl halides.⁵⁷ Caution must be applied when using PH_3 as a model ligand, as such, it is no longer an acceptable model used in DFT calculations. This is due to huge differences in cone angle and TEP when comparing PH_3 and PPh_3 (or other common phosphine ligands), which can led to divergent mechanisms (Table 1.3).^{46,58}

Table 1.3. TEP and cone angle for PH_3 and PPh_3 .

Ligand	TEP (cm^{-1})	Cone Angle ($^\circ$)
PH_3	2081.0	87
PPh_3	2068.9	143

Activation energies for the oxidative addition of Pd^0 to a variety of halides followed the same trends observed experimentally: methyl > benzyl > phenyl > vinyl (Figure 1.9).⁵⁷ This same trend was not observed in the overall reaction energies and energies were comparable meaning that the difference in reactivity cannot be explained thermodynamically (Figure 1.9).⁵⁷

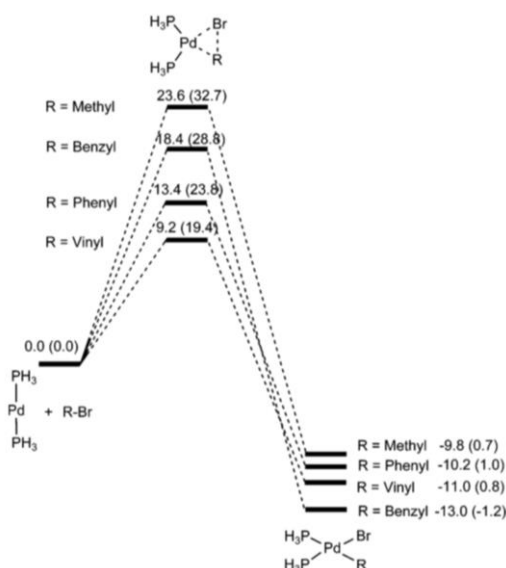
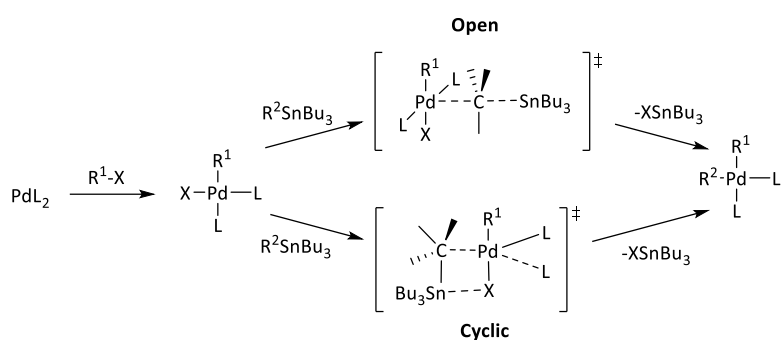


Figure 1.9. Potential energy profiles for the oxidative addition of different halides to Pd^0 .
Relative electronic energies shown and ΔG given in brackets.⁵⁷

The trend in activation energies can be attributed to the availability of the π^* orbitals in the substrate as back bonding from Pd to R-X dominates the transition state. Due to the lower conjugation in vinyl halides, the π^* orbital is of higher energy than aryl halides, which does not explain why vinyl halides have the smallest activation energy.⁵⁷ However, this smaller conjugated system means that the carbon bearing the halide has a higher contribution to the π^* orbital, meaning it is a better acceptor than an aryl halide, therefore lowering the activation barrier.⁵⁷ Benzyl bromide has a higher activation energy than aryl and vinyl bromides due to the lack of low lying π^* orbitals; however, it has a weaker carbon-bromine bond than methyl bromide, meaning that methyl bromide has the highest barrier of activation.⁵⁷

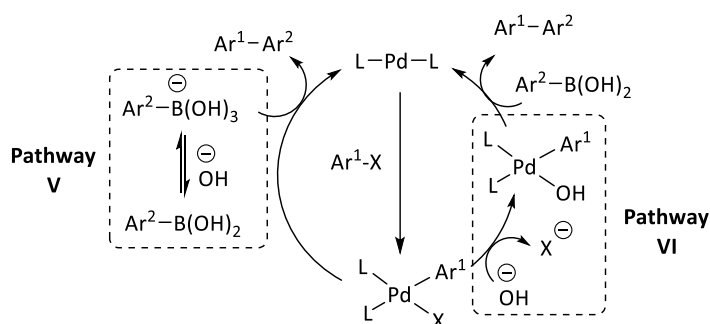
1.4.2. Transmetalation

Transmetalation is the transfer of an organic group from one metal to another and is the least well-understood step within palladium-catalysed cross-coupling reactions. Extensive studies on the transmetalation step in the Stille reaction have been carried out over the years and were summarised in a 2004 review by Espinet.⁵⁹ It was concluded that transmetalation can either occur *via* an open or cyclic transition state (Scheme 1.12) and the route taken depends on the reactions conditions (catalyst/ligand, solvents, aryl halide, tin reagent).^{60,61} A 1998 study by Espinet determined that transmetalation can be rate determining (as opposed to the oxidative addition step), but some of the intermediates were not isolable due to the rapid reductive elimination step.⁶⁰



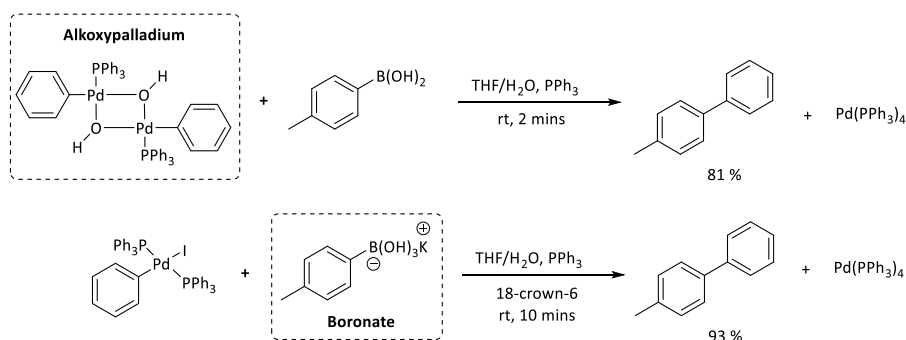
Scheme 1.12. Transmetalation transition states (cyclic and open) for the palladium catalysed Stille cross-coupling reaction.^{60,61}

The transmetalation step with boron in the Suzuki-Miyaura reactions has only thoroughly been explored over the last decade. This is probably due to the added complication that these reactions require activation using a base, unlike many other cross-coupling reactions (Stille, Negishi, Kumada-Tamao-Corriu). The uncertainty with this step lies with the role of the base - does the base interact with the boron to form a boronate (Path V in Scheme 1.13) or with the palladium complex to form an alkoxypalladium species (Path VI in Scheme 1.13)?⁶² It is of great importance to understand the mechanism of this step to help optimise catalytic reactions effectively.⁶²



Scheme 1.13. The two transmetalation pathways possible in the palladium catalysed Suzuki-Miyaura reaction.⁶²

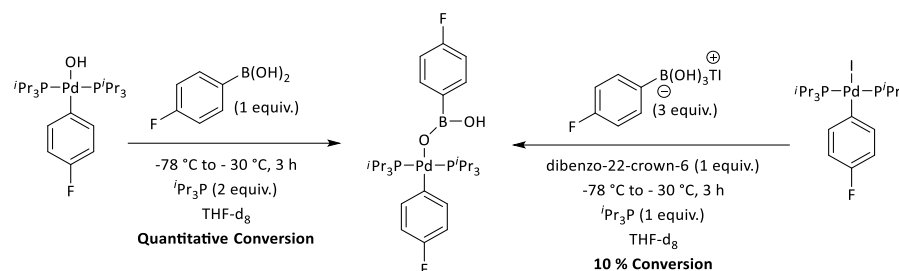
In 2011, Hartwig carried out stoichiometric reactions of the isolated alkoxypalladium species with boronic acids and a separate reaction of boronate with palladium halides; both reactions give the desired product in high yields (Scheme 1.14).⁶² High yields confirmed that both pathways were possible; however, they may react differently in when the Pd species is employed catalytically (not stoichiometrically).⁶²



Scheme 1.14. Stoichiometric reactions carried out by Hartwig to aid in establishing the mechanism for transmetalation in the Suzuki-Miyaura cross-coupling reactions.⁶²

The extremely slow rate of reaction of the boronate with the palladium halide complexes (four orders of magnitudes smaller) compared to the alkoxypalladium species with boronic acid under catalytic conditions was observed.⁶² From this, it was concluded that the alkoxypalladium pathway (VI) was a more likely route for transmetalation (Scheme 1.13). If any boronate forms over the course of the reaction, which is likely as the rates of formation of these intermediates is similar, then it will convert back to the boronic acid as it is in equilibrium.⁶²

The Denmark group developed rapid injection NMR (RI-NMR) that has provided invaluable structural data to confirm the presence of these intermediates described by Hartwig.⁶³ Stoichiometric amounts of alkoxopalladium complex $trans\text{-}[\text{Pd}(\textit{i}\text{Pr}_3\text{P})_2(4\text{-FC}_6\text{H}_4)(\text{OH})]$ and 4-fluorophenylboronic acid were combined. Separately, $trans\text{-}[\text{Pd}(\textit{i}\text{Pr}_3\text{P})_2(4\text{-FC}_6\text{H}_4)(\text{I})]$ and 4-fluorophenylboronate were also combined. Both stoichiometric reactions produced an intermediate species that could be characterised (Scheme 1.15).⁶³



Scheme 1.15. Reaction of $trans\text{-}[\text{Pd}(\textit{i}\text{Pr}_3\text{P})_2(4\text{-FC}_6\text{H}_4)(\text{OH})]$ and 4-fluorophenylboronic acid plus reaction of $trans\text{-}[\text{Pd}(\textit{i}\text{Pr}_3\text{P})_2(4\text{-FC}_6\text{H}_4)(\text{I})]$ and 4-fluorophenylboronate gave the same intermediate proposed to be active in transmetalation.⁶³

1.4.3. Reductive Elimination

With some mechanistic understanding of oxidative addition to Pd^0 complexes, Stille provided some insight into the mechanism of the opposing reaction, reductive elimination.⁶⁴ Six compounds were synthesised for study: the *cis* and *trans* isomers of both $[\text{Pd}(\text{PPh}_3)_2\text{Me}_2]$ and $[\text{Pd}(\text{PPh}_2\text{Me})_2\text{Me}_2]$, a *cis* spanning bidentate phosphine complex $[\text{Pd}(\text{dppe})\text{Me}_2]$ and a *trans* spanning bidentate phosphine complex $[\text{Pd}(\text{TransPhos})\text{Me}_2]$ (Figure 1.10).⁶⁴ Significant differences in both the ^1H and ^{31}P NMR spectra meant distinguishing between isomers was straightforward, the evolution of ethane from these complexes was used as proof of reductive elimination. No reductive elimination occurred from *trans* complexes, while ethane was produced from the *cis* complexes on heating in DMSO-d_6 .⁶⁴ *Cis-trans* isomerisation was observed in polar solvents or with excess ligands present in solution, assumingly *via* an association, rotation and dissociation pathway. When $trans\text{-}[\text{Pd}(\text{PPh}_3)_2\text{Me}_2]$ was heated in THF for 5 minutes and quenched, only the *cis* complex was observed, no ethane had evolved, meaning isomerisation must occur before reductive elimination can occur; the same behaviour was observed with $[\text{Pd}(\text{PPh}_2\text{Me})_2\text{Me}_2]$.⁶⁴

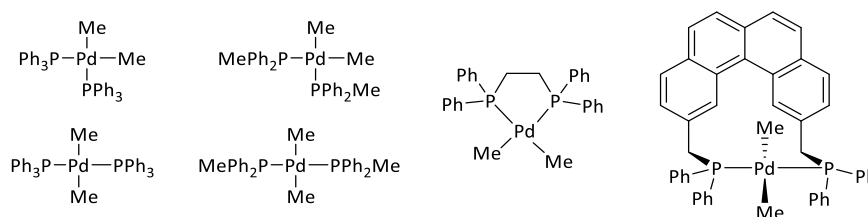


Figure 1.10. Complexes synthesised for mechanistic study of reductive elimination in Pd^{II} complexes.⁶⁴

The kinetic behaviour for reductive elimination for compounds shown in Figure 1.10 was measured *via* ³¹P NMR spectroscopy. The reaction of the *cis*-[Pd(PPh₃)₂Me₂] was found to be first order in Pd complex.⁶⁴ After a short induction period for rapid and complete isomerisation, the reaction was also first order in *trans*-[Pd(PPh₃)₂Me₂] and had an identical rate constant to the *cis* complex. Reductive elimination was first order in *cis*-[Pd(dppe)Me₂] but was significantly slower than *cis*-[Pd(PPh₃)₂Me₂].⁶⁴ Reductive elimination from [Pd(PPh₂Me)₂Me₂] (*cis* and *trans*) deviated from first order kinetics and only reached 60% conversion; a new singlet in the ³¹P NMR spectrum confirmed oxidative addition of the P-Me bond to the coordinatively unsaturated palladium complex. The addition of phenyl acetylene was used to help saturate the coordination sphere of palladium once reductive elimination had occurred; the resultant complex was isolated from the reaction mixture (Figure 1.11). Reductive elimination was now first order and went to completion.⁶⁴

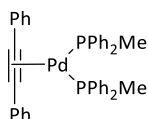
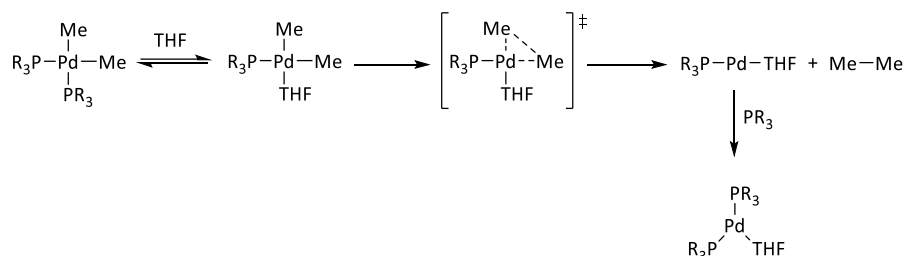


Figure 1.11. Complex isolated from the reductive elimination of [Pd(PPh₂Me)₂Me₂] in the presence of diphenylacetylene.⁶⁴

Rates of reductive elimination were in the order [Pd(PPh₃)₂Me₂] > [Pd(PPh₂Me)₂Me₂] > [Pd(dppe)Me₂]; this followed the same trend for the rate of dissociation of phosphine ligand.⁶⁴ Coupled with the observation that excess ligand inhibited reductive elimination, this suggested the necessity for the presence of polar, coordinating solvent was due to its ability to aid displacement of phosphine ligands or occupy the vacant site generated. This was confirmed by carrying out reactions in deuterated benzene; no *trans-cis* isomerisation was

observed for $[\text{Pd}(\text{PPh}_2\text{Me})_2\text{Me}_2]$ and no reductive elimination was observed from the *cis* isomer.⁶⁴ Once reductive elimination occurs, free ligand then re-coordinates to the Pd centre, as evident in the ^{31}P NMR spectra.⁶⁴ This proposed mechanism is shown in Scheme 1.16.



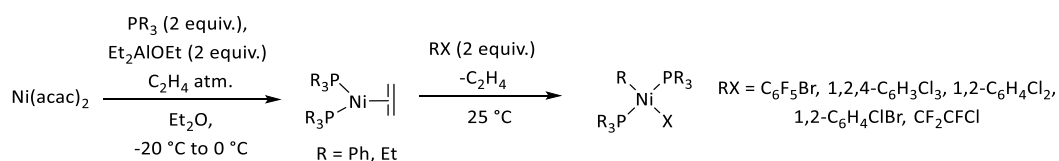
Scheme 1.16. Mechanism for the reductive elimination of Pd^{II} phosphine complexes.⁶⁴

1.5. Mechanisms of Nickel Catalysed Reactions

1.5.1. Oxidative Addition

Aryl

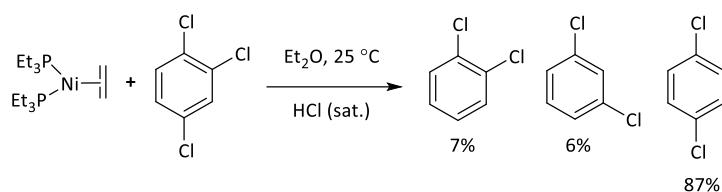
In 1970, Fahey was the first to shed some light onto the oxidative addition of Ni^0 to aryl and vinyl halides.⁶⁵ *In situ* formation of $[\text{Ni}(\text{PR}_3)_2(\text{C}_2\text{H}_4)]$ was achieved by the reduction of $[\text{Ni}(\text{acac})_2]$ in the presence of the phosphine ligand under an atmosphere of ethene (Scheme 1.17). The halide was then added and the reaction was stirred until evolution of ethene ceased. The oxidative addition product for various aryl and vinyl halides was isolated (Scheme 1.17).⁶⁵ IR spectroscopy was used to characterise the geometry for all the resultant oxidative addition products as *trans*-square planar.^{65,66}



Scheme 1.17. In situ formation of $[\text{Ni}(\text{PR}_3)_2(\text{C}_2\text{H}_4)]$ and subsequent oxidative addition with aryl and vinyl halides to form a stable product that could be isolated.⁶⁵

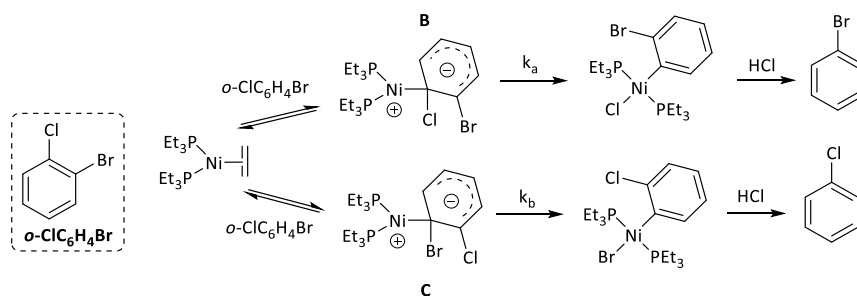
The mechanisms of these reactions were probed by product formation after quenching with HCl subsequent to oxidative addition. The analysis of the products formed after oxidative addition of $[\text{Ni}(\text{PET}_3)_2(\text{C}_2\text{H}_4)]$ to 1,2,4-trichlorobenzene gave the following product distribution

for isomeric dichlorobenzenes: *ortho* (7%), *meta* (6%) and *para* (87%) (Scheme 1.18) suggesting that oxidative addition preferentially occurs at the same position as nucleophilic substitution.⁶⁵



Scheme 1.18. Products distribution observed when oxidative addition product from reaction of $[\text{Ni}(\text{PEt}_3)_2(\text{C}_2\text{H}_4)]$ and 1,2,4-trichlorobenzene was saturated with HCl .⁶⁵

To determine whether a $\text{S}_{\text{N}}\text{Ar}$ mechanism was in operation, the oxidative addition of $[\text{Ni}(\text{PEt}_3)_2(\text{C}_2\text{H}_4)]$ to 1-bromo-2-chlorobenzene was carried out and then saturated with HCl ; the relative yields of bromobenzene and chlorobenzene were calculated (Scheme 1.19).⁶⁵ As oxidative addition is irreversible, the amount of products were directly proportional to the rate constants k_{a} and k_{b} . Ratio $k_{\text{a}}/k_{\text{b}}$ was calculated as 0.003, lower than expected for conventional $\text{S}_{\text{N}}\text{Ar}$ reactions (1 – 3.7 at 25°C).^{65,67} This low value was attributed to the propensity for intermediates **B** and **C** to revert back to reactants than proceed to products (Scheme 1.19).⁶⁵



Scheme 1.19. Oxidative addition of $[\text{Ni}(\text{PEt}_3)_2(\text{C}_2\text{H}_4)]$ to 1-bromo-2-chlorobenzene.

Saturation of oxidative addition gave bromobenzene and chlorobenzene depending on whether oxidative addition occurred via chloride or bromide.

To reliably draw comparisons between nickel and palladium, Cassar investigated the oxidative addition of $[\text{Ni}(\text{PPh}_3)_3]$ (formed *in-situ* from $[\text{Ni}(\text{PPh}_3)_4]$) to a variety of aryl halides in 1975.⁶⁸ Kinetic experiments were carried out for a variety of substituted aryl halides, and

a plot of relative rates vs Hammett σ parameter was drafted (Figure 1.12).⁶⁸ This plot was analogous to that obtained for the oxidative addition of $[\text{Pd}(\text{PPh}_3)_4]$ (Section 1.4.1.) to aryl halides, showing strong correlation for electron withdrawing substituents with $\sigma > 0.23$.^{26,68} The sharp change in gradient for substituents with $\sigma < 0.23$ is accompanied with a change in halogen used (from Cl to Br).⁶⁸

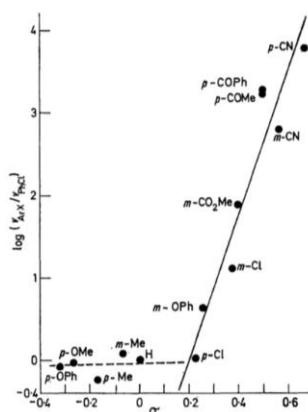
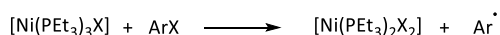
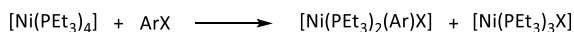


Figure 1.12. Hammett plot for the oxidative addition of $[\text{Ni}(\text{PPh}_3)_3]$ for various substituted aryl halides.⁶⁸

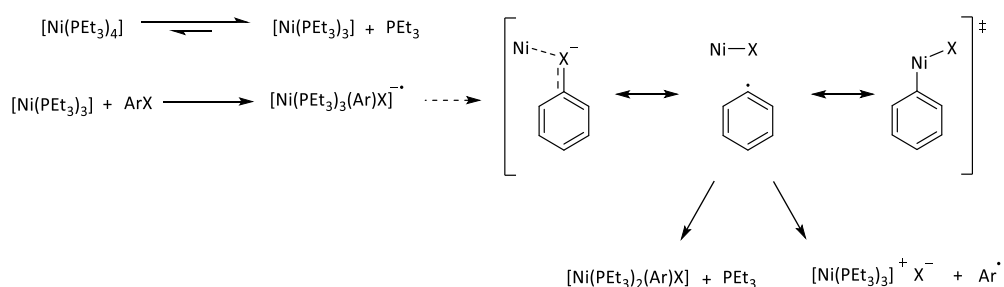
The mechanism of the reaction of $[\text{Ni}(\text{PEt}_3)_4]$ with aryl halides was extensively probed in 1979 by the Kochi group. The reaction of $[\text{Ni}(\text{PEt}_3)_4]$ and various *p*-substituted aryl halides yielded both $[\text{Ni}(\text{PEt}_3)_2(\text{Ar})\text{X}]$ and $[\text{Ni}(\text{PEt}_3)_2\text{X}]$ complexes as products (Scheme 1.20).⁶⁹ Notably, a slower further reaction of $[\text{Ni}(\text{PEt}_3)_2\text{X}]$ in a radical reaction with another molecule of aryl halide was observed, to form $[\text{Ni}(\text{PEt}_3)_2\text{X}_2]$ plus an aryl radical that likely abstracts hydrogen from the solvent (Scheme 1.20). Formation of $[\text{Ni}(\text{PEt}_3)_2(\text{Ar})\text{X}]$ was monitored *via* IR spectroscopy and $[\text{Ni}(\text{PEt}_3)_2\text{X}]$ *via* EPR spectroscopy. Comproportionation to form $[\text{Ni}(\text{PEt}_3)_2\text{X}]$ was ruled out as the reaction of $[\text{Ni}(\text{PEt}_3)_4]$ and $[\text{Ni}(\text{PEt}_3)_2\text{ArX}]$ gave no Ni^{I} products.⁶⁹ It was found that a number of factors affect the ratio of $[\text{Ni}(\text{PEt}_3)_2(\text{Ar})\text{X}]$ and $[\text{Ni}(\text{PEt}_3)_2\text{X}]$ during the reaction; these include: halide, aryl substituent, solvent, and phosphine ligand.⁶⁹ The amount of paramagnetic $[\text{Ni}(\text{PEt}_3)_2\text{X}]$ formed increased in the order $\text{I} \gg \text{Br} > \text{Cl}$ for aryl halides, an increase was also observed in more polar solvents (from hexane to THF). There were no clear outcomes with different *p*-substituents on the aryl substrates used, although positively charged substituents increased the amount of $[\text{Ni}(\text{PEt}_3)_2\text{X}]$, whilst negatively charged substituents decreased nickel(I) formation. Although the identity of the ligand on nickel

would influence the reactivity of Ni^0 initially, the speciation of the active Ni^0 species (NiL_4 , NiL_3 , NiL_2) had no effect on product distribution.⁶⁹



Scheme 1.20. Reactions of $[\text{Ni}(\text{PEt}_3)_4]$ with aryl halides formed both a Ni^{II} and Ni^{I} species, ratios of these differed with conditions.⁶⁹

In solution, $[\text{Ni}(\text{PEt}_3)_4]$ readily dissociates to form $[\text{Ni}(\text{PEt}_3)_3]$ ($K_{\text{eq}} = 1.2 \times 10^{-2} \text{ mol L}^{-1}$ in benzene at 25 °C) which is accompanied with a change in TEP; $[\text{Ni}(\text{PEt}_3)_4]$ 290 μm (n-heptane) and $[\text{Ni}(\text{PEt}_3)_3]$ 502 μm (benzene).⁷⁰ After this pre-equilibrium is established, the proposed mechanism for this reaction involves the collapse of a charged ion pair in the rate-limiting transition state (Scheme 1.21).⁶⁹ This was supported by previous studies that showed that a one-electron transfer from nickel to an electron-acceptor was facile; $[\text{Ni}(\text{PEt}_3)_4]$ rapidly reduced tetracyanoethylene (amongst other electron-acceptors) to generate radical anions that were analysed by EPR spectroscopy.⁷¹ The cage collapse of this charged ion pair and the ratios of products formed (either $[\text{Ni}(\text{PEt}_3)_2\text{ArX}]$ or competing $[\text{Ni}(\text{PEt}_3)_2\text{X}]$) depends on the stability and lifetime of the ion pair which in turn depends on reaction variables (halide identity, *p*-substituent, solvent and ligands).⁶⁹



Scheme 1.21. Proposed mechanism for the reaction of $\text{Ni}(\text{PEt}_3)_4$ with aryl halides involving a charged ion pair in the transition state.⁶⁹

To confirm this mechanism, cyclic voltammetry was used for the reactions of $[\text{Ni}(\text{PEt}_3)_3]$ with various substituted iodo-, bromo- and chlorobenzenes.⁶⁹ A Hammett plot with a positive slope, indicating a build-up of negative charge in the transition state, was consistent with the proposed formation of a radical anion.⁶⁹ A linear relationship was found between the rate

constants for reactions of $[\text{Ni}(\text{PEt}_3)_3]$ with aryl halides and the reduction of aryl halides (Figure 1.13), suggesting a similar transition state was involved.⁶⁹

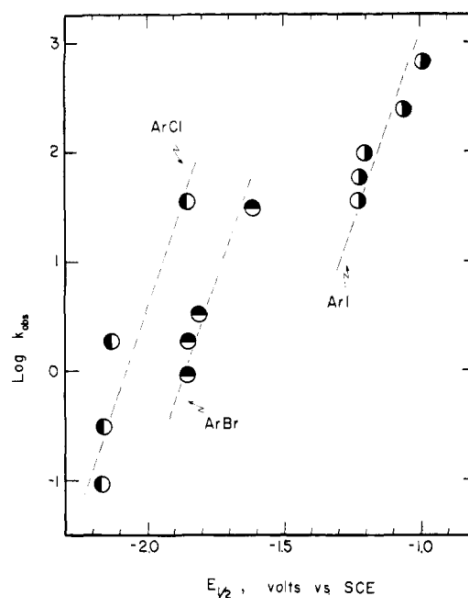


Figure 1.13. Correlation of half-wave potentials for various substituted iodo-, bromo- and chlorobenzenes with second order rate constants for reactions with $[\text{Ni}(\text{PEt}_3)_4]$.⁶⁹

Nelson and Maseras later explored (*via* DFT calculations) the formation of $[\text{Ni}(\text{PMe}_3)_2(\text{Ar})\text{X}]$ and $[\text{Ni}(\text{PMe}_3)_2\text{X}]$ in the reaction of $[\text{Ni}(\text{PMe}_3)_3]$ with aryl halides. These products arise from two competing mechanistic pathways: an $\text{S}_{\text{N}}2$ type oxidative addition (to form $[\text{Ni}(\text{PMe}_3)_2(\text{Ar})\text{X}]$) and a halide abstraction (to form $[\text{Ni}(\text{PMe}_3)_2\text{X}]$) (Figure 1.14).⁷² Both mechanisms were shown to proceed through $[\text{Ni}(\text{PMe}_3)_3]$ as opposed to $[\text{Ni}(\text{PMe}_3)_4]$ or any other nickel speciation. The identity of halide used had little influence on the $\text{S}_{\text{N}}2$ mechanism; however, a broad range of energies were obtained for the halide abstraction pathway for aryl chlorides, bromide and iodides separately.⁷² The selectivity for the reaction to form $[\text{Ni}(\text{PMe}_3)_2(\text{Ar})\text{X}]$ and $[\text{Ni}(\text{PMe}_3)_2\text{X}]$ was found to depend on the competition between the transition states of the $\text{S}_{\text{N}}2$ type mechanism and the halide abstraction mechanism (Figure 1.14). The transition state barriers for the halide abstraction mechanism indicate a slow and moderate rate of reaction for the aryl iodide and bromide respectively. A high energy transition state was observed for the aryl chloride, leading to slow reactivity, ultimately effecting the products observed.⁷²

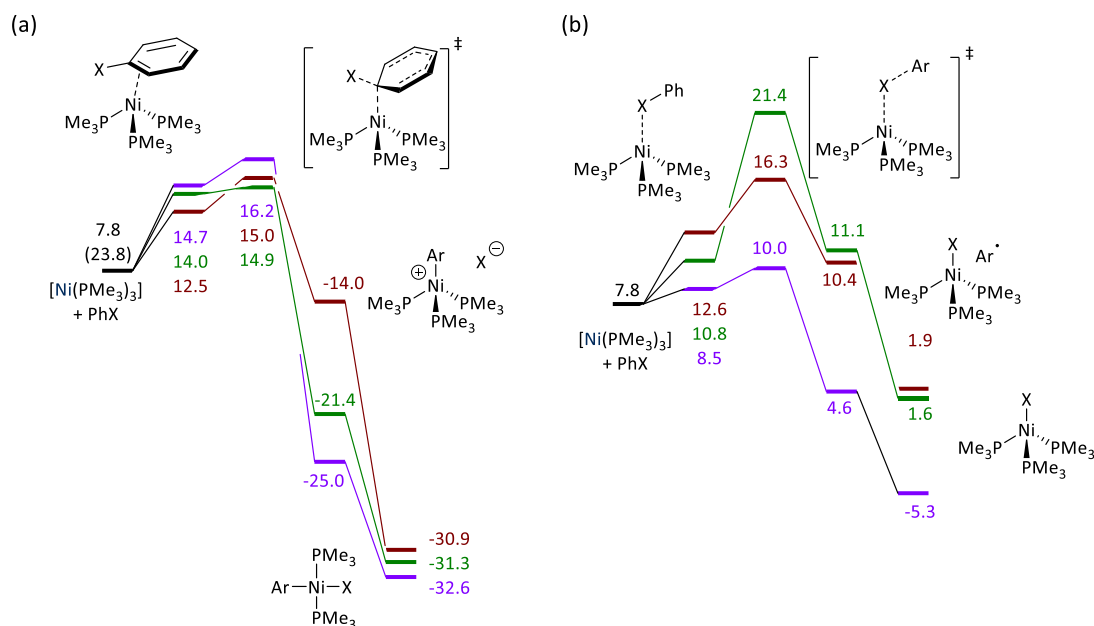
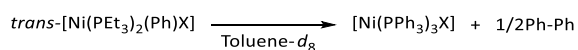


Figure 1.14. Energy profiles for (a) S_N2 type oxidative addition and (b) halide abstraction mechanisms. Oxidative addition for PhI (purple), PhBr (orange) and PhCl (green) by $\text{Ni}(\text{PMe}_3)_3$. Energies are free energies in kcal mol^{-1} relative to $\text{Ni}(\text{PMe}_3)_4$ plus aryl halide in THF.⁷²

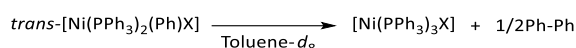
Experimental evidence for these two competing mechanisms was provided by Baird whilst studying the reactions of $[\text{Ni}(\text{PPh}_3)_4]$ with halobenzene substrates *via* NMR spectroscopy.⁷³ In reactions of $[\text{Ni}(\text{PPh}_3)_4]$ with chlorobenzene or bromobenzene, the major product was found to be *trans*- $[\text{Ni}(\text{PPh}_3)_2(\text{Ph})\text{X}]$, a diamagnetic complex characterised by ^1H NMR spectroscopy (Scheme 1.22). However, when using iodobenzene as a substrate, the major product formed was the paramagnetic $[\text{Ni}(\text{PPh}_3)_2\text{X}]$, consistent with previous observations by Kochi whilst studying reactions of $[\text{Ni}(\text{PEt}_3)_4]$ (Scheme 1.22).^{69,73}



Scheme 1.22. Decomposition of *trans*- $[\text{Ni}(\text{PPh}_3)_2(\text{Ph})\text{X}]$ to $[\text{Ni}(\text{PPh}_3)_2\text{X}]$ and biphenyl.⁷³

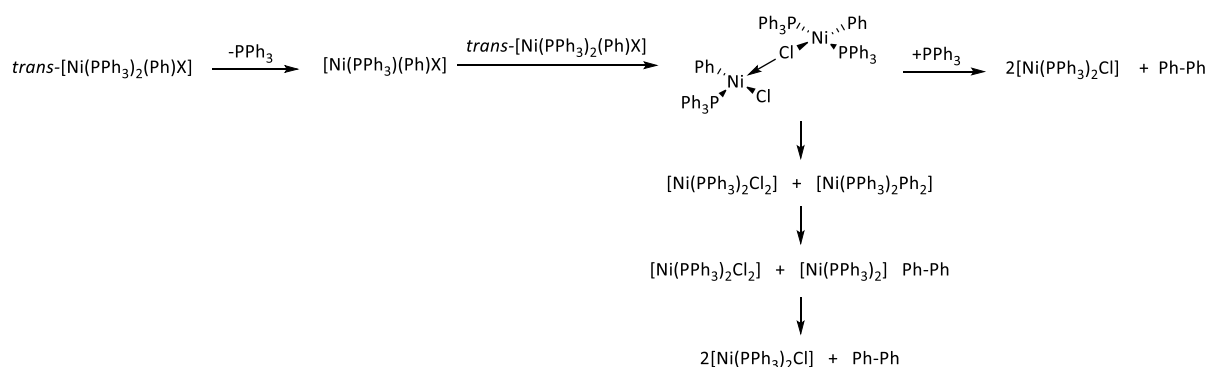
After oxidative addition of $[\text{Ni}(\text{PPh}_3)_4]$ to chlorobenzene was complete, slow decomposition of *trans*- $[\text{Ni}(\text{PPh}_3)_2(\text{Ph})\text{X}]$ to $[\text{Ni}(\text{PPh}_3)_2\text{X}]$ and biphenyl was observed at 298 K (Scheme 1.23).⁷³

However, dissolving isolated crystals of *trans*-[Ni(PPh₃)₂(Ph)X] in toluene-*d*₈ led to full decomposition in minutes, suggesting that the presence of PPh₃ inhibits the decay. This is in contrast to observations made by Kochi, where a similar oxidative addition complex, [Ni(PEt₃)₂(Ar)X], is indefinitely stable in solution at room temperature.^{69,73} This observation has been attributed to the better donor properties of PEt₃ meaning this does not dissociate as quickly under the same conditions.⁷³



Scheme 1.23. Decomposition of *trans*-[Ni(PPh₃)₂(Ph)X] to [Ni(PPh₃)₂X] and biphenyl.⁷³

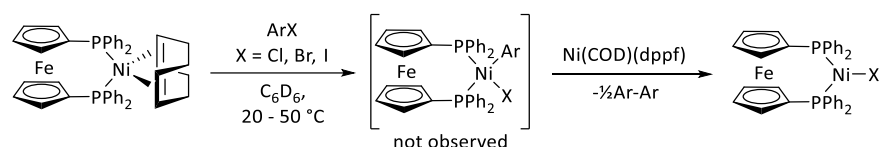
The mechanism of the decomposition of *trans*-[Ni(PPh₃)₂(Ph)X] to [Ni(PPh₃)₂X] and biphenyl (Scheme 1.23) has been probed by conducting DFT calculations. A feasible mechanism suggests initial PPh₃ dissociation from *trans*-[Ni(PPh₃)₂(Ph)X] is followed by a reaction with a second molecule of *trans*-[Ni(PPh₃)₂(Ph)X] to form a dinuclear species (Scheme 1.24).⁷³ This dinuclear species could undergo reductive elimination to form [Ni(PPh₃)₂X] and biphenyl (Scheme 1.24). Alternatively, it could undergo metathesis, followed by reductive elimination (to form biphenyl) and a comproportionation to form [Ni(PPh₃)₂X] (Scheme 1.24).⁷³



Scheme 1.24. Mechanism possibilities for the degradation of *trans*-[Ni(PPh₃)₂(Ph)X] to [Ni(PPh₃)₂X] and biphenyl.⁷³

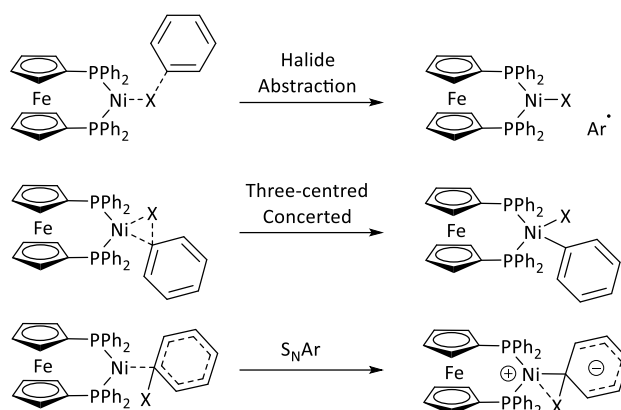
The Nelson group have extended oxidative addition mechanistic understanding, by studying a nickel complex containing a bidentate phosphine ligand.⁷⁴ Oxidative addition reactions of [Ni(COD)(dppf)] (COD = 1,5-cyclooctadiene, dppf = 1,1'-bis(diphenylphosphino)ferrocene) with various aryl halides were monitored *via* ³¹P NMR spectroscopy. Reaction rates were

found to be first order with respect to Ni^0 and aryl halide, and showed an inverse dependence on COD.⁷⁴ An initial reversible displacement of COD with aryl halide was proposed, followed by an irreversible oxidative addition step. The oxidative addition product, $[\text{Ni}(\text{dppf})(\text{Ar})\text{X}]$, then comproportionated with $[\text{Ni}(\text{dppf})(\text{COD})]$ to form $[\text{Ni}(\text{dppf})\text{X}]$ which was the only nickel-containing product observed (confirmed *via* EPR spectroscopy); notably, no oxidative addition product was observed in the ^{31}P NMR spectra at ambient temperatures (Scheme 1.25).⁷⁴ The oxidative addition product was observed as two doublets in the ^{31}P NMR spectra at lower temperatures and when bulky aryl halides were employed as substrates.



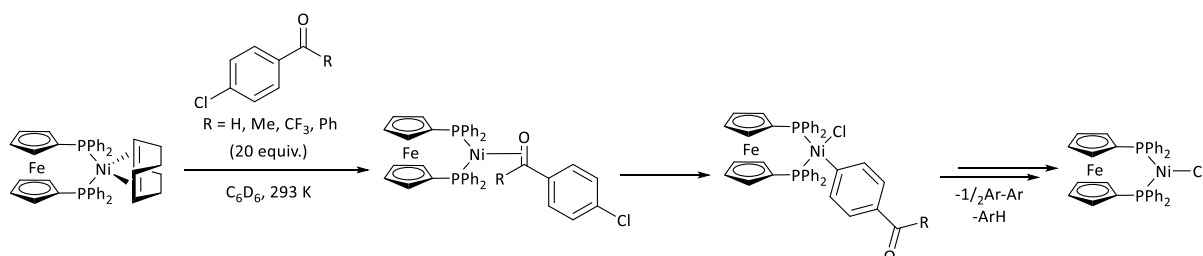
Scheme 1.25. Oxidative addition of $[\text{Ni}(\text{COD})(\text{dppf})]$ to aryl halides to give $[\text{Ni}(\text{dppf})\text{X}]$ and biphenyl as products.⁷⁴

Three mechanisms previously proposed for oxidative addition of Ni^0 and Pd^0 complexes to various halides were considered for the oxidative addition of $[\text{Ni}(\text{COD})(\text{dppf})]$ to aryl halides (Scheme 1.26). Radicals were ruled out; the addition of TEMPO had no impact on the rates of oxidative addition. Subsequent studies have shown TEMPO not to be a reliable radical probe in this system as it reacts with $[\text{Ni}(\text{COD})(\text{dppf})]$.⁷⁵ The Hammett plot and activation parameters obtained were similar to the oxidative addition of $[\text{Pd}(\text{PPh}_3)_4]$ to aryl halides studied by Amatore.^{28,74} Notably, the Hammett plot obtained showed that for electron-rich substrates $\rho = 1.2$ whereas electron-poor substrates appeared to show an opposing trend, consistent with a change in rate-determining step.⁷⁴ Shallow gradients obtained from Hammett plots ruled out an $\text{S}_{\text{N}}\text{Ar}$ type mechanism and a small $\Delta S^\ddagger$ of $0(3) \text{ kcal K}^{-1} \text{ mol}^{-1}$ led to a three-centre transition state being proposed.⁷⁴



Scheme 1.26. Mechanisms considered for the oxidative addition of $[\text{Ni}(\text{COD})(\text{dppf})]$ to aryl halides.⁷⁴

The Nelson group have also given insight into how common functional groups, aldehydes and ketones, interact with Ni^0 centres.⁷⁶ Aldehyde and ketone-substituted aryl chlorides underwent rapid oxidative addition to $[\text{Ni}(\text{COD})(\text{dppf})]$ when compared to previous data. The kinetic data obtained implied the same three-centred concerted mechanism as previously described by the Nelson group.⁷⁴ An initial dissociation of COD was thought to be favoured when the aryl halide bears an aldehyde or ketone (not esters or amides) and improved the equilibrium position (Scheme 1.27). In the reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**10**) and 4-chlorobenzaldehyde, two doublets in the ^{31}P NMR spectrum were attributed to the nickel-carbonyl coordinated compound.⁷⁶ This exceptional reactivity of aromatic halides bearing aldehyde or ketone groups with $[\text{Ni}(\text{COD})(\text{dppf})]$ was exploited to achieve selective Suzuki-Miyaura cross-coupling reactions; similarly, aldehydes/ketones (without halides) can act as inhibitors in these reactions.⁷⁶ Palladium has been shown not to interact strongly enough to induce these selectivity and inhibition effects observed with nickel.⁷⁷



Scheme 1.27. Reactions of aldehydes and ketones with $[\text{Ni}(\text{COD})(\text{dppf})]$.⁷⁶

DFT calculations were used to model the nickel-carbonyl complexes and illustrated the ease with which they are formed from $[\text{Ni}(\text{dppf})(\eta^2\text{-benzene})]$ (Figure 1.15a).⁷⁶ Once coordinated to the carbonyl, the nickel centre will undergo a ring-walking process and then undergo oxidative addition.^{78–80} The intermediates in this process are all lower in energy than $[\text{Ni}(\text{dppf})(\eta^2\text{-benzene})]$ therefore ligand exchange does not occur (Figure 1.15b).⁷⁶

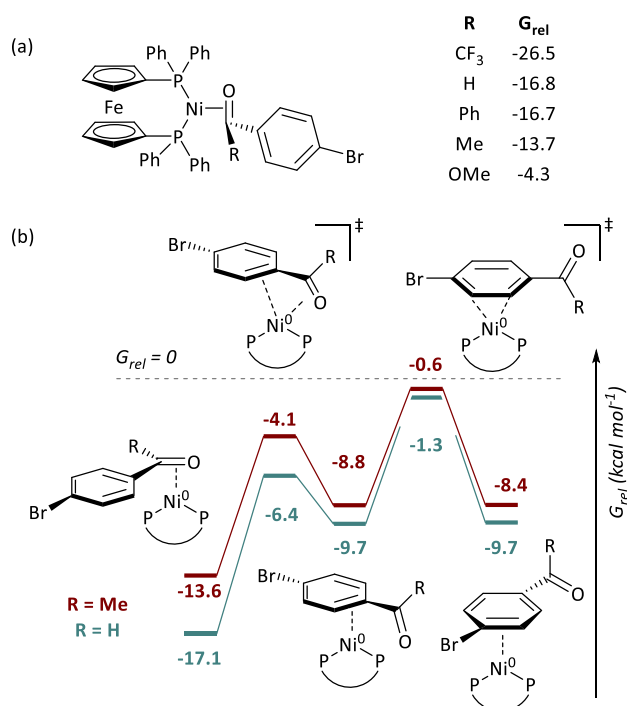
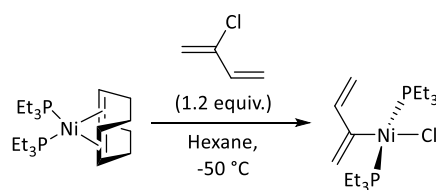


Figure 1.15. (a) Coordination to aldehydes, ketones and esters. (b) DFT calculations on the ring-walking process. All energies are free energies in toluene and are quote in kcal mol⁻¹.⁷⁶

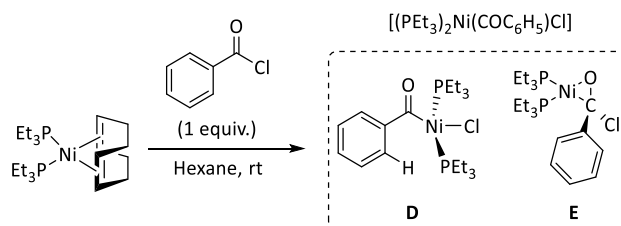
Vinyl and Acyl

Fahey has studied oxidative addition of vinyl halides to nickel complexes.⁸¹ Along with aryl halides, vinyl bromide and chloroprene reacted rapidly with $[\text{Ni}(\text{PEt}_3)_2(\text{COD})]$ to give the corresponding halo-organo-nickel complexes.⁸¹ The product from oxidative addition of the vinyl bromide decomposed at ambient temperatures and therefore was not subjected to full characterisation. However, the nickel product from the oxidative addition of the chloroprene was stable under argon for months and was fully characterised as the trans-allyl nickel complex (Scheme 1.28).⁸¹



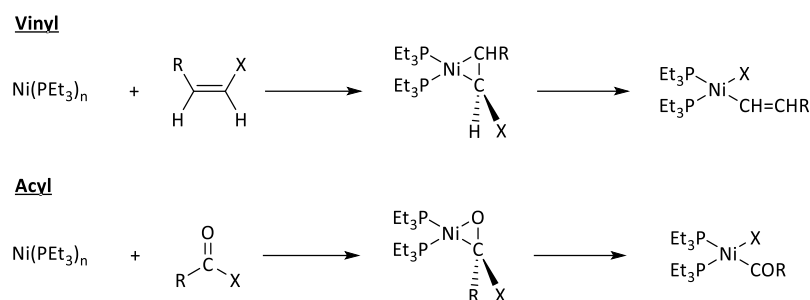
Scheme 1.28. Reaction of $[\text{Ni}(\text{PEt}_3)_2(\text{COD})]$ with chloroprene to form a stable allyl product.⁸¹

The oxidative addition of acyl halides including pivaloyl chloride and adamantanecarbonyl chloride were also studied.⁸¹ Few examples of oxidative addition of acyl halides had been previously reported therefore full characterisation was required to determine the structures of nickel-acyl halide complexes. The product from the reaction of benzoyl chloride and $[\text{Ni}(\text{PEt}_3)_2(\text{COD})]$ (**D** or **E** in Scheme 1.29) was treated with anhydrous HCl in hexane to give benzaldehyde. This product would only be formed if the initial structure of complex $[\text{Cl}(\text{COC}_6\text{H}_5)\text{Ni}(\text{PEt}_3)_2]$ was **D**. ^1H NMR spectroscopy was used to support this structure, with the *ortho* proton on the aryl ring being substantially deshielded, due to the close proximity to the metal centre that was only present in **E**.⁸¹



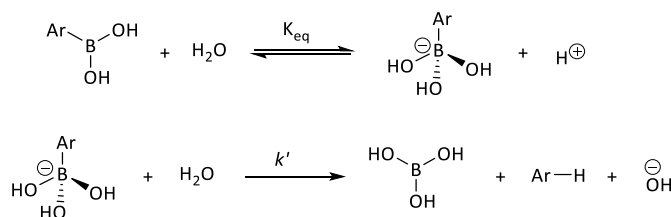
Scheme 1.29. Oxidative addition of $[\text{Ni}(\text{PEt}_3)_2(\text{COD})]$ to benzoyl chloride. Potential structures for the product formed A and B.⁸¹

The mechanism proposed for the vinyl and acyl halides suggested a coordination of the π -system to the Ni^0 and then a rearrangement to give the oxidative addition products.⁸¹ Intermediates in this mechanism were not isolated and therefore the mechanism was speculative but may be similar to ring-walking processes known for nickel complexes.⁷⁶ These predicted mechanisms are presented in Scheme 1.30. Radical processes were ruled out for both vinyl and acyl substrates; stereochemistry was retained when *trans*- β -bromostyrene was used and no decarbonylation of acyl substrates was observed.⁸¹



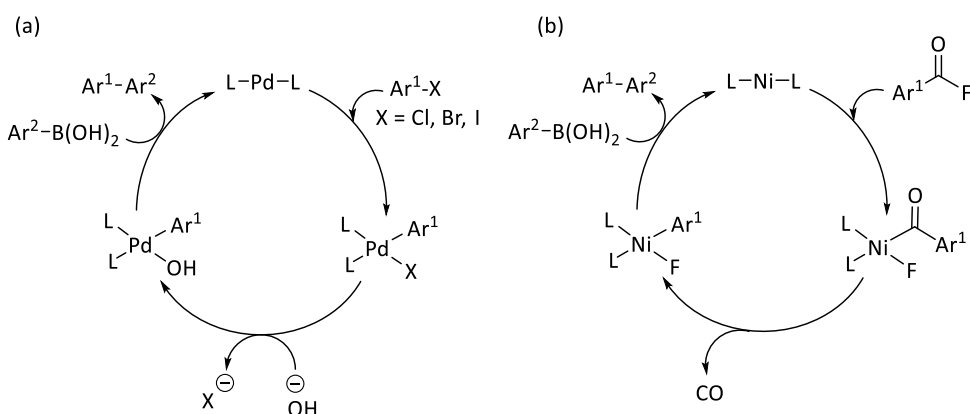
Scheme 1.30. Proposed mechanism by Fahey and Mahan for oxidative addition of vinyl and acyl halides to $\text{Ni}(\text{PEt}_3)_n$.⁸¹

The presence of a base in a typical Suzuki-Miyaura cross-coupling reaction, essential for transmetalation, can catalyse degradation of boronic acids. The mechanism in which this deactivation of boronic acids *via* protodeboronation has been explored as early as the 1960s (Scheme 1.31).^{82,83}



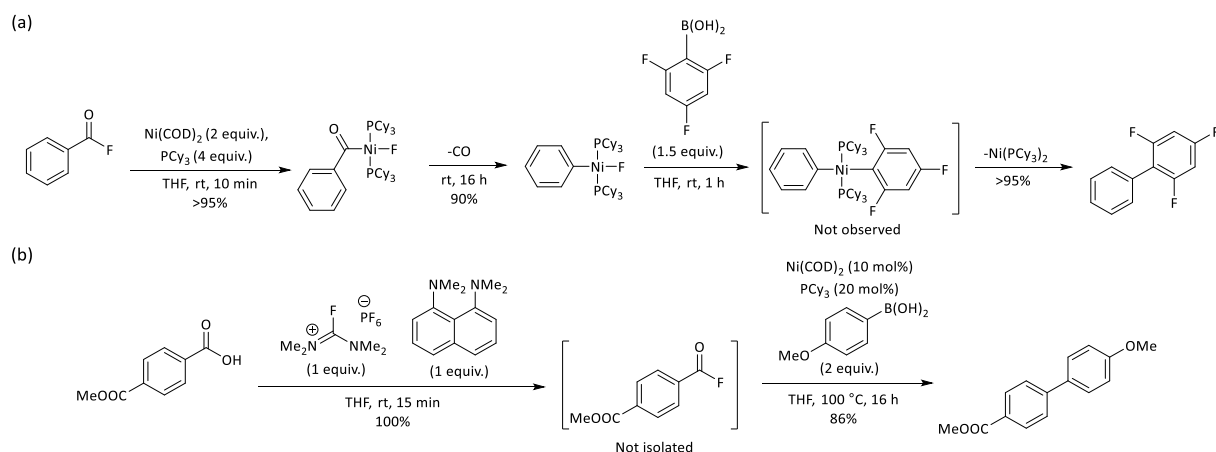
Scheme 1.31. Proposed mechanism by Kuivila (1963) for the protodeboronation of arylboronic acids.⁸²

This deleterious role base can play in Suzuki-Miyaura reactions prompted investigations into base-free cross-coupling reactions, whilst still utilising boronic acids as transmetalating reagents. Sanford proposed the use of an acyl fluoride (formed *in situ* from a carboxylic acid) in a nickel catalysed process would form an equivalent 'alkoxy' species formed in traditional Suzuki-Miyaura cross-couplings (Scheme 1.32).⁸⁴ This aryl fluoride can undergo transmetalation without requiring reaction with a base.



Scheme 1.32. (a) Typical palladium Suzuki-Miyaura cross-coupling reaction requiring base. (b) Sanford's proposal for a nickel catalysed Suzuki-Miyaura reactions without requiring base.⁸⁴

Rapid oxidative addition of acyl fluorides to Ni^0 was observed followed by a decarbonylation at room temperature gave the desired arylnickel fluoride in high yields (Scheme 1.33a).⁸⁴ These were successfully transmetalated with boronic acids, subsequent reductive elimination gave desired cross-coupled product in high yields (Scheme 1.33b).⁸⁴ Sanford successfully carried out nickel catalysed Suzuki-Miyaura cross-couplings of a range of acyl fluorides without the use of an external base.



Scheme 1.33. (a) Stoichiometric reaction for steps involved in the cross-coupling of acyl fluorides with arylboronic acids. (b) Catalytic cross-coupling reaction of acyl fluoride (formed in situ from carboxylic acid) with an arylboronic acid.⁸⁴

1.5.2. Transmetalation

In 2011, Garg focused on the coupling of aryl carbamates and sulfamates, as pseudo halides, in the Suzuki-Miyaura reaction. The reactions were optimised and DFT calculations used to help understand the mechanism. Energy profiles were produced for the $[\text{Ni}(\text{PCy}_3)_2]$ catalysed coupling of both phenyl *N,N*-dimethylcarbamate and phenyl *N,N*-dimethylsulfamate with phenyl boronic acid. In both cases, transmetalation was found to be rate limiting as oxidative addition was facile (Figure 1.16).⁸⁵ This was further supported with experimental observations: the use of electron rich boronic acids increased the rate of reaction (monitored *via* ^1H NMR spectroscopy).⁸⁵

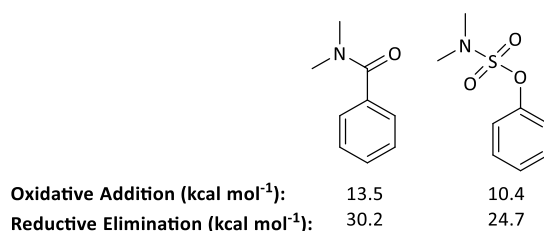
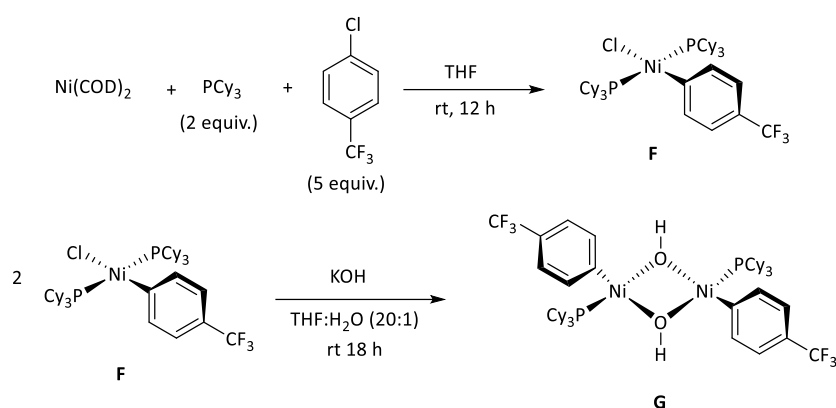


Figure 1.16. Activation energies given for oxidative addition and transmetalation (relative to $[\text{Ni}(\text{PCy}_3)_2]$) when phenyl dimethylcarbamate and phenyl dimethylsulfamate were used in cross-coupling reactions with phenylboronic acid catalysed by $[\text{Ni}(\text{PCy}_3)_2]$.⁸⁵

In 2014, researchers at Pfizer (Monfette *et al.*) synthesised and characterised intermediates involved in the nickel-catalysed Suzuki-Miyaura reaction and demonstrated how these intermediates behaved in catalysis. Oxidative addition to $[\text{Ni}(\text{PCy}_3)_2(\text{COD})]$ was carried out using 1-chloro-4-trifluoromethylbenzene as the substrate to give oxidative addition complex (**F**), which reacted with base and water to give the hydroxo-dimer (**G**), both complexes were isolated and characterised (Scheme 1.34).⁸⁶ Both the oxidative addition complex (**F**) and hydroxo-dimer (**G**) were found to be competent catalysts in the coupling of 1-chloro-4-trifluoromethylbenzene and phenylboronic acid, and quantitative conversion was achieved at room temperature.⁸⁶



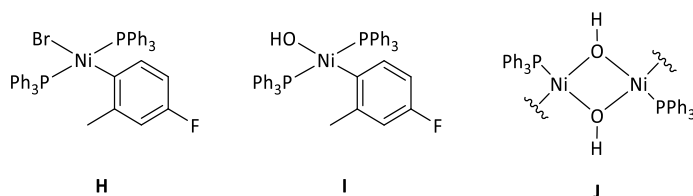
Scheme 1.34. Complexes formed by oxidative addition of $[\text{Ni}(\text{PETe}_3)_2(\text{COD})]$ to 1-chloro-4-trifluoromethylbenzene and subsequent reaction in the presence of base and water.⁸⁶

To probe the mechanism of the cross couplings, both the oxidative addition complex (**F**) and hydroxo-dimer (**G**) were reacted with stoichiometric amounts of phenylboronic acid both with and without base and water. No reaction occurred when reacting the oxidative addition complex (**F**) with the boronic acid in the absence of base or water. In contrast, the hydroxo-dimer (**G**) gave quantitative conversion to cross-coupled product in less than 2 minutes in the absence of both base and water.⁸⁶ This showed the crucial role that the hydroxo-dimer (**G**) must play in the catalytic cycle and without generation of this intermediate from **F** then the cycle does not proceed.⁸⁶

The boronate mechanism proposed for palladium-catalysed cross-coupling reactions was ruled out.⁶² Reactions of both the oxidative addition complex (**F**) and hydroxo-dimer (**G**) in cross-coupling reactions using boronate did not yield any of the desired product; instead, the solution changed from orange to green in colour, suggesting the formation of inactive $[\text{Ni}(\text{OH})_2]$ species.⁸⁶ This was supported by work in the Lloyd-Jones group that saw the equilibrium favouring the boronic acid rather than the boronate under the low water concentrations employed here.⁸⁷

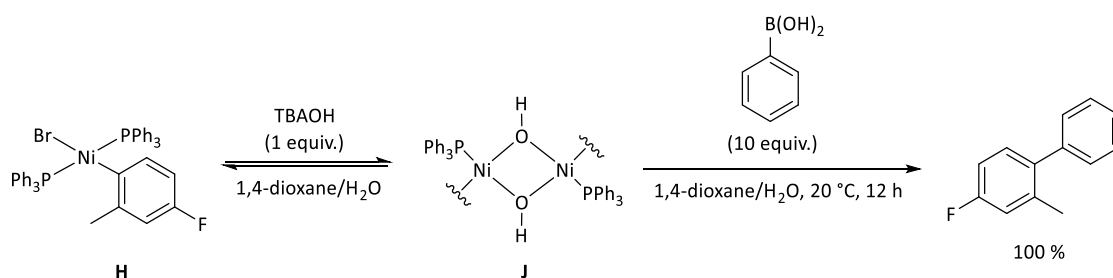
It was concluded that the oxidative addition complex (**F**) was the resting state of the catalyst (supported by ^{31}P NMR spectroscopy) and that the rate determining step was the conversion of the oxidative addition product (**F**) to the hydroxo-dimer (**G**).⁸⁶ To fully optimise Suzuki-Miyaura cross-couplings, favourable conditions to form hydroxo-dimer (**G**) are required; this requires the presence of base and water.

Grimaud probed the role of these hydroxo-dimer species proposed by Monfette both experimentally and using DFT calculations. The synthesis and characterisation of a nickel bromide (**H**), nickel hydroxide (**I**) and hydroxo-dimer (**J**) were carried out (Scheme 1.35).⁸⁸



Scheme 1.35. Synthesis of nickel bromide (**H**), nickel hydroxide (**I**) and hydroxo-dimer (**J**) for use in probing the mechanism of nickel catalysed Suzuki-Miyaura cross-couplings.⁸⁸

Hydroxo-dimer (**J**) is formed by the addition of TBAOH (tetrabutylammonium hydroxide) to the nickel bromide complex (**H**). PhB(OH)₂ was added to this sample and monitored over time (*via* ³¹P NMR spectroscopy), which regenerates significant amounts of the nickel bromide (**H**).⁸⁸ After 12 hours at room temperature, full conversion to the coupled product is achieved (Scheme 1.36). These observations suggest that an equilibrium exists between nickel bromide (**H**) and hydroxo-dimer (**J**) but that the active species necessary for transmetalation is actually the nickel bromide (**H**), in contrast to conclusions made by Monfette.⁸⁸ This was verified with kinetic experiments on transmetalation that were first order in nickel bromide (**H**), confirming that the hydroxo-dimer is not involved in transmetalation.⁸⁸

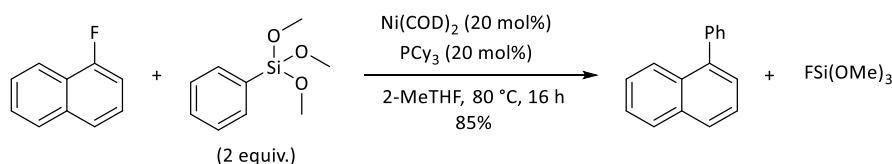


Scheme 1.36. Equilibrium between bromide and hydroxo-dimer and subsequent transmetalation to give quantitative conversion to coupled product.⁸⁸

Grimaud suggested conditions that can aid in high conversions whilst maintaining short reaction times possible at low temperatures for Suzuki-Miyaura cross-coupling reactions. It was established that keeping the concentration of the hydroxo-dimer (**J**) low is key for

efficient transmetalation, and this can be achieved by keeping ratios of base/boronic acid down.⁸⁸ The choice of boronic acid and its pKa can also influence the amounts of dimer (**J**) formed. Finally, excess ligands (such as PPh₃ and Br⁻) should be kept to a minimum as they hinder the rate at which nickel bromide (**H**) transmetalates with boronic acids.⁸⁸

Keaveney set out to induce selectivity for C-F functionalisation over C-Cl in the transmetalation step, exploiting the known reactivity of a Ni-F intermediate in a base-free transmetalation.^{84,89} A Hiyama cross-coupling between 1-fluoronaphthalene and trimethoxyphenylsilane was achieved employing a [Ni(COD)₂] and PCy₃ catalytic system (Scheme 1.37). Notably, under these optimised conditions, no conversion was observed for 1-chloronaphthalene. In a competition experiment, with both 1-fluoronaphthalene and 1-chloronaphthalene present, no coupled product was observed.⁸⁹



Scheme 1.37. Hiyama cross-coupling of 1-fluoronaphthalene (**13**) and trimethoxyphenylsilane.⁸⁹

DFT calculations were used to give insight into the mechanism of this reaction (Figure 1.17). Optimisation experiments suggested a [Ni(PCy₃)] active species, as an increase in ligand to Ni ratio led to a decrease in yield, thus energies given are relative to [Ni(COD)(PCy₃)(2-MeTHF)].⁸⁹ As expected, the barriers for oxidative addition were much higher for 1-fluoronaphthalene (28.4 kcal mol⁻¹) than 1-chloronaphthalene (8.0 kcal mol⁻¹). For transmetalation, a low energy transition state could be located for the Ni-F pathway, however, no low energy transition state could be located for the Ni-Cl pathway (>50 kcal mol⁻¹).⁸⁹ Consistent with the experimental observation in the competition reaction, irreversible oxidative addition with 1-chloronaphthalene is favoured and forms the oxidative addition product (-26.1 kcal mol⁻¹) which ultimately inhibits cross-coupling.⁸⁹

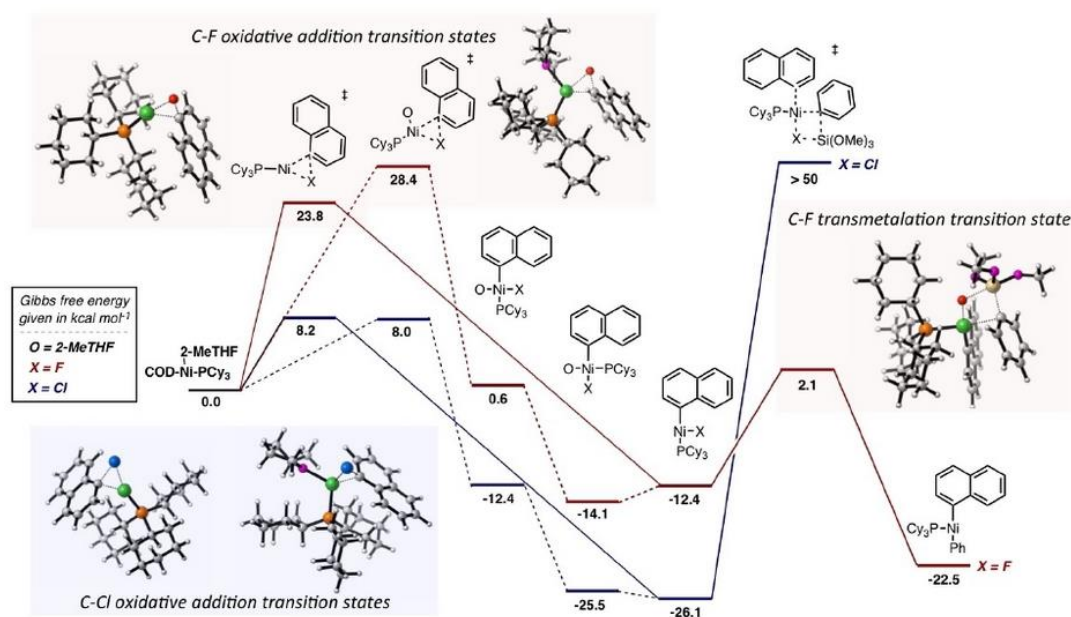


Figure 1.1.17. Calculated reaction profiles for cross-coupling between trimethoxyphenylsilane and either 1-fluoronaphthalene (red) or 1-chloronaphthalene (blue).⁸⁹

Developing a ligand system to promote a reversible oxidative addition to 1-chloronaphthalene would induce the desired selectivity of C-F over C-Cl. Whilst the oxidative addition of 1-fluoronaphthalene does not proceed if the ligand is too bulky, reversible oxidative addition of 1-chloronaphthalene required a bulky ligand. The contradictory results encountered meant that the desired selectivity of C-F over C-Cl was not successful.⁸⁹

1.5.3. Reductive Elimination

Reductive elimination from Ni^{II} species is thought to occur *via* the same mechanism as given by Stille for palladium,⁶⁴ where organic groups require to be *cis* on the centre for successful reductive elimination to occur.

Whilst optimising the nickel catalysed amination of aryl triflates, Hartwig used DFT calculations to aid mechanistic understanding.⁹⁰ The reductive elimination transition state was modelled as a three-centre transition state with a barrier of 16.4 kcal mol⁻¹ (Figure 1.18).⁹⁰ The barrier for reductive elimination was reduced when more electron withdrawing ligands were bound to the nickel centre.⁹⁰

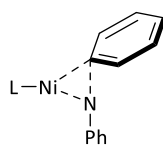
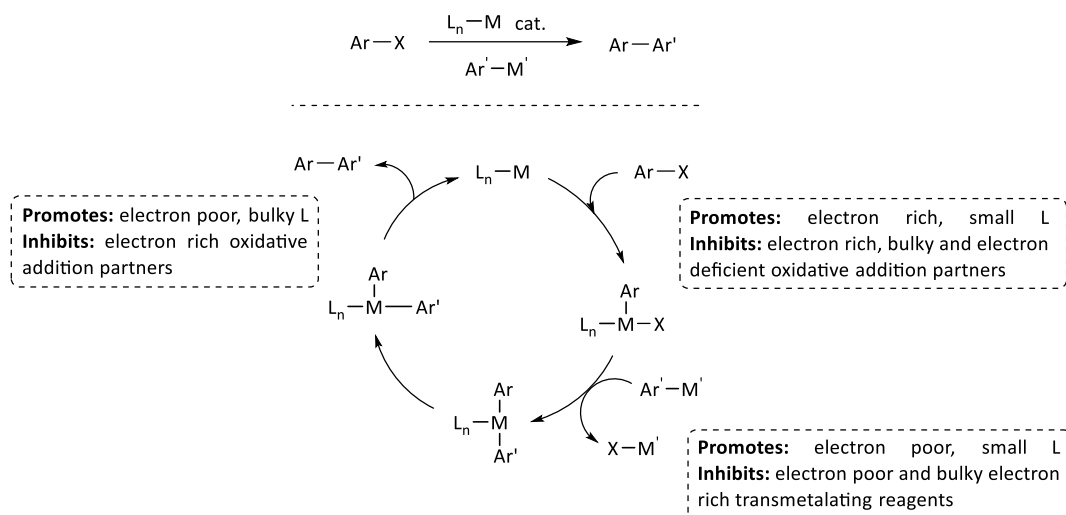


Figure 1.18. Transition state for the reductive elimination step in the amination of aryl triflates. L = dppf.⁹⁰

It is clear from mechanistic studies that active nickel complexes can be extremely sensitive to ligands, temperature, solvent systems, water content and base (identity and equivalents). Thus, cementing the fact that nickel often lacks the robustness that palladium possesses. Rigorous mechanistic studies on different nickel catalysed systems can help optimise reactions intelligently therefore making them more reproducible overall.

1.5.4. Promoting Steps in Catalysis

A general catalytic cycle is summarised in Scheme 1.38, illustrating what factors can promote and inhibit the fundamental steps in a catalytic cross-coupling reaction.^{91,92} The given scheme is a general cross-coupling of an aryl halides with an aryl transmetalating reagent including the following steps; oxidative addition, transmetalation, rearrangement and reductive elimination.



Scheme 1.38. Factors that contribute to the success of steps in a given catalytic cycle.^{91,92}

Oxidative Addition

Oxidative addition is promoted by increasing electron density on the metal centre of the active species, with σ -donor ligands (such as phosphines).⁹³ Bulky ligands can help with ligand dissociation, often necessary to generate the active species for oxidative addition.⁹⁴

Transmetalation

The driving force for transmetalation is the difference in electronegativity between the catalytically active metal and the metal in the transmetalating reagent.⁹³

Reductive Elimination

As the reverse reaction to oxidative addition, reductive elimination is promoted by an electron deficient metal centre in the active species. This can be aided by the use of bulky, strong π -acceptor ligands.⁹³ The elimination of a stable organic molecule from the oxidised metal centre is the main driving force for reductive elimination.

Aims

The aims of this PhD project were to expand the mechanistic understanding of the oxidative addition step in nickel catalysis. As discussed, the Nelson group has already proposed a mechanism for the reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ and aryl halides,⁷⁴ this work aimed to expand on this previous study by continuing to study the reactions of $[\text{Ni}(\text{COD})(\text{dppf})]$. With a better understanding of these fundamental steps in catalysis, it will allow for a more intelligent approach to optimisation.

The overall aims for this PhD were:

- Understand the mechanism of oxidative addition of alkyl halides (2-haloethyl)benzene substrates with the combination of kinetic experiments and DFT calculations.
- Investigate the reactions of both vinyl and aryl triflates to identify any differences in reactivity and ultimately understand the mechanism of oxidative addition of vinyl substrates.
- Explore if $[\text{Ni}(\text{COD})(\text{dppf})]$ is a competent catalyst in a range of cross-coupling reactions with the substrates investigated during this study.
- To determine the effect the ancillary ligand has on the rate of oxidative addition of aryl halides with $[\text{Ni}(\text{dppf})\text{L}]$ complexes.

Chapter 2 - Unexpected Nickel Complex Speciation Unlocks Alternative Pathways for the Reactions of Alkyl Halides with dppf-Nickel(0)

ACS Catal. 2020, **10**, 10717–10725

A published journal article entitled 'Unexpected Nickel Complex Speciation Unlocks Alternative Pathways for the Reactions of Alkyl Halides with dppf-Nickel(0)' with an extended introduction prior to the article and an extended discussion after. The supporting information for this article can be found in Chapter 7: Experimental.

Contributing authors to this manuscript and their roles are given below:

- Megan E. Greaves – Designed and performed experiments, analysed data, drafted initial manuscript
- Thomas O. Ronson – Helpful discussions as industrial supervisor
- Guy C. Lloyd-Jones – Assistance with data analysis
- Feliu Maseras – Assistance with DFT calculations
- Stephen Sproules – Conducted EPR experiments and analysed the resulting data
- David J. Nelson – Principal Investigator

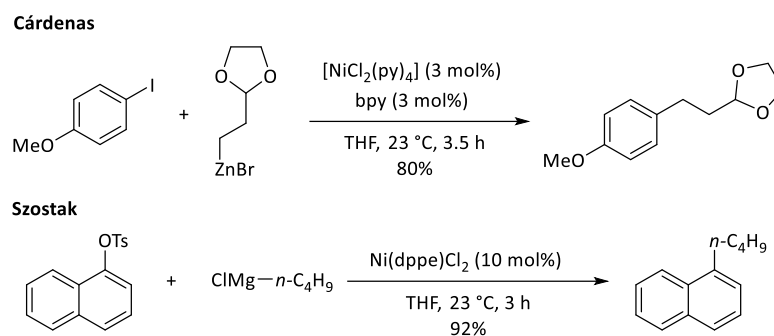
2.1. Abstract from Manuscript

The mechanism of the reactions between dppf-Ni⁰ complexes and alkyl halides has been investigated using kinetic and mechanistic experiments and DFT calculations. The active species is [Ni(κ^2 -dppf)(κ^1 -dppf)], which undergoes a halide abstraction reaction with alkyl halides and rapidly captures the alkyl radical that is formed. The rates of the reactions of [Ni(COD)(dppf)] with alkyl halides and the yields of prototypical nickel-catalyzed Kumada cross-coupling reactions of alkyl halides are shown to be significantly improved by the addition of free dppf ligand.

2.2. Extended Introduction

Since the discovery of sp^2 cross-coupling reactions, as early as the mid-20th century, mechanisms of oxidative addition for several different systems for both palladium and nickel have been investigated.^{29,65} The initial step for these reactions involves oxidative addition of an aryl halide or pseudo halide to the Ni⁰ species present. Understanding the mechanism of this is vital to efficiently optimise reactions using new catalyst systems.

More recently, coupling of sp^3 centres has become a more desirable reaction as this gives access to a broader range of useful molecules, which can then be employed within several industries including pharmaceutical and agricultural. However, the mechanism of oxidative addition varies from sp^2 systems and side reactions (such as β -H elimination) often dominates to give unwanted side products. To overcome the problematic formation of side products, several groups have employed alkyl transmetalation reagents and used aryl halides to avoid β -H elimination of the oxidative addition product.^{95–97} Negishi cross-couplings of this type with a Ni^{II} pre-catalyst were shown to be effective by Cárdenas.⁹⁸ An initial oxidative addition step of aryl halides to the active nickel(0) species followed by transmetalation using alkyl zinc reagents gave good conversions to sp^3 - sp^2 coupled products.⁹⁸ Similarly, Szostak carried out Kumada-Corriu-Tamao cross-couplings employing a Ni^{II} precatalyst to couple aryl tosylates with alkyl Grignard reagents in good yields under mild conditions (Scheme 2.1).⁹⁷



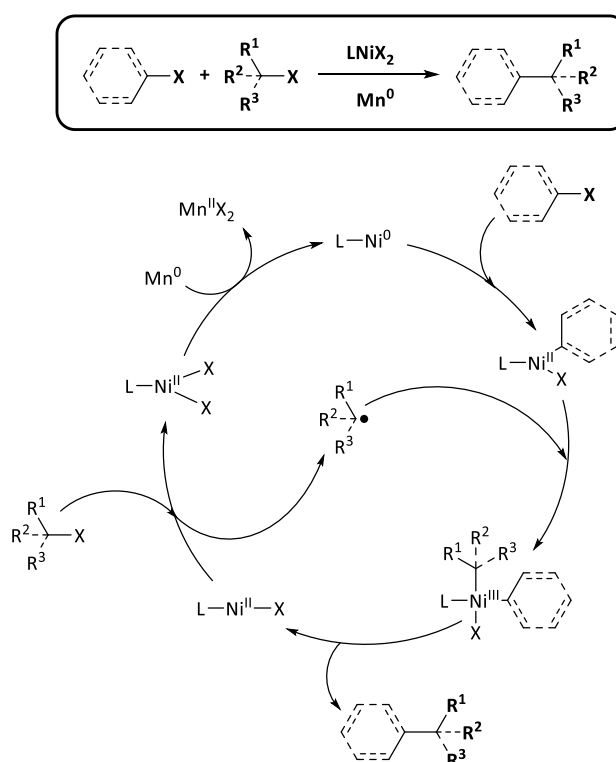
Scheme 2.1. sp^2 - sp^3 cross-coupling reactions carried out by Cárdenas (Negishi) and Szostak (Kumada-Corriu-Tamao) groups.^{97,98}

Although this negates the undesirable β -H elimination occurring after oxidative addition, the ideal reaction would allow the coupling of inexpensive and widely available alkyl halides, which can also be synthesised from alcohols *via* Appel reactions, with common transmetalating reagents.⁹⁹ Understanding the mechanism of these transformations is vital to allow continued development in this field.

It is apparent that the mechanisms of oxidative addition are not the same for aryl and alkyl halides. Aryl halides most frequently oxidatively add *via* S_N2 or concerted pathways (as supported by recent work published by the Nelson group) whereas alkyl halides are much more likely to oxidatively add *via* radical pathways; however, this does often depend on the structure of the halide involved.^{74,100}

The exploitation of this different reactivity can be used to develop new reactions using nickel catalysis, as demonstrated (and accompanied by an extensive mechanistic study) by Weix (Scheme 2.2).¹⁰¹ Weix used the difference in reactivity of aryl and alkyl halides to achieve selective sp^2 - sp^3 reductive cross-electrophile couplings employing a Ni^{II} pre-catalyst. Several species could be used as reductants (Zn, Mn and tetrakis-(dimethylamino)ethylene); from this it was assumed that the reducing agent was not playing a huge role in the observed reaction, and was used only to reduce Ni^{II} to Ni⁰ to create the active species. Oxidative addition of the aryl halide (selectively over the alkyl halide, due to a difference in rate) formed the Ni^{II} intermediate. This intermediate was found to stoichiometrically react with alkyl halides to reform the initial Ni^{II} precatalyst, without the requirement for an external reductant. Radical-clock experiments carried out using cyclopropylmethyl bromide as the

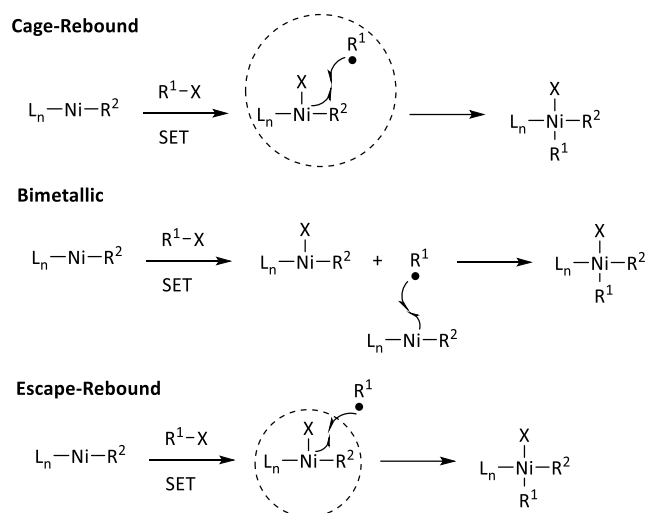
alkyl halide confirmed the presence of radical intermediates, as the ring-opened product was the only one observed. The increase of observed rearranged product with increased nickel concentration suggested radicals were being formed and consumed within different points in the catalytic cycle. Finally, from the analysis of the products reaction mixtures (after quenching), the Ni^{II} oxidative addition product was found to be the resting state of the catalyst which helps explain the selectivity of the reaction.¹⁰¹ These observations support the proposed catalytic cycle shown in Scheme 2.2.¹⁰¹



Scheme 2.2. Weix catalytic cycle for coupling of sp^2 halides with alkyl electrophiles.¹⁰¹

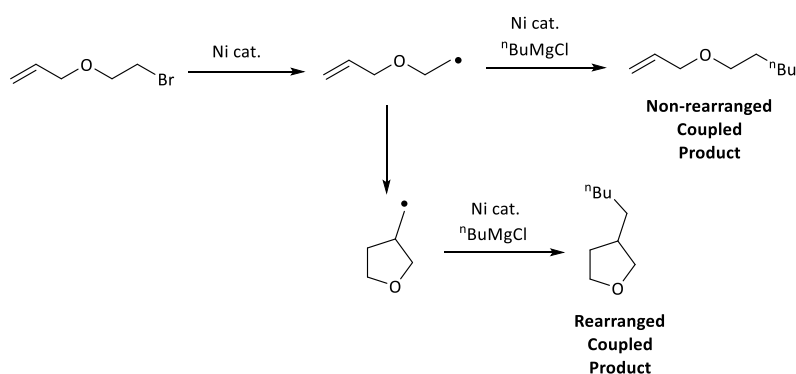
Another good example of mechanistic investigation into oxidative addition came from Hu *et al.* in 2013. Using a Ni^{II} pincer complex, the mechanism of oxidative addition with an alkyl halide along with the remainder of the Kumada-Corriu-Tamao cross-coupling mechanism was elucidated.¹⁰² Initially, radicals were established to be involved from radical-clock experiments and this was then investigated further. It was established that the nickel(0) active species was activating the alkyl halide *via* a single electron transfer (SET) and that this was most likely to be *via* an inner sphere mechanism. For this, there were three possible

mechanisms: cage-rebound where the alkyl halide quickly recombines with the same nickel species; a bimetallic mechanism where the alkyl radical escapes the cage and combines with a different molecule of nickel; or an escape-rebound mechanism where the alkyl radical escapes the cage but also then recombines with the same molecule of nickel complex (Scheme 2.3).¹⁰² To distinguish between these three mechanisms, experiments were carried out with a radical-clock substrate.¹⁰²



Scheme 2.3. Three possible mechanisms for oxidative addition in an alkyl-alkyl Kumada-Corriu-Tamao cross-coupling reaction.¹⁰²

When radicals interact with (2-allyloxy)ethyl bromide causing homolytic cleavage of the bromide, the radical formed can then rearrange to give the cyclised radical; this will react with the transmetalating reagent to form the rearranged coupled product (Scheme 2.4). This is in addition to forming the non-rearranged coupled product; the ratio of these two products as the nickel concentration is varied can be used to differentiate between the three mechanisms shown in Scheme 2.3. The cage-rebound mechanism is zero-order with respect to the nickel species meaning the ratio of rearranged/unrearranged product is independent of the concentration of nickel and is a constant value. Both the bimetallic and escape-rebound mechanism are first-order with respect to the nickel species meaning the ratios of products would have a linear dependence on concentration. Ratios of products were plotted against the concentration of nickel and gave a linear dependence, ruling out the cage-rebound mechanism.¹⁰²

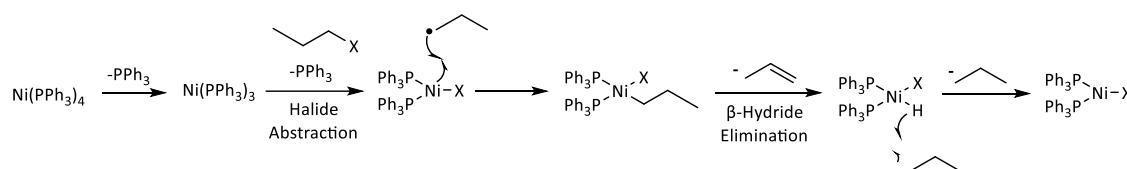


Scheme 2.4. Radical-clock experiments used to rule out the cage-rebound mechanism for alkyl-alkyl cross coupling reactions.¹⁰²

To distinguish between the bimetallic and escape-rebound mechanism, density functional theory (DFT) computations were used to model and compare energies of the two different nickel species reacting with an ethyl radical. The reaction of the species in the bimetallic mechanism with the ethyl radical was found to be barrierless. However, the species in the escape-rebound mechanism reacting with the radical was found to have a transition state barrier of 24 kcal/mol. To further support the bimetallic mechanism, it was also noted that the concentration of this second nickel molecule would be much higher than the nickel molecule used in the escape-rebound mechanism. Therefore, DFT helps to exclude the escape-rebound mechanism and identifies the bimetallic mechanism as the proposed mechanism of formal oxidative addition.¹⁰²

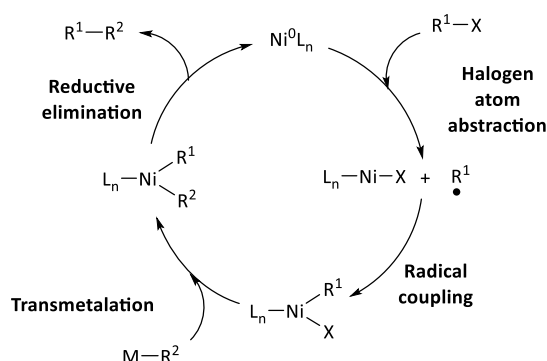
The most relevant piece of literature related to this body of work comes from Baird.¹⁰³ The ligands and conditions used in this published work are analogous to the work carried out within the Nelson group.⁷⁴ Variable temperature techniques were used to elucidate the mechanism of oxidative addition of various alkyl halides to $[\text{Ni}(\text{PPh}_3)_4]$. The ^{31}P NMR spectra of $[\text{Ni}(\text{PPh}_3)_4]$ at room temperature contains a single broad resonance at 24 ppm. When cooled to 200 K, the ^{31}P NMR spectrum contains two resonances ($\delta_{\text{P}} = 25$ ppm and 8 ppm), attributed to $[\text{Ni}(\text{PPh}_3)_3]$ and free PPh_3 , confirming that the dominant species in reaction mixtures is $[\text{Ni}(\text{PPh}_3)_3]$.¹⁰³ The major products from the reactions of $[\text{Ni}(\text{PPh}_3)_3]$ with iodoalkanes are alkanes and alkenes, with a nickel hydride as the minor product (Scheme 2.5). This product ratio suggested oxidative addition was occurring followed by a subsequent β -H elimination event. The order in rate of oxidative addition is as follows; *tert*-BuX > *sec*-BuX

> *n*-BuX (where X = Cl, Br, I) and I > Br > Cl which is consistent with a radical mechanism in operation, especially as the trend supports the trend of the stability of alkyl radicals.¹⁰³ With experimental evidence and previous work by Tsou and Kochi, a halide abstraction and a subsequent β -H elimination was proposed as the mechanism of oxidative addition for this reaction.¹⁰⁴



Scheme 2.5. Origin of alkene and alkane products in the reaction of ethylhalide with $[\text{Ni}(\text{PPh}_3)_4]$.¹⁰³

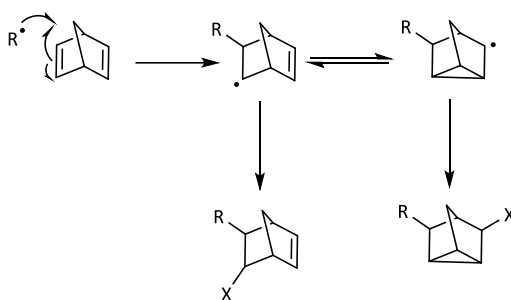
Due to the low concentrations of the nickel hydride complex found in the reaction mixtures, further investigations were carried out to determine where this was being consumed. It was established that alkyl radicals have the ability to escape the cage and do not necessarily all recombine to form the oxidative addition product. These radicals have three preferred reactions: self-reaction, disproportionation (to form alkane and alkene), combination to form longer chain alkanes, or abstraction of a proton from either the solvent or the nickel hydride complex. Equal amounts of alkene and alkane products consistent with disproportionation were observed, however, a lack of longer chain alkanes that would be consistent with combination reactions ruled out self-combination. There was also no evidence of any deuterated substrates, despite these reactions being carried out in toluene-*d*₈; only protic alkanes/alkenes were observed ruling out hydrogen atom abstraction from the solvent. The conclusion was that the alkyl radicals escaping from the cage were reacting preferentially with the nickel hydride (supported by DFT calculations) and this explained the low concentrations observed. The transmetalation and reductive elimination steps were as expected in traditional nickel catalysed processes therefore a final catalytic cycle was proposed for this transformation shown in Scheme 2.6.¹⁰³



Scheme 2.6. Experimentally supported mechanism of radical based cross-coupling of alkyl halides with $\text{Ni}(\text{PPh}_3)_3$.¹⁰³

2.2.1. Radical Clock Experiments

The rearrangement of norbornenyl to nortricycyl has been utilised as a radical clock substrate since the mid-1960s.¹⁰⁵ This rearrangement (Scheme 2.7) and the ratio of products in reaction mixtures can be used as a timing device, as product ratios are entirely dependent on whether the equilibrium has been established.¹⁰⁶



Scheme 2.7. Norbornenyl-nortricycyl rearrangement.¹⁰⁵

For this method to be useful in reactions containing organic radicals, the rearrangement reactions of common radical probes have been measured *via* EPR spectroscopy. For primary alkyl radical rearrangements, rate constants cover 7 orders of magnitude meaning at least one probe should be comparable for most reactions involving a primary alkyl radical.¹⁰⁵ A first-order rate constant for methylcyclopropane, one of the most commonly used substrates used in radical clock experiments, was published in 1979. The rate of ring opening was found to be $1.3 \times 10^8 \text{ s}^{-1}$ at 25 °C, which is an extremely rapid rearrangement.¹⁰⁷ Another common

radical clock substrate, 5-hexenyl radical which irreversibly cyclises to form the cyclopentenylmethyl radical, also had the rate of isomerisation measured ($1.3 \times 10^5 \text{ s}^{-1}$ at 25°C).¹⁰⁸ These rate constants obtained for rearrangement of radical clock substrates are calculated from EPR spectra. After initiation of radical substrates *via* hydrogen atom abstraction, the concentration of rearranged and unrearranged products were measured and a rate constant calculated from this.¹⁰⁹

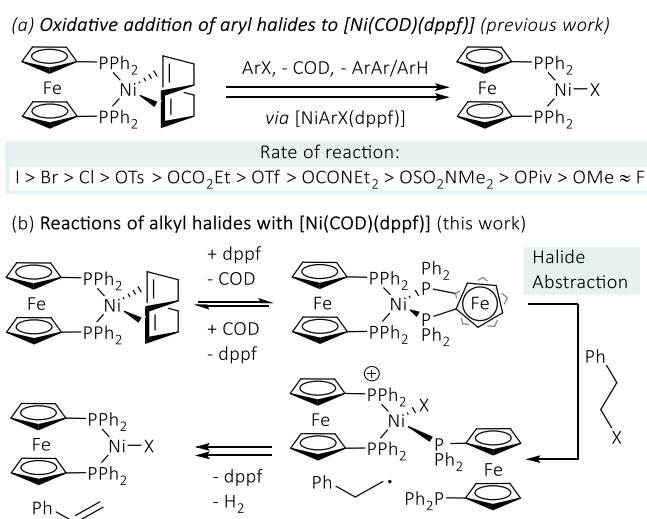
2.3. Introduction from Manuscript

The coupling of sp^3 centres is a frontier in modern cross-coupling catalysis research^{110,111} and is closely aligned to the drive in areas such as pharmaceutical industry to target sp^3 -rich molecules.^{112,113} Due to differences in oxidative addition behaviour and the occurrence (and often the dominance) of deleterious side reactions such as β -hydride elimination, couplings of sp^3 centres are typically far more challenging than the palladium catalysed sp^2 - sp^2 couplings that have become a routine in academia and industry. In order to overcome these synthetic challenges, chemists have looked toward alternative catalyst systems, often based on metals such as iron,¹¹⁴ cobalt,¹¹⁵ and nickel.^{9,98,116} Several useful catalytic systems have been disclosed. Practical nickel-catalysed reductive cross-electrophile couplings have also been developed, which allow sp^3 - sp^2 couplings of an aryl halide and an alkyl halide.¹⁰¹ However, despite synthetic advances in this field, we require further and deeper mechanistic understanding to underpin future developments.

Mechanistic studies of the reactions of alkyl halides with nickel are relatively few, and many studies of sp^3 couplings (both synthetic and mechanistic) invoke nickel(I) intermediates.^{117–121} Tilley *et al.* have reported the oxidative addition of methyl iodide to a nickel(I) species, forming a nickel(III) complex.^{122,123} Baird *et al.* have studied the reactions of alkyl halides with $[\text{Ni}^0(\text{PPh}_3)_4]$, which occurred via halide abstraction and which generate mixtures of alkane and alkene products, with the latter arising from β -hydride elimination;¹⁰³ studies were typically carried out by combining Ni^0 and alkyl halide at low temperatures and carefully increasing the temperature and observing NMR spectral changes. Wang *et al.* explored the reactions of a diphosphinodithio-ligated nickel(0) complex with alkyl halides, which were followed by the addition of NaBPh_4 ; this led to alkylnickel(II) complexes, which degenerated to hydride species via β -hydride elimination.¹²⁴ Diao *et al.* probed the reactions

of $[\text{Ni}^{\text{I}}(\text{Ar})(\text{Xantphos})]$ with alkyl halides and also proposed a halide abstraction mechanism (Xantphos = 4,5-bis-(diphenylphosphino)-9,9-dimethyl-xanthene).¹²⁵ Jarvo *et al.* studied the nickel/dppm-mediated synthesis of cyclopropanes from 1,3-dimesylates and uncovered a halide abstraction mechanism involving the initially formed 1,3-diiodide (dppm = bis(diphenylphosphino)methane).¹²⁶

The present study builds on our recent investigations of the oxidative addition of aryl halides to Ni^0 ,^{72,74,76,77,127} and works towards the understanding of reaction mechanisms and structure/reactivity relationships in nickel catalysis (Scheme 2.8). We work with bidentate phosphine ligands because they exhibit favorable reactivity in cross-coupling reactions;^{128–130} $[\text{Ni}^0(\text{COD})(\text{dppf})]$ (**1**), a thermally-stable and readily-prepared model Ni^0 complex, has been used for mechanistic studies of nickel catalysis and for catalytic reactions in organic synthesis (dppf = 1,1'-bis(diphenylphosphino)ferrocene).¹³¹ This is known to be the catalyst that is formed in reactions where $[\text{Ni}(\text{COD})_2]$ and dppf are combined in situ.¹³¹ Our key finding in this study is that the active Ni^0 species *must bear two dppf ligands*, even though most pre-catalysts with bidentate phosphine ligands have a 1:1 ligand to nickel ratio.



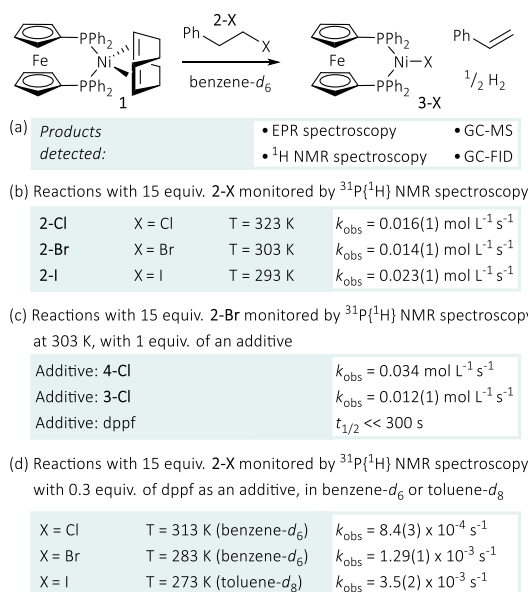
Scheme 2.8. (a) Previous work. (b) This work.

2.4. Results and Discussion from Manuscript

2.4.1. Kinetic Studies of Reactions With [(Ni(COD)(dppf))]

Stoichiometric experiments in which [Ni(COD)(dppf)] (**1**) was exposed to (2-haloethyl)benzene reagents (**2-X**) showed that the major products were styrene and [NiX(dppf)] (**3-X**), as confirmed by GC-FID/GC-MS analysis and EPR spectroscopy, respectively (Scheme 2.9(a));ⁱ these Ni^I complexes have been reported previously.^{131,132} No ethylbenzene was detected in any of these reactions. Styrene must arise from a β -hydride elimination process. The reactions between [Ni(COD)(dppf)] (**1**) and an excess of each of the three alkyl halides (**2-X**, 15 equiv.) in benzene-*d*₆ solution were monitored over time using ³¹P{¹H} NMR spectroscopy (Scheme 2.9(b)). Surprisingly, these reactions were pseudo-zero order in **1** (Figure 2.1(a)) and displayed saturation behavior in **2-Br**. This is in stark contrast to the reactions of **1** with aryl halides, which are pseudo-first order in **1** under the same conditions.⁷⁴ These results suggested that **1** was not the active species in these reactions.

ⁱ Authentic samples of styrene, ethylbenzene, and [NiX(dppf)] were used to calibrate the relevant analyses.



Scheme 2.9. (a) Stoichiometric reactions. (b) Initial kinetic studies, exhibiting zero order kinetic behaviour. (c) Control experiments. (d) Kinetic studies with added dppf, exhibiting pseudo-first order behaviour.

2.4.2. Identification of $[\text{Ni}(\text{dppf})]_2$ as the Active Species

Control reactions were conducted with additives to understand what the active species in these reactions might be (Scheme 2.9(c)). The addition of $[\text{NiCl}_2(\text{dppf})]$ (**4-Cl**) led to an increase in the rate of reaction, prompting speculation that $[\text{NiCl}(\text{dppf})]$ (**3-Cl**), formed from comproportionation between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and **4-Cl**,^{74,131,133} might be the active species. However, added **3-Cl** did not affect the reaction rate. When additional dppf ligand was present there was a significant increase in the reaction rate. Further analysis of $[\text{NiCl}_2(\text{dppf})]$ (**4-Cl**) by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy revealed small quantities of free dppf, thus accounting for its accelerating effect. $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) contained approximately 1% of what was assigned as $[\text{Ni}(\text{dppf})_2]$ (**5**) by comparison with literature ^{31}P NMR data ($\delta_{\text{P}} = ca. 15 \text{ ppm}$).¹³⁴ Complex **1** is prepared from dppf and $[\text{Ni}(\text{COD})_2]$ which yields **1** as the major product,^{131,135} but the presence of **5** appears to be essential for these reactions with alkyl halides. The equilibrium constant for the formation of **5** from **1** plus dppf was measured ($K_{\text{eq}} = 6.8$).

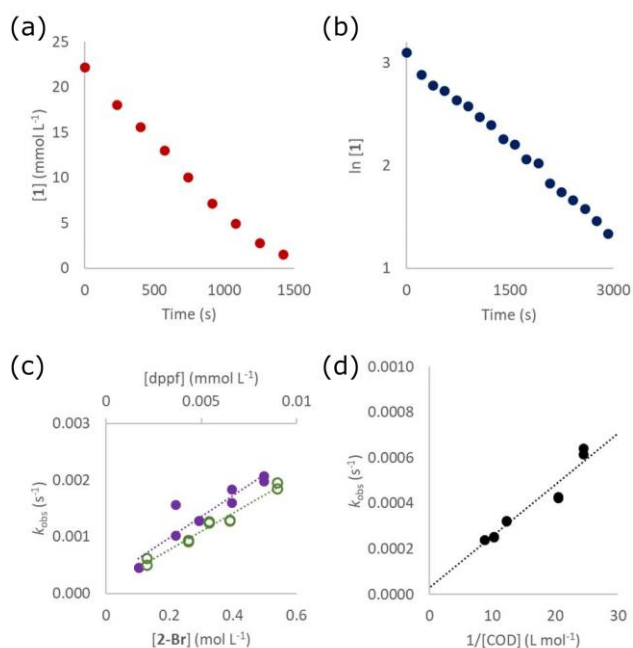


Figure 2.1. Kinetic data from the reactions of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) (2.2 mmol L^{-1}) in benzene- d_6 at 283 K with 0.33 mol L^{-1} (2-bromoethyl)benzene (**2-Br**) (unless otherwise stated): (a) pseudo-zero order behaviour (no added dppf; 303 K); (b) pseudo-first order behaviour (2.2 mmol L^{-1} dppf; 283 K); (c) first order in dppf (open green circles) and **2-Br** (closed purple circles) (6.6 mmol L^{-1} dppf for varied **2-Br**); and (d) by COD (6.6 mmol L^{-1} dppf).

2.4.3. Kinetic Studies of Reactions with $[\text{Ni}(\text{dppf})_2]$

Attempts were made to prepare a sample of **5** for kinetic studies but a sufficiently pure sample could not be obtained. Instead, a series of experiments were carried out in which additional dppf was present during the reactions of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with (2-haloethyl)benzene substrates (**2-X**) (Scheme 2.9(d)). The products of these reactions were again styrene and $[\text{NiX}(\text{dppf})]$ (**3-X**).

In the presence of added dppf these kinetic studies showed pseudo-first order behaviour in **1**, were first order in **2-X** and dppf, and were inhibited by COD (Figure 2.1(b) – (d)). *Notably the reactions of aryl halides with 1 are inhibited by added dppf, as established*

by control experiments; the reactions of aryl halides therefore proceed *via* [Ni(dppf)], but the reactions of alkyl halides proceed *via* [Ni(dppf)₂] (**5**).

A rate expression can be formulated for the reactions of alkyl halides with **1**. If an equilibrium between [Ni(COD)(dppf)] (**1**) plus dppf and [Ni(dppf)₂] (**5**) plus COD is rapidly established then the concentration of **5** can be defined according to eq. 2.1.

Equation 2.1

$$K_1 = \frac{[\mathbf{5}][\text{COD}]}{[\mathbf{1}][\text{dppf}]} \therefore [\mathbf{5}] = K_1 \cdot [\mathbf{1}] \cdot [\text{dppf}] \cdot [\text{COD}]^{-1}$$

If the reaction proceeds through a rate determining reaction between **5** and the alkyl halide (**2-X**) with rate constant k_2 then the reaction rate can be expressed as in eq. 2.2; the expression for [5] can then be substituted to give eq. 2.3.

Equation 2.2

$$\text{Rate} = k_2 \cdot [\mathbf{5}] \cdot [\mathbf{2X}]$$

Equation 2.3

$$\text{Rate} \approx k_{obs} \cdot [\text{Ni}]_{tot}; \text{ where}$$

$$k_{obs} = K_1 \cdot k_2 \cdot [\mathbf{1}] \cdot [\mathbf{2X}] \cdot [\text{dppf}] \cdot [\text{COD}]^{-1}$$

An alternative treatment based on the steady-state approximation leads to the same rate expression (see the Supporting Information).

An Eyring-Polanyi treatment of the reaction between [Ni(COD)(dppf)] (**1**) and 15 equiv. of **2-Cl** in the presence of 0.3 equiv. dppf yielded activation parameters (see the Supporting Information); $\Delta S^\circ \approx 0$ for the equilibrium between **1** and **5** and so $\Delta H^\ddagger$ is estimated at 26.2 kcal mol⁻¹ and $\Delta S^\ddagger$ at 15 cal K⁻¹ mol⁻¹. The latter value indicates a decrease in order as the reaction proceeds through the transition state.

2.4.4. Evidence for Radical Intermediates

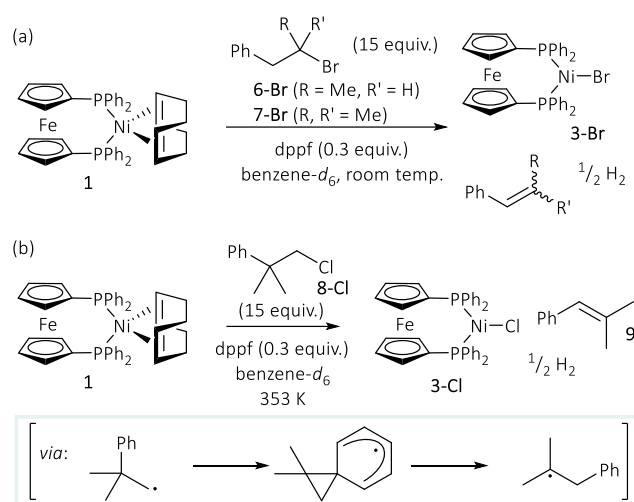
The formation of styrene in the reactions of (2-haloethyl)benzene substrates requires the intermediacy of alkylnickel(II) halide complexes that then undergo β-hydride elimination; however, it is possible that these might form directly from Ni⁰ or through the formation of

Ni^I and a radical, which then recombine to form Ni^{II}. The direct formation of styrene from ethylbenzene radical is ruled out as recombination to produce 1,4-diphenylbutane is favored by *ca.* 7-fold over disproportionation to styrene and ethylbenzene;¹³⁶ no 1,4-diphenylbutane or ethylbenzene is detected in any of these reactions.

The reactions of secondary and tertiary alkyl halides with [Ni(COD)(dppf)] (**1**) (and added dppf) were studied (Scheme 2.10(a)). The reactions of (2-bromopropyl)benzene (**6-Br**) and (2-bromo-2-methylpropyl)benzene (**7-Br**) were both far too fast to allow the measurement of rate constants. A distinct colour change occurred within 30 seconds of substrate addition at room temperature (*ca.* 293 K) so k_{obs} is at minimum *ca.* 0.2 s⁻¹ and therefore at least two orders of magnitude faster than for the reaction of **2-Br**; the colour change is proposed to be due to the formation of [NiBr(dppf)] (**3-Br**) which is darker in colour than [Ni(COD)(dppf)] (**1**). This significant rate enhancement on moving from primary to secondary and tertiary alkyl halides is consistent with a reaction that generates alkyl radicals.

Reasoning that styrene formation occurs due to a β -hydride elimination process, (1-chloro-2-methylpropan-2-yl)benzene (**8-Cl**) was used as the reaction substrate (Scheme 2.10(b)). The putative alkylnickel(II) bromide intermediate cannot undergo β -hydride elimination. Instead, 2-methyl-1-phenylprop-1-ene (**9**) was obtained as the organic product. No *tert*-butylbenzene was detected in the reaction mixture. This result is further evidence of radical intermediates; a [1,2]-phenyl shift explains the observation of **9** in the reactions of **8-Cl**.

Attempts to trap a radical intermediate with TEMPO or BHT were unsuccessful (TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; BHT = 2,6-di(*tert*-butyl)-4-methylphenol). TEMPO reacts directly with [Ni(COD)(dppf)] (**1**), while reactions with 1 – 15 equiv. BHT with respect to **1** yielded no alkane products. The radical intermediate formed is therefore rapidly trapped by the nickel complex – as is required to yield the β -hydride elimination products – more quickly than it can undergo reaction with BHT. Intramolecular rearrangement processes such as the [1,2]-phenyl shift in Scheme 2.10(b), with a rate constant of 500 s⁻¹ at 20 °C,¹³⁷ can outpace the capture of the primary alkyl radical by Ni^I.



Scheme 2.10. Experiments to probe the involvement of radicals.

2.4.5. Events After Radical Capture and β -Hydride Elimination

The evidence points to a mechanism in which $[\text{Ni}(\text{dppf})_2]$ (**5**) reacts with alkyl halides to form a Ni^{I} complex and an alkyl radical, which in turn combine to form a Ni^{II} complex that can undergo β -hydride elimination to form styrene. This would also produce $[\text{Ni}(\text{H})(\text{X})(\text{dppf})]$ (**10-X**), which must then form $[\text{NiX}(\text{dppf})]$ (**3-X**), as this is the ultimate product identified by EPR spectroscopy.

Attempts to obtain an authentic sample of $[\text{NiCl}(\text{CH}_2\text{CH}_2\text{Ph})(\text{dppf})]$ (**11-Cl**) by reaction of $[\text{NiCl}_2(\text{dppf})]$ (**4-Cl**) with the appropriate Grignard reagent led only to decomposition products including styrene and ethylbenzene; no Ni^{I} products were detected by EPR analysis, suggesting that the Ni^{I} in the reactions between Ni^0 and alkyl halides must arise through comproportionation and therefore does not form in the absence of Ni^0 . The instability of **11-Cl** makes any comproportionation pathways between this complex and Ni^0 unlikely. Attempts to prepare $[\text{Ni}(\text{H})(\text{Cl})(\text{dppf})]$ (**10-X**) by reaction of $[\text{NiCl}_2(\text{dppf})]$ (**4-Cl**) with various hydride sources did not produce any tractable nickel hydrides and no structurally-similar nickel hydrides have been reported in the literature.¹³⁸

We propose that putative hydride complex **10-X** undergoes decomposition to form $[\text{NiX}(\text{dppf})]$ (**3-X**) *via* comproportionation with Ni^0 . Reactions between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and 1 equiv. of **2-X** (in the presence of 0.3 equiv. dppf) were followed by ^1H NMR spectroscopy, and showed a signal consistent with that for hydrogen;¹³⁹ when the sample

was placed under a hydrogen atmosphere, the intensity of this signal increased, supporting the assignment. It has been shown using computational techniques that complexes of the form $[\text{NiH}_2(\text{PR}_3)_2]$ exist most favourably as non-classical dihydrogen complexes, suggesting the release of hydrogen from such a species to be facile;¹⁴⁰ no such complexes have been experimentally characterized. A sample of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) placed under a hydrogen atmosphere at room temperature decomposed slightly over the course of several hours, forming free dppf and COD; the analogous experiment with additional dppf formed COD and cyclooctene, with the latter presumably arising from COD hydrogenation by a putative nickel hydride intermediate.¹⁴¹

2.4.6. Ruling Out Outer-Sphere Electron Transfer

Two possible mechanisms for the reactions of $[\text{Ni}(\text{dppf})_2]$ (**5**) with alkyl halides can lead to the formation of alkyl radicals: outer-sphere electron transfer or halide abstraction.^{72,103,127,142} These differ in that the latter requires a vacant site for coordination of the substrate prior to halide abstraction. A sample of $[\text{Ni}(\text{dppe})_2]$ (**12**) was prepared¹⁴³ and exposed to alkyl halides (dppe = 1,2-bis(diphenylphosphino)ethane); this complex is known to be unreactive towards a range of species found in typical cross-coupling reactions¹³⁵ but is capable of undergoing outer-sphere electron transfer.⁷¹ The dppe ligand has similar electronic properties to dppf, as judged from IR spectra of $[\text{Ni}(\text{CO})_2(\text{dppf})]$ (ν_{CO} (DCM) = 2001, 1939 cm^{-1})¹⁴⁴ and $[\text{Ni}(\text{CO})_2(\text{dppe})]$ (ν_{CO} (CHCl_3) = 2006, 1945 cm^{-1}).¹⁴⁵ $[\text{Ni}(\text{dppe})_2]$ (**12**) does not undergo reaction with alkyl halides at all. If the reaction proceeded *via* outer-sphere electron transfer, then both $[\text{Ni}(\text{dppf})_2]$ (**5**) and $[\text{Ni}(\text{dppe})_2]$ (**12**) should be competent. However, only **5**, which can open a vacant site, undergoes reaction while **12**, which cannot open a vacant site, is inert.

2.4.7. DFT Calculations Support a Halide Abstraction Mechanism

The halide abstraction pathway was modelled using DFT calculations.ⁱⁱ Pathways *via* $[\text{Ni}(\text{dppf})_2]$ (**5**) are discussed here; alternative pathways that are ruled out based on

ⁱⁱ All calculations were carried out in Gaussian16 using the B3LYP functional with Grimme's D3 dispersive corrections. Optimisation was carried out without symmetry corrections or solvation, with the LANL2TZ(f) basis set on Ni and Fe, the LANL2DZ(dp) basis set on Br and I, and the 6-31G(d) basis set on all other atoms. Frequency calculations were used to verify the nature of stationary points. Potential energies were refined using single point

experimental evidence are discussed in the Supporting Information. Throughout this manuscript energies from DFT calculations are quoted as free energies in benzene solvent with respect to [Ni(COD)(dppf)] (**1**) unless otherwise stated;ⁱⁱⁱ a 1.89 kcal/mol correction is applied to the free energy of each molecule so that the standard state is then 1 mol/L rather than 1 atm.¹⁴⁶

The formation of [Ni(dppf)₂] (**5**) from [Ni(COD)(dppf)] (**1**) is energetically favourable (Figure 2.2); [Ni(κ^2 -dppf)(κ^1 -dppf)] (**5'**) in which one phosphine is dissociated from the nickel centre is slightly higher in energy than **5** (by 2.6 kcal mol⁻¹) so is also a plausible intermediate. DFT calculations overestimate the stability of **5**, compared to experimental data for the equilibrium between **1** and **5**, but qualitatively agrees in that the formation of **5** is favourable. Complexes **5** or **5'** might be able to undergo outer-sphere electron transfer to the alkyl halide, and so the barrier for these processes was estimated using Marcus-Hush theory;¹⁴⁷ the barriers are rather high (26 – 33 kcal mol⁻¹ for **5**; 31 – 38 kcal mol⁻¹ for **5'**; see the Supporting Information).

Halide abstraction provides an alternative pathway; it is proposed to be the predominant mechanism in this reaction due to the lack of reactivity of [Ni(dppe)₂] with alkyl halides (*vide supra*). The binding of alkyl halides to **5'** *via* the halide is endergonic by *ca.* 2 - 3 kcal mol⁻¹, but the halide abstraction transition state is then accessible (19 – 26 kcal mol⁻¹ from **5**).

Halide abstraction by [Ni(η^2 -COD)(dppf)]¹²⁶ is ruled out based on the experimentally-determined first order behavior in dppf. In addition, computational studies of halide abstraction by [Ni(dppf)(η^2 -ethene)] (as a model for [Ni(η^2 -COD)(dppf)]) show that this

calculations in benzene solvent (SMD), and with the 6-311+G(d,p) basis set on all atoms except I. Full details and coordinates for all structures can be found in the Supporting Information.

ⁱⁱⁱ Optimisation was carried out in the gas phase, because attempts to optimise these structures in solvent using PCM or SMD models were unsuccessful. Some structures could be optimised in solvent, but this made rather little difference to the energetics of the relevant steps. See the Supporting Information for more details.

process is less competent than halide abstraction by **5'**, with a barrier that is 5.7 kcal/mol higher in energy (see the Supporting Information for details).

The radical formed by halide abstraction recombines with the Ni^I complex to form an alkylnickel(II) halide species with the concomitant loss of a dppf ligand (Figure 2.2). The resulting complex [Ni(CH₂CH₂Ph)(X)(dppf)] (**11-X**) is known to be unstable (*vide supra*) and so a bimolecular comproportionation pathway for this species is ruled out. Instead β-hydride elimination forms [Ni(H)(X)(dppf)(η²-styrene)] which can then dissociate styrene to form [Ni(H)(X)(dppf)] (**10-X**). We have not modelled the subsequent processes but propose that **10-X** undergoes comproportionation with Ni⁰ present in the reactions to form [NiX(dppf)] (**3-X**) and [Ni(H)dppf]. The latter complex could undergo disproportionation to Ni⁰ and [Ni(H)₂(dppf)], which would then reductively eliminate hydrogen.

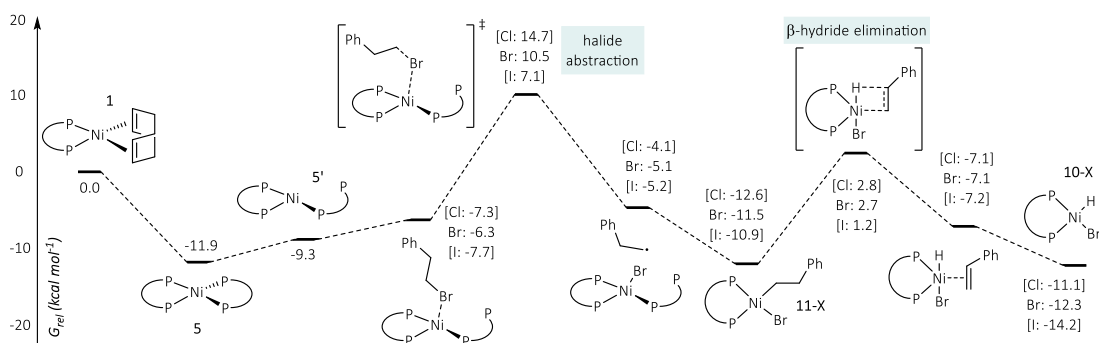


Figure 2.2. DFT studies of the reaction between [Ni(COD)(dppf)] (**1**) and (2-haloethyl)benzene substrates (**2-X**) via [Ni(dppf)₂] (**5**). All energies are free energies in kcal mol⁻¹ in benzene solution and are quoted relative to complex **1**. The profile is drawn for the case of (2-bromoethyl)benzene (**2-Br**) with energies provided in square brackets for the reactions of (2-chloroethyl)benzene (**2-Cl**) and (2-iodoethyl)benzene (**2-I**). The dppf ligand is abbreviated to two linked P atoms for clarity.

We have studied the corresponding reactions with an *aryl* halide (bromobenzene) to understand why these proceed more slowly in the presence of added dppf (Figure 2.3). The oxidative addition of bromobenzene to [Ni(COD)(dppf)] (**1**) proceeds *via* an intermediate η²-complex, presents a modest barrier of 10.7 kcal/mol (from **1**), and is exergonic. We were unable to locate a corresponding halide abstraction transition state, but this would be preceded by [Ni(dppf)(BrPh)] (*G*_{rel} = 12.5 kcal/mol), in which bromobenzene ligates the nickel

center *via* a bromine lone pair. This structure is higher in energy than the oxidative addition transition state by 1.8 kcal/mol. Two pathways were also considered for reactions *via* $[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})]$ (**5'**): direct oxidative addition, which has previously been modelled for $[\text{Ni}(\text{PR}_3)_3]$ complexes ($\text{PR}_3 = \text{PMe}_3, \text{PMe}_2\text{Ph}, \text{PMePh}_2, \text{PPh}_3$),⁷² and halide abstraction. Oxidative addition would require the formation of an intermediate η^2 - complex that is very high in energy ($G_{\text{rel}} = 13.5$ kcal/mol), followed by a transition state that is higher in energy still ($G_{\text{rel}} = 14.1$ kcal/mol). Halide abstraction would proceed through $[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})(\text{BrPh})]$ ($G_{\text{rel}} = 0.9$ kcal/mol), leading to a halide abstraction transition state that is even higher in energy ($G_{\text{rel}} = 14.4$ kcal/mol). These data establish that **1** will react with bromobenzene through oxidative addition to a dppf-Ni(0) species; the formation of $[\text{Ni}(\text{dppf})_2]$ as a low-energy off-cycle species would impede this reaction by increasing the barrier to oxidative addition, consistent with the observed rate decrease when dppf is added to the reaction of aryl bromides with **1**.

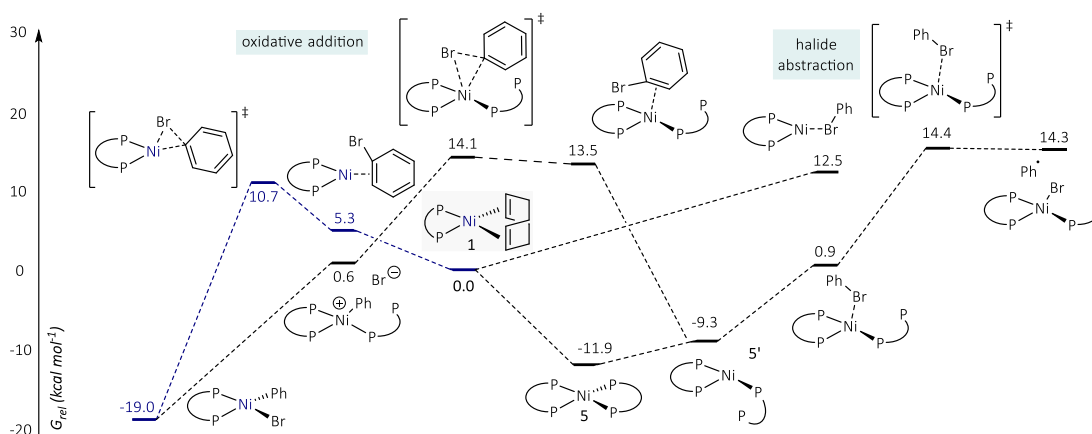


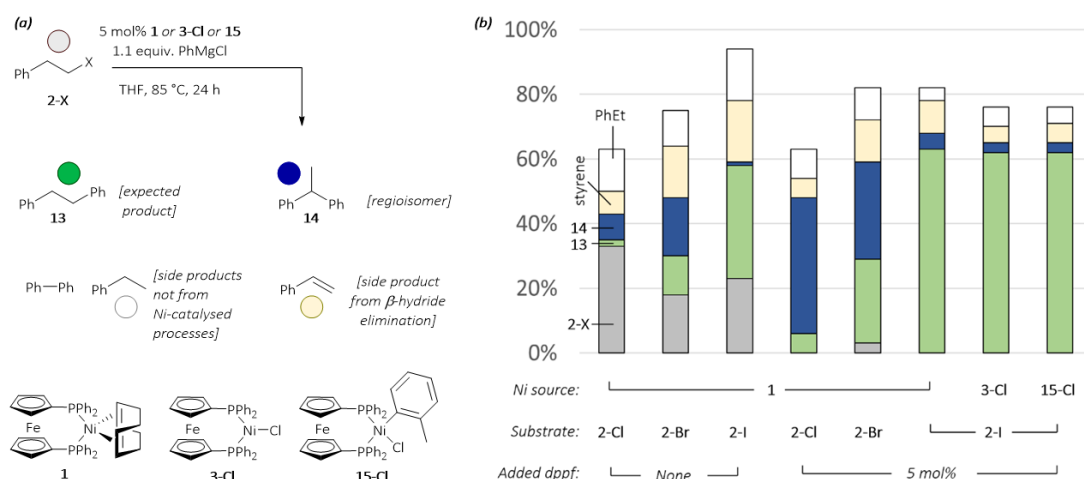
Figure 2.3. DFT studies of the reaction between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and bromobenzene. All energies are free energies in kcal mol^{-1} in benzene solution and are quoted relative to complex **1**. The dppf ligand is abbreviated to two linked P atoms for clarity.

2.4.8. Relevance to Catalysis

The results discussed above allow new insight into steps that can proceed under cross-coupling reaction conditions. It is important to link these to an understanding of synthetically-relevant catalytic reactions. This is especially important given the significant interest in the synthesis of sp^3 -rich molecules for medicinal chemistry and other applications,

especially in fields such as pharmaceuticals and agrochemicals.^{112,113} The prototypical cross-coupling reactions of (2-haloethyl)benzene substrates (**2-X**) with phenylmagnesium chloride were selected (Scheme 2.11(a)). These produced 1,2-diphenylethane (**13**), regioisomeric side product 1,1-diphenylethane (**14**), styrene, biphenyl, and ethylbenzene. Control reactions without catalyst showed that the latter two products do not arise *via* nickel-catalysed processes. Complexes [Ni(COD)(dppf)] (**1**), [NiCl(*o*-tol)(dppf)] (**15-Cl**), and [NiCl(dppf)] (**3-Cl**) were deployed as catalysts (Scheme 2.11(b)).^{iv} Reactions catalysed by **1** but without additional phosphine ligand yield very poor results in catalysis, with incomplete conversion of **2-X** and low yields of product **13** and side-product **14**. The addition of 5 mol% dppf significantly improved reaction outcomes, enabling full (or close to full) conversion of **2-X**. Reactions catalysed by [Ni(COD)(dppf)] (**1**), [NiCl(dppf)] (**3-Cl**), and [NiCl(*o*-tol)(dppf)] (**15-Cl**) with 5 mol% of added dppf converged on the same reaction outcome. This suggests that they proceed *via* a common pathway, despite the different pre-catalyst oxidation states. Ni^I complexes such as **3-Cl** form Ni^I-aryl species upon reaction with Grignard reagents, and so can serve as Ni⁰ sources for catalysis.^{74,148} Complex **15-Cl** undergoes transmetalation with Grignard reagents, followed by reductive elimination to form Ni⁰.^{74,133}

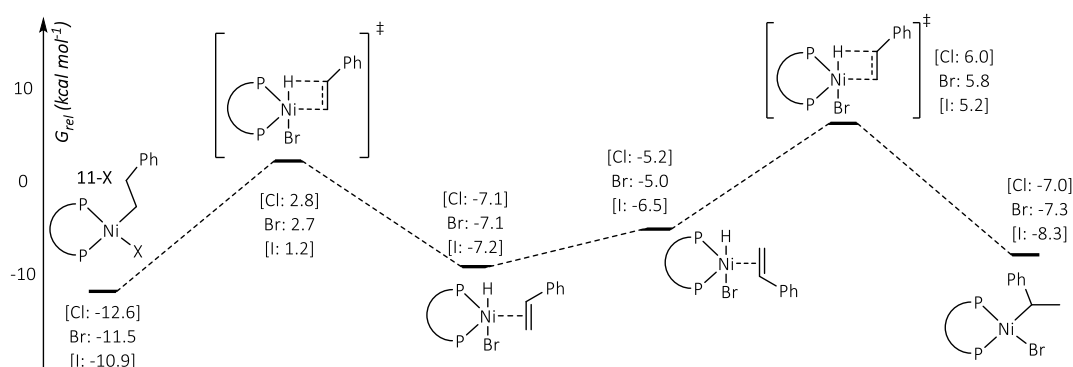
^{iv} Reaction outcomes were determined using GC-FID analysis with an internal standard, which was calibrated using authentic samples of all products. See the Supporting Information for full details and reaction data.



Scheme 2.11. (a) Prototypical Kumada-Tamao-Corriu reactions. (b) Outcomes of reactions.

The concentration of biphenyl is not plotted.

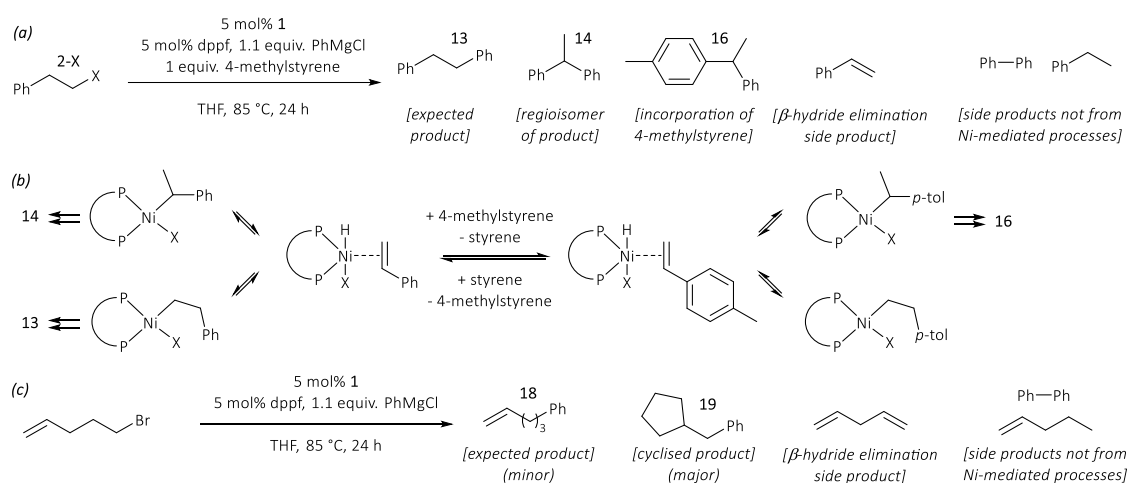
2.4.9. Reactions Involve Both Radical Intermediates and β -Hydride Elimination



Scheme 2.12. DFT calculations of the migratory insertion pathway to form the regioisomeric alkylnickel(II) halide species implicated in the formation of **14**.

The analysis of the side products in catalytic reactions gives additional information about plausible reaction pathways. Side-product **14** (1,1-diphenylethane) could be generated by β -hydride elimination from $[\text{Ni}(\text{CH}_2\text{CH}_2\text{Ph})(\text{X})(\text{dppf})]$ (**11-X**) followed by reinsertion to form the regioisomeric alkylnickel(II) halide species $[\text{Ni}(\text{CH}(\text{Me})(\text{Ph}))(\text{X})(\text{dppf})]$ (an overall “ β -hydrogen transfer” process) and subsequent transmetalation and reductive elimination; the plausibility of this pathway is supported by DFT calculations (Figure 2.12), which indicate relatively low barriers of *ca.* 16 – 19 kcal mol⁻¹ from **11-X** to the highest energy transition state on the

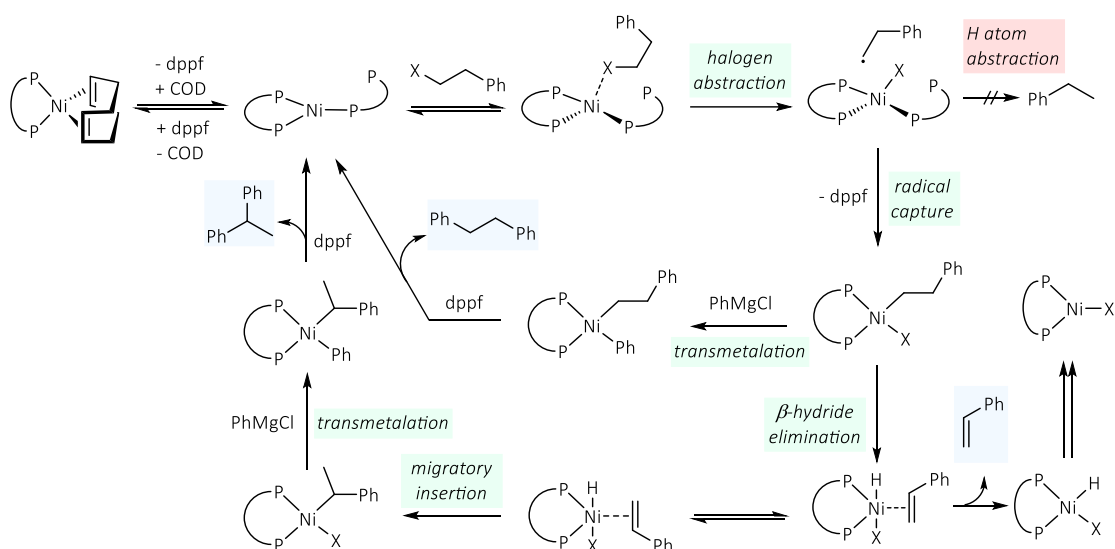
pathway, and led to isomeric alkylnickel(II) halide species that are only *ca.* 4 – 6 kcal mol⁻¹ higher in energy. Consistent with this proposal, when a prototypical Kumada reaction was carried out in the presence of a 4-methylstyrene additive, 1-(4-methylphenyl)-1-phenylethane (**16**) was also observed (Scheme 2.13(a)). We note that nickel-catalyzed migratory Suzuki-Miyaura cross-coupling reactions have been developed by Yin and co-workers,¹⁴⁹ and that our reactions share some mechanistic features with such reactions, specifically the formation and recombination of an alkyl radical and the transposition of the nickel center along an alkyl chain. We propose that this results from migratory insertion into a nickel hydride intermediate, followed by transmetalation and reductive elimination (Scheme 2.13(b)). While the secondary alkylnickel(II) complexes are higher in energy than the corresponding primary alkylnickel(II) complexes (**11-X**), subsequent events in the Kumada cross-coupling reaction such as transmetalation and reductive elimination may have different barriers that depend on the isomer of the alkyl ligand the identity of the halide; this will be explored in more detail in a subsequent study.



Scheme 2.13. (a) Reactions in the presence of a 4-methylstyrene additive. (b) Proposed pathway for the incorporation of 4-methylstyrene into cross-coupling products via migratory insertion into a nickel hydride intermediate. (c) Cross-coupling reactions with 6-bromohex-1-ene.

Cross-coupling reactions were carried out using substrates that can act as radical traps. (Chloromethyl)cyclopropane underwent a nucleophilic substitution reaction with the dppe ligand. The reactions of 6-bromohex-1-ene (**17-Br**) were more informative and led to

(phenylmethyl)cyclopentane (**19**) as the major product, along with 6-phenylhex-1-ene (**18**) and side products biphenyl, hexa-1,5-diene, and hex-1-ene (Scheme 2.13(c)). Product **19** is proposed to arise from the cyclization of the intermediate primary radical ($k = 1.8 \times 10^5 \text{ s}^{-1}$ at 20°C)¹³⁷ followed by capture by Ni^{I} . This provides further evidence of the intermediacy of radical species in these reactions.



Scheme 2.14. Processes occurring during the Kumada coupling reactions of (2-haloethyl)benzene substrates (2-X) with PhMgCl , catalysed by $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) in the presence of additional dppf; the dppf ligand is simplified to two linked P atoms for clarity.

2.5. Extended Discussion

2.5.1. Evidence of $[\text{Ni}(\text{dppf})\text{Cl}]$

Crystals suitable for X-ray diffraction studies were grown from the reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and 2-chloroethylbenzene (**2-Cl**) (Figure 2.4). A full data collection was not completed on this sample, as crystals of $[\text{Ni}(\text{dppf})\text{Cl}]$ (**3-Cl**) had already been isolated and fully analysed in a previous study within the Nelson group.⁷⁴

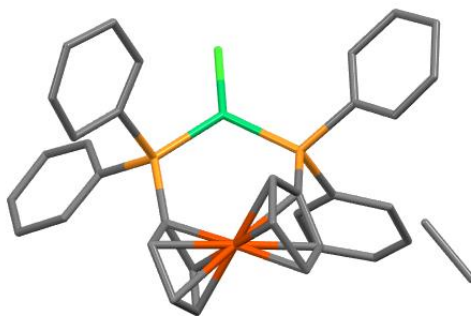
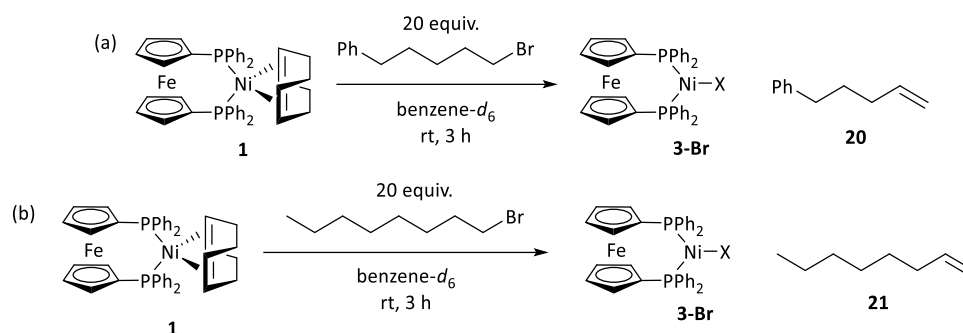


Figure 2.4. Crystal structure of [Ni(dppf)Cl] (**3-Cl**).

Samples of [Ni(COD)(dppf)] (**1**) and 2-bromoethylbenzene (**2-Br**) after kinetic studies were analysed by EPR spectroscopy to confirm the presence of [Ni(dppf)Br] (**3-Br**).

2.5.2. Nonactivated Alkyl Halides

Although the substrates used in this study are not benzylic in nature, the phenyl ring in these homobenzylic systems can still have some activating effect on the substrate and promote oxidative addition. To establish the direct effect the aryl ring is having on the rates of reactions, reactions were repeated using (5-bromopentyl)benzene and 1-bromooctane as a nonactivated alkyl halides. Reactions between [Ni(COD)(dppf)] (**1**) and an excess of halide (15 equiv.) in benzene-*d*₆ were monitored via ³¹P{¹H} NMR spectroscopy. The products from this reaction were analysed by GC-MS and were confirmed to be the corresponding alkene products **20** and **21** that arise from β-H elimination after oxidative addition (Scheme 2.15). These results mirrored what was observed with 2-haloethylbenzene substrates used in our study with the corresponding alkenes present in product analysis.



Scheme 2.15. Reactions analysed by GC-MS to show presence of alkene products occurring from β -H elimination. (a) Using 5-bromopentylbenzene as substrate. (b) Using 1-bromooctane as substrate.

Initial kinetic plots from the reaction of $[Ni(COD)(dppf)]$ (**1**) with excess halide (for both 5-bromopentylbenzene and 1-bromooctane) confirmed a zero-order dependence on nickel as observed for 2-haloethylbenzene substrates. Once it was confirmed that the active species was $[Ni(dppf)_2]$ (**5**), the kinetic experiment with 1-bromooctane was repeated with added dppf (0.3 equiv.) and an excess of alkyl halide (15 equiv.). As with the 2-haloethylbenzene substrates, the kinetic behaviour changed and the plots were now pseudo-first order with respect to $[Ni(COD)(dppf)]$ (**1**) (Figure 2.5). When comparing 1-bromooctane to the 2-bromoethylbenzene kinetic plots, it was observed that the presence of the aryl ring gave an enhanced rate (*ca.* 8-fold). This confirmed that the aryl ring did have some activating effect, however, this did not cause any change in the kinetic behaviour, meaning the same mechanism is likely to be in operation, and only a change in the overall rate of the reaction was observed.

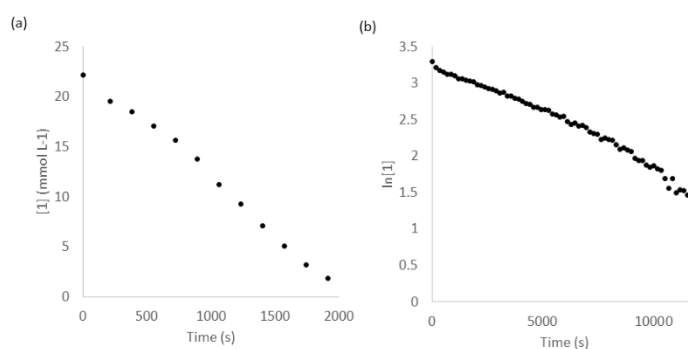
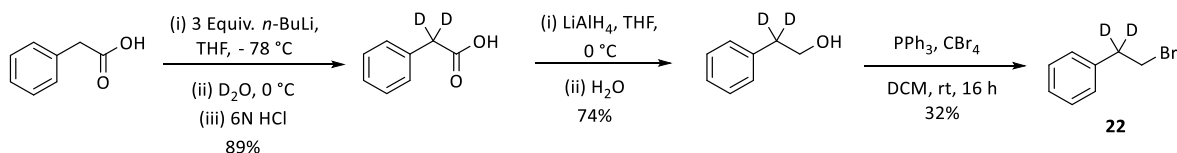


Figure 2.5. (a) Kinetic data from reactions of [Ni(COD)(dppf)] (**1**) (22 mmol L⁻¹) in benzene-d₆ at 303 K with 0.33 mol L⁻¹ 1-bromooctane, pseudo-zero order behaviour. (b) Kinetic data from reaction as in (a) with 6.6 mmol L⁻¹ dppf added, reaction conducted at 283 K in toluene-d₈, pseudo-first order behaviour.

2.5.3. Deuterated Substrates

As discussed in section 2.4.5., hydrogen was observed in the ¹H NMR spectrum of a 1:1 reaction with [Ni(COD)(dppf)] (**1**) and 2-bromoethylbenzene in benzene-d₈. In order to probe the origin of the hydrogen produced and the incorporation of hydrogen in the styrene produced, a deuterated version of 2-bromoethylbenzene was synthesised according to literature preparations (Scheme 2.16).^{150–152}

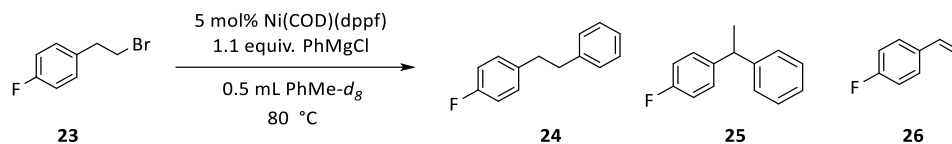


Scheme 2.16. Synthesis of a deuterated form of 2-bromoethylbenzene to probe mechanism further.

Deuterated substrate **22** (2 equiv.) was added to [Ni(COD)(dppf)] (**1**) (22 mmol L⁻¹), dppf (6.6 mmol L⁻¹) in benzene-d₆ and was heated to 323 K for 2 hours. After this, the sample was analysed by ²H NMR spectroscopy and GC-MS. Due to the low sensitivity of ²H NMR spectroscopy, it was difficult to fully characterise products, however, there was a lack of a peak consistent with D₂.¹³⁹ A doublet of doublets consistent with deuterated styrene was observed in the ²H NMR spectrum.¹⁵³ This assignment was corroborated by GC-MS analysis where a mass consistent with deuterated styrene was also observed.

2.5.4. Fluorinated Substrates

To enable the monitoring of Kumada-Corriu-Tamao reactions, 4-fluorophenethyl bromide **23** was employed to allow the use of $^{19}\text{F}\{^1\text{H}\}$ NMR spectroscopy to monitor the depletion of the starting material and the appearance of the products (Scheme 2.17).



Scheme 2.17. Kumada-Corriu-Tamao cross-coupling reaction with 0.125 mmol 4-fluorophenethyl bromide and phenylmagnesium chloride in toluene- d_8 at 80 °C.

The similarity of both the expected product **24** and regioisomer **25** led to difficulties in characterising these in the $^{19}\text{F}\{^1\text{H}\}$ NMR spectra. However, the fluorinated styrene side product **26** had a sufficiently different chemical shift to enable monitoring of its appearance over time. Figure 2.5 shows the concentrations of both alkyl halide **23** and styrene side product **26** over time. As expected, there is a sharp decrease in the concentration of alkyl halide **23** and then a plateau that corresponds to 96% conversion, a typical conversion for these Kumada-Corriu-Tamao cross-couplings. The initial increase and then decrease of the styrene by-product **26** is consistent with the proposed mechanism in Scheme 2.14; styrene is formed by β -hydride elimination which is followed by reinsertion which ultimately forms regioisomer **25**.

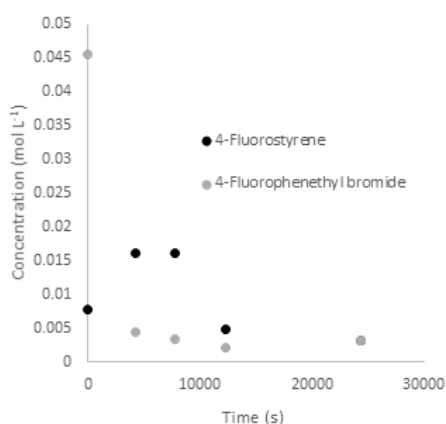
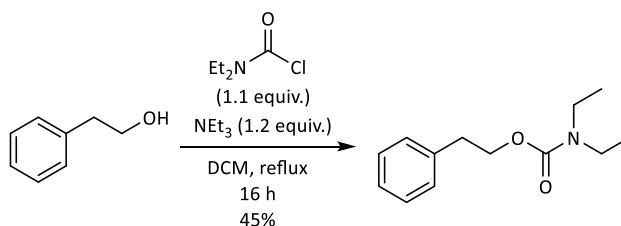


Figure 2.6. Concentration of 4-fluorophenethyl bromide and 4-fluorostyrene over an 8 hour period during a Kumada-Corriu-Tamao cross-coupling reaction.

2.5.5. Alkyl Carbamate

With the aim to create a reactivity series, as previously done for aryl halides within the Nelson group, phenylethyl diethylcarbamate **27** was synthesised used in kinetic experiments (Scheme 2.18).⁷⁴



Scheme 2.18. Synthesis of phenylethyl diethylcarbamate.

Initially, it was obvious that the oxygen electrophiles underwent reaction *via* a different mechanism when compared to alkyl halides. This was apparent from the *pseudo*-first order dependence on nickel, without any added dppf being present (Figure 2.6(a)). With added dppf, the reaction remained *pseudo*-first order with respect to nickel (Figure 2.6(b)) with only a small increase in rate observed (a factor of 2). The order in substrate was also investigated and the reaction was shown to be first order in substrate; however, as opposed to alkyl halides, this trendline did not pass through zero as would be expected (Figure 2.6(c)).

It was clear that these other electrophiles did not operate *via* the same mechanism as alkyl halides and the decision was made to focus on the halides. At this point, it is not entirely clear what the mechanism of this reaction is, and significant further study is required to fully understand it.

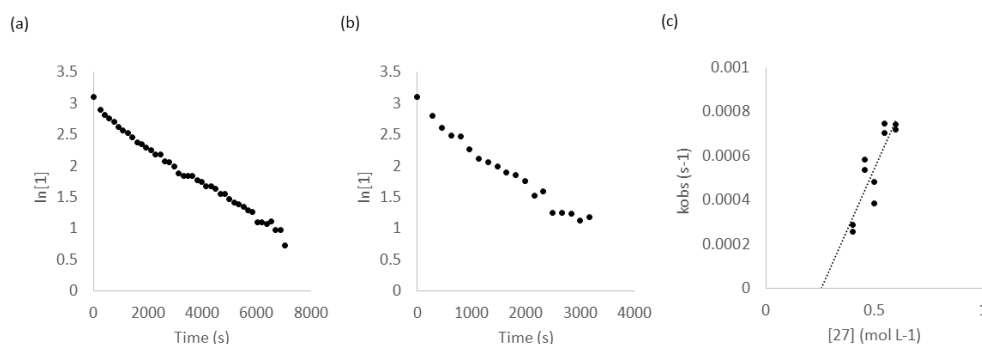


Figure 2.7. Kinetic data for the reactions of $[(Ni(COD)(dppf))]$ (**1**) (22 mmol L^{-1}) in benzene- d_6 at 343 K with 0.44 mol L^{-1} phenylethyl diethylcarbamate **27** (unless otherwise stated). (a) Pseudo-first order behaviour (with no dppf added). (b) Pseudo-first order behaviour (6.6 mmol L^{-1} dppf added). (c) First order in phenylethyl diethylcarbamate **27**.

2.5.6. Solvents

To ensure that the water content of the solvent being used was not having a significant impact on the kinetic data collected, different drying methods were employed, and kinetic studies were carried out with these solvents. It was observed that there was no difference in rate in benzene- d_6 treated in the following ways: not dried (fresh from commercial bottle); overnight drying on $4 \text{ \AA}$ molecular sieves; and overnight drying over powdered calcium hydride. This ensured that the water content of the solvent did not have an effect on kinetic data and it could be treated reliably.

2.5.7. Nickel Hydrides

In an extensive review of nickel hydride complexes (2016), all nickel hydrides that have been successfully isolated and characterised were published.¹³⁸ Notably, none of these hydrides incorporated dppf as a ligand. The most common phosphine ligands used in the synthesis of hydrides contain cyclohexyl groups (tricyclohexylphosphine (PCy_3) or 1,2-bis(dicyclohexylphosphino)ethane (dcpe)). A complex using PCy_3 as a ligand was reported to

be stable under air for several hours in the solid state and rapid degradation was only observed in solution.¹⁵⁴ The excessive bulk encountered in hydrides containing PCy₃ are thought to be insusceptible to rearrangement from a square planar to tetrahedral geometry which is thought to cause degradation, explaining why this extra bulk increases stability.¹⁵⁴ These findings help explain why it was unlikely for us to be able to synthesise and successfully isolate hydrides thought to be present in our system, as the dppf ligand is not bulky enough to prevent degradation.

2.6. Conclusions

We have conducted a thorough study of the reactions of alkyl halides with dppf-Ni⁰ complexes. Scheme 2.14 outlines a mechanism for this process that is supported by experimental and DFT studies. The key points from this study are as follows.

2.6.1. The Nature and Reactivity of the Active Catalyst

Reactions proceed through [Ni(dppf)₂] (**5**), which bears two dppf ligands, in contrast to the reactions of aryl halides which proceed through complexes with one dppf ligand. The key mechanistic event is halide abstraction to form a Ni^I species and a radical; these then recombine to form a Ni^{II} species. Some alkyl radicals, such as those derived from alkyl halides without β-hydrogens, can undergo rearrangement reactions before capture by Ni^I. The lack of reactivity of Ni⁰ complexes bearing alternative bidentate phosphine ligands which more readily form [Ni(L)₂] complexes, such as [Ni(dppe)₂] (**12**), show that it is necessary to generate a vacant site for the reaction to occur.

2.6.2. The Fate of the Ni^{II} Intermediate

The Ni^{II} intermediate thus formed can either undergo transmetalation during a cross-coupling cycle or can undergo β-hydride elimination to form styrene. Re-insertion of styrene is proposed to lead to a regioisomer of the alkylnickel(II) species; this is also able to undergo transmetalation and reductive elimination, leading to a side product. The putative nickel hydride complex [Ni(H)(X)(dppf)] (**10-X**) formed from β-hydride elimination then undergoes comproportionation with Ni⁰ to form [Ni(X)(dppf)] (**3-X**) and (ultimately) hydrogen.

This study provides insight into the activation of *sp*³ C-X bonds for cross-coupling reactions, as part of our ongoing programme to interrogate and understand reaction

mechanisms in nickel catalysis, with the aim of exploiting this understanding for catalyst and reaction design. Further mechanistic studies of oxidative addition to Ni^0 , and how these depend on ligand and substrate structure, are currently underway in our laboratory.

Chapter 3 - The Effect of Added Ligands on the Reactions of $[\text{Ni}(\text{COD})(\text{dppf})]$ with Alkyl Halides: Halide Abstraction may be Reversible

Organometallics, 2021, **40**, 1997 – 2007.

A published journal article entitled 'The Effect of Added Ligands on the Reactions of [Ni(COD)(dppf)] with Alkyl Halides: Halide Abstraction may be Reversible' with an extended introduction prior to the article and an extended discussion after.¹⁵⁵ The supporting information for this article can be found in the Chapter 7: Experimental.

Contributing authors to this manuscript and their roles are given below:

- Megan E. Greaves – Designed and performed experiments, analysed data, drafted initial manuscript
- Thomas O. Ronson – Helpful discussions as industrial supervisor
- Feliu Maseras – Assistance with DFT calculations
- David J. Nelson – Principal Investigator

3.1. Abstract from Manuscript

The reactions of dppf-nickel(0) with alkyl halides proceed *via* three-coordinate nickel(0) intermediates of the form [Ni(dppf)(L)]. The effect of the identity of the added ligand (L) on catalyst speciation and the rates of reactions of [Ni(COD)(dppf)] with alkyl halides has been investigated using kinetic experiments and DFT calculations. A series of monodentate ligands have been investigated in attempts to identify trends in reactivity. Sterically bulky and

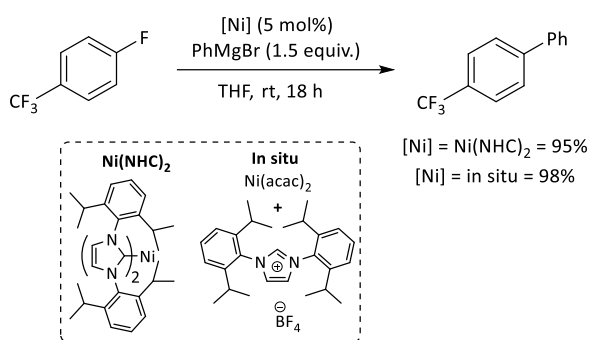
electron donating ligands are found to decrease the reaction rate. It was found that (i) the halide abstraction step is not always irreversible, and the subsequent recombination of a nickel(I) complex with an alkyl halide can have a significant effect on the overall rate of the reaction; and (ii) some ligands led to very stable $[\text{Ni}(\text{dppf})(\text{L})_2]$ species. The yields of prototypical (dppf)nickel-catalysed Kumada cross-coupling reactions of alkyl halides are significantly improved by the addition of free ligand, which provides another important variable to consider when optimizing nickel-catalysed reactions of alkyl halides.

3.2. Extended Introduction

3.2.1. Additives in Nickel Catalysed Cross-coupling Reactions

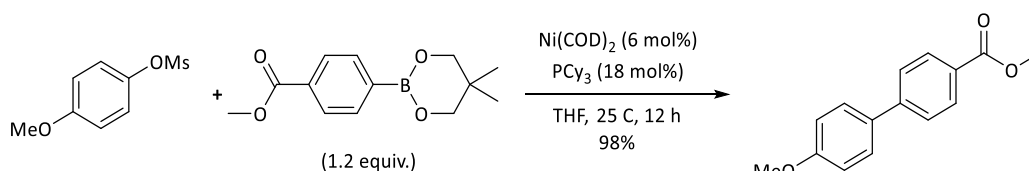
One of the most important factors to consider during the optimisation of nickel catalysed cross-couplings is the catalyst. Catalyst systems are often specific to certain reaction conditions. For many reactions published in the literature, the active species is not isolated and instead a mixture of nickel source and ligand are added separately and the active catalyst is generated *in situ*.^{156–160}

In situ methods of generating a Ni^0 active species have the advantage of easier handling (Ni^{II} pre-catalysts are typically bench stable) and can even lead to higher conversions in catalytic reactions. For example, Herrmann optimised a nickel catalysed cross-coupling of aryl fluorides with aryl Grignard reagents and employed a nickel catalyst with a sterically hindered NHC.¹⁵⁶ Isolated $[\text{Ni}(\text{NHC})_2]$ and an *in situ* generated catalyst (from $[\text{Ni}(\text{acac})_2]$ and 1 equiv. imidazolium salt) were compared as catalysts for this reaction (Scheme 3.1). The generation of the active species, where only one NHC was bound to Ni^0 , was found to be favoured when the catalyst was generated *in situ*.¹⁵⁶ Previous DFT studies showed $[\text{Ni}(\text{NHC})_2]$ was much lower in energy when compared to the mono-NHC species and therefore the most likely species to form under catalytic conditions.¹²⁷ Nelson and Maseras carried out an extensive study on the effect of the NHC used on the mechanism in operation, when $[\text{Ni}(\text{NHC})_2]$ was exposed to an aryl halide. Bulkier NHC ligands favoured a halide abstraction mechanism over an oxidative addition pathway generating a Ni^{I} species.¹²⁷ Herrmann's coupling of aryl fluorides in which $[\text{Ni}(\text{I}^{\text{t}}\text{Pr})_2]$, $\text{I}^{\text{t}}\text{Pr}$ (1,3-diisopropylimidazol-2-ylidene), was employed was found to undergo a traditional oxidative addition mechanism (Scheme 3.1).^{127,156}



Scheme 3.1. Nickel catalysed cross-coupling of aryl fluorides, comparing isolated Ni⁰ and in situ generated Ni⁰.¹⁵⁶

After optimisation, when the identity and quantity of ligand is determined, these reactions often give good yields of coupled products. However, these single time point measurements give no information on the mechanism in operation, nor the active species responsible for the catalytic reaction taking place. Using this method means that the active species is not known and with ligands often in excess with respect to the nickel source, this can be expensive. Notably, ligands that are not simple phosphines/amines are expensive and can often be more costly than the nickel source itself. Understanding the mechanism can help in tailoring catalytic systems so that active species can be rapidly formed completely *in situ*, without formation of other unwanted nickel complexes. An example of this comes from Percec and the nickel catalysed cross-coupling of chlorides, mesylates and tosylates with phenyl boronic acid neopentylglycol ester (Scheme 3.2).¹⁵⁸ No optimisation varying the amount of added PCy₃ was carried out to establish if good conversions could be achieved with less ligand. The 1:3 ratio of Ni⁰ to PCy₃ is a rather strange proportion and as such there may be multiple nickel species present in solution, with anywhere from one to three PCy₃ ligands included in the active nickel species.¹⁶¹



Scheme 3.2. Nickel catalysed cross-coupling of an aryl mesylate with phenyl boronic acid neopentylglycol ester.¹⁵⁸

In 2015, Schoenebeck investigated the active catalytic species in the nickel catalysed trifluoromethylthiolation of aryl chlorides.¹⁶⁰ Reaction profiles for the trifluoromethylthiolation of 4-chloroanisole were carried out to compare catalytic systems. The isolated complex $[\text{Ni}(\text{COD})(\text{dppf})]$ was found to be a superior catalyst compared to the formation of a catalyst *in situ* from $[\text{Ni}(\text{COD})_2]/\text{dppf}$ (Figure 3.1). The *in situ* catalyst system produced the same active species, $[\text{Ni}(\text{COD})(\text{dppf})]$, along with a free molecule of COD, and this excess COD was found to impede oxidative addition (Figure 3.1). Coupled with DFT calculations, it was concluded that the active species was $\text{Ni}(\text{dppf})$ and dissociation of COD was crucial for successful cross-coupling reactions.¹⁶⁰ Further studies have provided more evidence for a pre-equilibrium of dissociation of COD prior to oxidative addition.⁷⁴

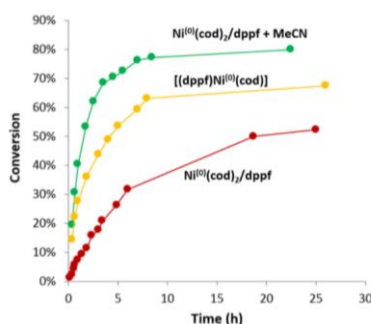


Figure 3.1. Time studies for the trifluoromethylthiolation of 4-chloroanisole in toluene at 40 °C.¹⁶⁰

Various additives have been shown to increase the yield of cross-coupled product in the literature. These will be explored below.

Nitriles

Schoenebeck's product studies from the trifluoromethylthiolation of 4-chloroanisole, showed that $[\text{Ni}(\text{COD})(\text{dppf})]$ gave a maximum product conversion of 70%.¹⁶⁰ It was hypothesised that with a ligand that is a weaker coordinating ligand than COD, the barrier for oxidative addition would decrease. With the knowledge that nitrile groups can bind to Ni^0 in a η^2 fashion and can perform as effective ligands,¹⁶² MeCN was used as a co-solvent in the cross-coupling reactions. Using MeCN as an additive with a $[\text{Ni}(\text{COD})_2]/\text{dppf}$ catalytic system improved the yield of trifluoromethylthiolated anisole to 80% (Figure 3.1), as the

[Ni(dppf)(MeCN)] complex formed was thought to undergo a more facile oxidative addition step.¹⁶⁰

To understand the intermediates and decomposition routes in the α -arylation of ketones with chloroarenes, Hartwig investigated the reactions of the active species, [(*R*)-BINAP]Ni(COD)] (where (*R*)-BINAP is (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene), with a series of chloroarenes.¹⁶³ The only reaction which afforded a stable Ni^{II} chloride complex was 4-chlorobenzonitrile; this complex was isolated in 77% yield. It was speculated that the nitrile group was responsible for oxidative addition and this was confirmed when a catalytic amount of benzonitrile was added to the reaction of [(*R*)-BINAP]Ni(COD)] and previously unreactive 4-chlorobenzotrifluoride, which afforded the Ni^{II} oxidative addition product in 75% yield.¹⁶³ ³¹P NMR spectroscopy was used to probe the nickel species present when [(*R*)-BINAP]Ni(COD)] and benzonitrile (22 equiv.) were mixed in toluene. The resultant ³¹P NMR spectrum showed 95% conversion to [(*R*)-BINAP]Ni(η^2 -N $\equiv$ C-Ph)], the assignment of which was confirmed by single-crystal X-ray diffraction (Figure 3.2).¹⁶³

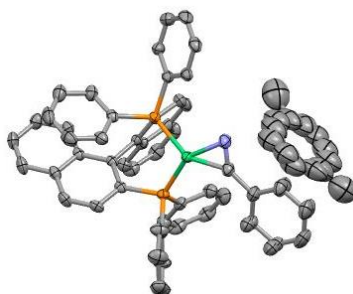
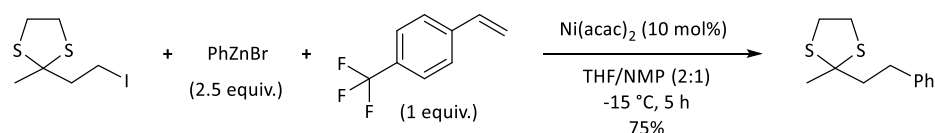


Figure 3.2. Crystal structure of [(*R*)-BINAP]Ni(η^2 -N $\equiv$ C-Ph).¹⁶³

Styrene and Other Olefins

In the 1990's, Knochel developed efficient methods for the nickel catalysed cross-coupling of sp^3 centres.^{164–166} The first report was the optimisation of the cross-coupling of alkyl halides with arylzinc bromides, which required the presence of 4-trifluoromethylstyrene (Scheme 3.3). The styrene was thought to complex to the Ni^{II} intermediate thereby reducing electron density on the nickel centre, promoting reductive elimination in the final step of the catalytic cycle.¹⁶⁴ Further studies found that reactions with *m*-trifluoromethylstyrene as an additive had similar reaction rates to those with *p*-trifluoromethylstyrene. However, *o*-

trifluoromethylstyrene was much less effective as an additive and a slower reaction was observed, illustrating a much more difficult complexation to the nickel centre due to additional steric hinderance.¹⁶⁶



Scheme 3.3. Ni^{II} catalysed cross-coupling of alkyl iodides with arylzinc bromides in the presence of 4-trifluoromethylstyrene.¹⁶⁴

The hypothesis that styrene aids in reductive elimination is supported by an earlier study by Yamamoto in 1971.¹⁶⁷ The reactions of [Ni(bipy)(Et)₂] (where bipy is 2,2-bipyridine) in the presence of various olefins showed that the olefins promoted reductive elimination to form butane and the resultant [Ni(dipy)(olefin)] complex.¹⁶⁷ Reactions were found to be first order with respect to [Ni(bipy)(Et)₂] and olefins. [Et₂Ni(bipy)(olefin)] was observed as an intermediate by IR spectroscopy and the olefin was confirmed to be in a η^2 π -bound geometry. Electron deficient systems formed the strongest π complexes, drawing electron density from the Ni centre more efficiently therefore activating the Ni-Et bond more readily.¹⁶⁷ The rates of reaction of [Ni(bipy)(Et)₂] with olefins to form [Ni(bipy)(olefin)] and butane were measured for several different olefins (Figure 3.3). Coordination to the olefin functional moiety rather than carbonyl or nitrile if present was confirmed through repeating experiments with the corresponding unsaturated compounds and no elimination of butane was observed.¹⁶⁷ Vinyl acetate was an exceptional case, where the carbonyl shift in the IR spectrum (upon coordination to nickel) was shifted to extraordinarily low frequencies when compared to other alkenes. This was coupled with an unusual bright green colour (all other alkene complexes were red-brown in colour), suggesting coordination is both through the carbonyl and alkene.¹⁶⁷ The phenyl group in styrene was not thought to coordinate to nickel as the ethene nickel complex was perfectly stable when dissolved in benzene.

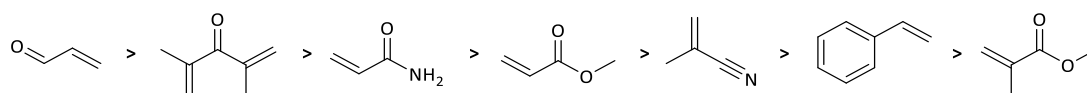
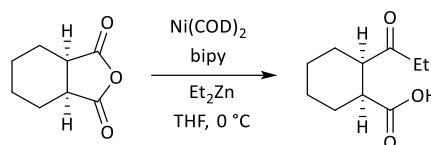


Figure 3.3. Reaction rates of olefins reacting with $[\text{Ni}(\text{bipy})(\text{Et})_2]$ to form $[\text{Ni}(\text{bipy})(\text{olefin})]$ in THF at 27 °C. As reactions with styrene and methyl methacrylate were slow in dilute solutions, rate constants were approximated from rate equation (rate = $k[\text{Ni}(\text{bipy})(\text{Et})_2][\text{olefin}]$).¹⁶⁷

In 2007, Rovis investigated the role of styrene in nickel-catalysed anhydride cross-coupling reactions. The reaction chosen for kinetic studies is shown in Scheme 3.4; the reaction is typically carried out with 4-fluorostyrene as an additive.¹⁶⁸



Scheme 3.4. Nickel catalysed alkylation of cis-1,2-cyclohexanedicarboxylic anhydride with diethylzinc.¹⁶⁸

Although initial reaction rates (up to 15% conversion) were shown to be independent of the concentration of 4-fluorostyrene (Figure 3.4(a)), this did not explain the increased rate of reaction in the presence of styrene.¹⁶⁸ Monitoring of the entire reaction *via* IR spectroscopy, in the presence and absence of styrene, helped observe shorter reaction times when the additive was present (Figure 3.4(b)).¹⁶⁸ In the absence of styrene, conversion ends prior to complete anhydride consumption. This observation, coupled with the observation that initial reaction rates are similar for both reactions (Figure 3.4(b)), implies that styrene prevents catalyst degradation (thought to be due to a self-catalysed process that can depend on the temperature of the reaction) over the course of this reaction.^{168,169}

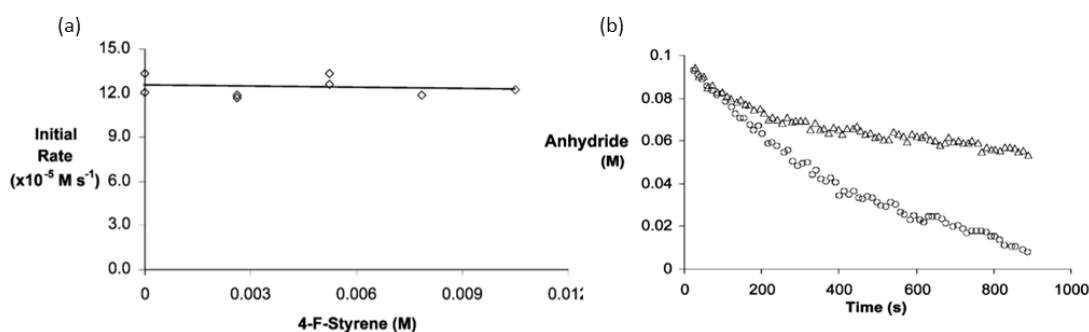
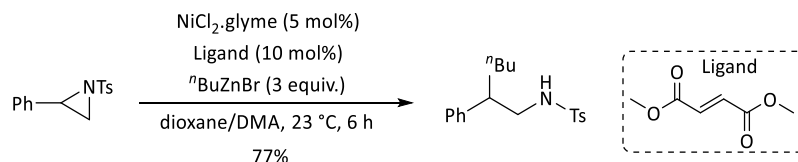


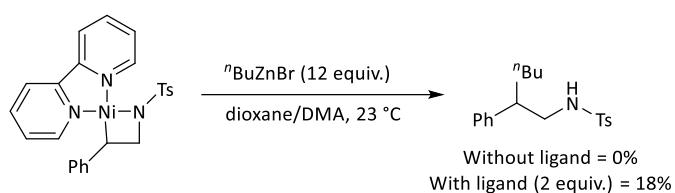
Figure 3.4. (a) Plot of initial rate of anhydride alkylation vs the concentration of 4-fluorostyrene, exhibiting zero-order dependence. (b) Plot of anhydride concentration vs time with 4-fluorostyrene (O) and without styrene (Δ).¹⁶⁸

In 2012, Doyle focused attention of the development on the cross-coupling of aziridines as a method to prepare synthetically useful β -substituted amines.¹⁷⁰ A Ni^{II} precatalyst with a dimethyl fumarate co-ligand was found to successfully alkylate styrenyl aziridines at room temperature (Scheme 3.5), conventional ligands in nickel catalysis (phosphines and amines) were found to be ineffective in this transformation.



Scheme 3.5. Nickel catalysed cross-coupling of *n*-butylzinc bromide with 2-phenyl-*N*-tosylaziridine. Quantitative conversion was achieved, yield shown is isolated product.¹⁷⁰

As Yamamoto had already shown that electron deficient alkenes promoted reductive elimination in nickel catalysed reactions, Doyle suggested a similar role of the dimethyl fumarate employed here.^{167,170} To test this hypothesis, an azametallacyclobutane was synthesised and subjected to catalytic conditions. Alkylated product was only formed in the presence of dimethyl fumarate (Scheme 3.6), confirming its necessary role in reductive elimination.¹⁷⁰



Scheme 3.6. Stoichiometric study between azametallacyclobutane and *n*-butylzinc bromide both in the presence and absence of dimethylfumarate as a ligand.¹⁷⁰

This work was further developed by Doyle in 2015, where a more sophisticated ligand was synthesised to form quaternary centres via Negishi cross couplings of 1,1-disubstituted styrenyl aziridines.¹⁷¹ The ligand developed (Fro-DO) still contained the electron deficient alkene moiety but was developed as a more tuneable and selective ligand (Figure 3.5). Fro-DO (used as the racemate) was found to be a superior ligand to dimethyl fumarate under these reaction conditions. The use of dimethyl fumarate yielded small amounts of desired coupled product and gave mainly alkene and alkane side products associated with β -hydride elimination.¹⁷¹

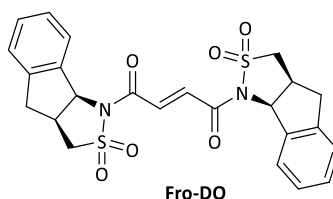
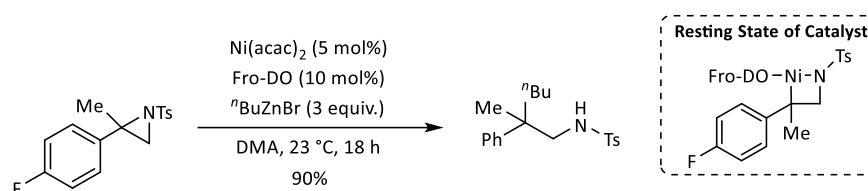


Figure 3.5. Ligand developed for the Negishi cross-coupling of 1,1-disubstituted styrenyl aziridines, named Fro-DO.¹⁷¹

Mechanistic studies *via* ^{19}F NMR spectroscopy into the coupling of 2-(4-fluorophenyl)-2-methyl-1-tosylaziridine with *n*-butylzinc bromide confirmed a $\text{Ni}^0/\text{Ni}^{\text{II}}$ catalytic cycle, evident from the trapping of the resting state of the catalyst with bipyridine (Scheme 3.7).¹⁷² DFT calculations confirmed that both dimethyl fumarate and Fro-DO are both able to reduce the energy barrier for reductive elimination, however, Fro-DO has more favourable binding to Ni^{II} due to its ability for strong π -backbonding and an additional interaction *via* the sulfonyl group.¹⁷²

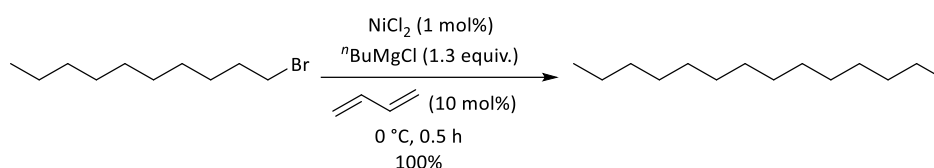


Scheme 3.7. Nickel catalysed cross-coupling of 2-(4-fluorophenyl)-2-methyl-1-tosylaziridine with *n*-butylzinc bromide which was used for kinetic studies. Inset, the resting state of the catalyst confirmed by trapping in situ.¹⁷²

Dienes

As noted previously, $[\text{Ni}(\text{COD})_2]$ is the most widely used source of Ni^0 . It is obvious from the facile synthesis of this complex *via* the reduction of $[\text{Ni}(\text{acac})_2]$ in the presence of 1,5-cyclooctadiene (developed by Wilke in 1966), that nickel readily complexes with dienes.¹⁷³ As such, it comes as no surprise that various dienes can be used as additives in reactions to form complexes in situ that can aid catalysis.¹⁷⁴

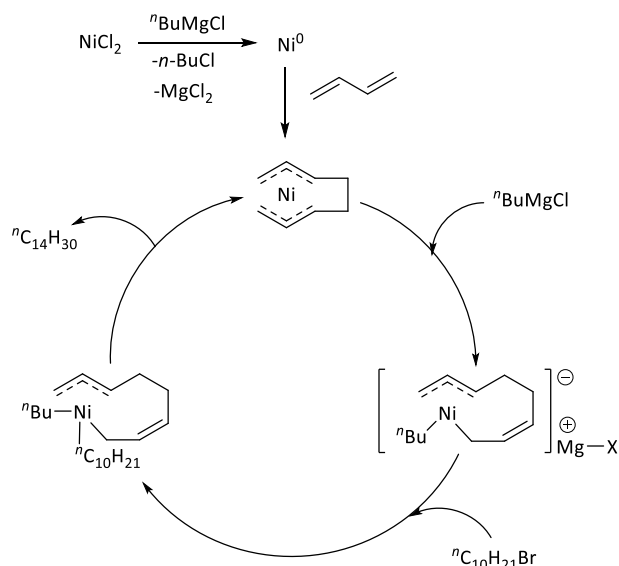
In 2002, Kambe developed the first nickel catalysed Kumada couplings of alkyl halides with alkyl Grignard reagents, in the presence of 1,3-butadiene as an additive (Scheme 3.8), which was a major development for nickel catalysis.¹⁷⁵ In the absence of a diene additive, significant amounts of decane and decene (from protodebromination and β -hydride elimination, respectively) were formed and only low yields of cross-coupled product were obtained (2%).



Scheme 3.8. Quantitative conversion of 1-bromodecane to *n*-tetradecane via a nickel catalysed Kumada cross-coupling.¹⁷⁵

Mechanistic studies were carried out to establish the role of 1,3-butadiene. The oxidative addition of alkyl halide to Ni^0 was eliminated as a mechanistic pathway as reaction of *n*-Oct-Ni-Br (expected from oxidative addition) under catalytic conditions formed no coupled product (only decane and decenes). A radical pathway was also eliminated due to the

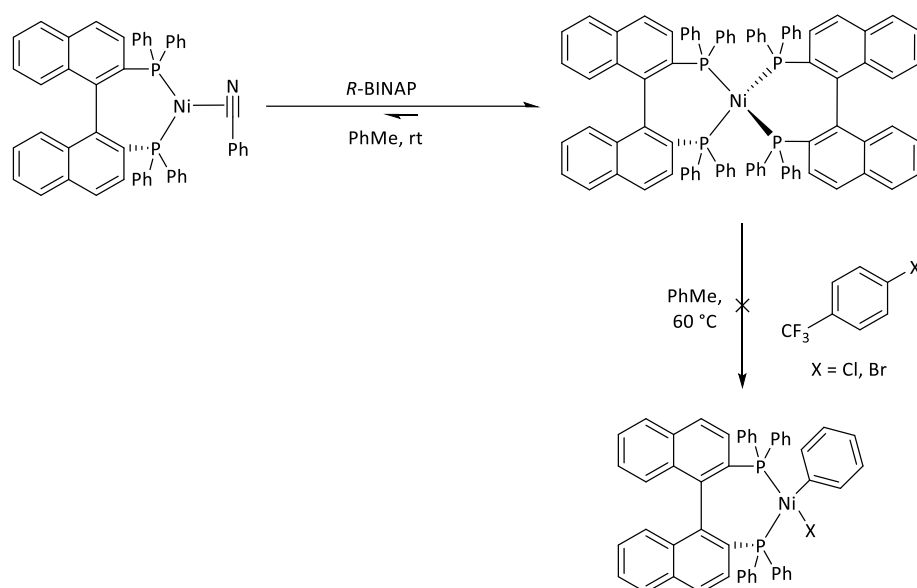
cyclopropane ring remaining intact when (bromomethyl)cyclopropane was used as the alkyl halide.¹⁷⁵ A plausible mechanistic pathway was proposed where the active species is formed by reduction of the NiCl_2 pre-catalyst to Ni^0 which then forms a bis- π -allyl nickel complex with the 1,3-butadiene additive (Scheme 3.9).



Scheme 3.9. Proposed catalytic cycle for the cross-coupling of alkyl halides with alkyl Grignard reagents with an active bis- π -allyl nickel complex species.¹⁷⁵

Phosphines

Whilst optimising the arylation of ketones (with aryl chlorides) and the amination of aryl chlorides, Hartwig observed formation of $[\text{Ni}(\text{rac-BINAP})_2]$.^{163,176} In both cases, *rac*-BINAP was complexed with Ni^0 using either COD (to form $[\text{Ni}(\text{COD})(\text{rac-BINAP})]$) or benzonitrile (to form $[\text{Ni}(\text{rac-BINAP})(\eta^2\text{-CN-Ph})]$) as the secondary ligand. In both instances, the formation of $[\text{Ni}(\text{rac-BINAP})_2]$ was observed over the course of the reaction. The generation of $[\text{Ni}(\text{rac-BINAP})_2]$ was found to be reversible in the presence of benzonitrile with the equilibrium lying largely towards $[\text{Ni}(\text{rac-BINAP})_2]$ and free benzonitrile (Scheme 3.10).¹⁷⁶ Stoichiometric reactions of $[\text{Ni}(\text{rac-BINAP})_2]$ with aryl chlorides and bromides did not lead to oxidative addition at 60 °C and as such, $[\text{Ni}(\text{rac-BINAP})_2]$ was deemed a catalytically inactive off-cycle species (Scheme 3.10).¹⁶³ Full consumption of the nickel source was observed in the reaction of $[\text{Ni}(\text{R-BINAP})(\text{COD})]$ and 4-chlorobenzotrifluoride in one hour, showing that the catalytic active species only required complexation of one *rac*-BINAP ligand.¹⁶³



Scheme 3.10. Formation of [Ni(*rac*-BINAP)₂], which does not undergo oxidative addition with aryl chlorides and bromides.^{163,176}

This precedent for the formation of catalytically inactive [Ni(*rac*-BINAP)₂] prompted Louie in 2018 to carry out an extensive study of bidentate phosphine ligands with [Ni(COD)₂].¹³⁵ [Ni(COD)₂] and each of thirteen different bidentate phosphine ligands were mixed in a 1:1 ratio and the mixtures were monitored *via* ³¹P NMR spectroscopy. Eleven of the ligands tested formed different ratios of [Ni(COD)L] and [NiL₂] (where L = bidentate phosphine ligand).¹³⁵ Benzonitrile was then added to these mixtures to displace a phosphine ligand in [NiL₂]; this was successful for all phosphines except dppe, as [Ni(dppe)₂] is extremely stable (with a barrier to oxidative addition of chlorobenzene of 43.4 kcal mol⁻¹).¹⁷⁷ Trends were difficult to determine and the link between ligand structure and coordination behaviour is not always clear. However, some general patterns were unearthed, with most phosphines converging on these. The stability of the [NiL₂] complexes formed was analysed (by displacement of one ligand by benzonitrile), and it was found that complexes were less stable if seven-membered rings were formed with Ni (for dppb) than six- (dppp) or five-membered rings (dppe) (Figure 3.6(a)).¹³⁵ Bite angle also played a role in the ratios of [Ni(COD)L]/[NiL₂] and the ease of displacement with benzonitrile (Figure 3.6(b)). Ligands with bite angles of less than 100° favoured formation of NiL₂ and were not displaced by benzonitrile. Ligands with bite angles between 102° and 110° formed mixtures of [Ni(COD)L] and [NiL₂], and the

replacement of one ligand on $[\text{NiL}_2]$ with benzonitrile was facile. Ligands with bite angles above 110° were more likely to form $[\text{NiL}_2]$ and the second ligand was easily displaced with the nitrile.¹³⁵ This extensive study shows how susceptible many bidentate phosphine ligands are to forming $[\text{NiL}_2]$ and the extent that this can be displaced with an additive, illustrating a method to avoid to generation of – often catalytically inactive – $[\text{NiL}_2]$ in cross-coupling reactions.

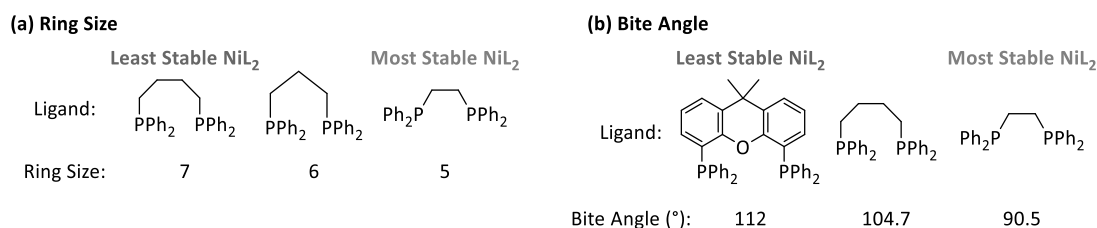
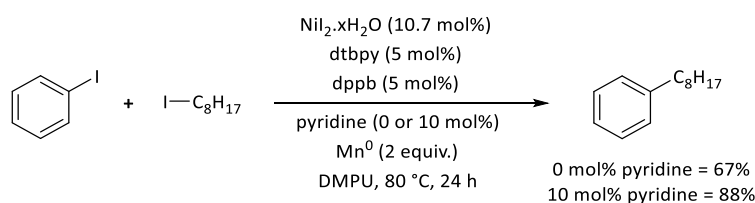


Figure 3.6. Effect of bite ring size (formed when bound to Ni^0) and bite angle on the stability of $[\text{NiL}_2]$ formed.¹³⁵

Pyridine

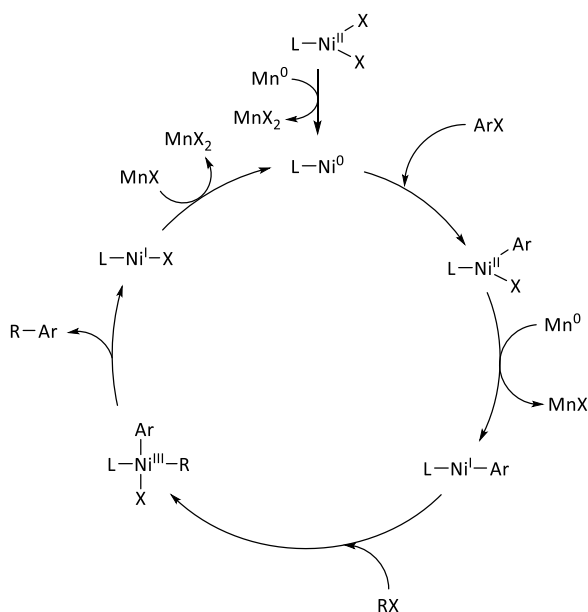
In 2010, Weix described the successful nickel catalysed reductive coupling of aryl and alkyl halides using manganese as the terminal reductant (Scheme 3.11).¹⁷⁸ When using pyridine as an additive (10 mol%) in the coupling of iodobenzene and 1-iodooctane, fewer alkene side products associated with β -hydride elimination were observed.



Scheme 3.11. Nickel catalysed reductive coupling of iodobenzene and 1-iodooctane using Mn^0 as the reductant and pyridine as an additive.¹⁷⁸

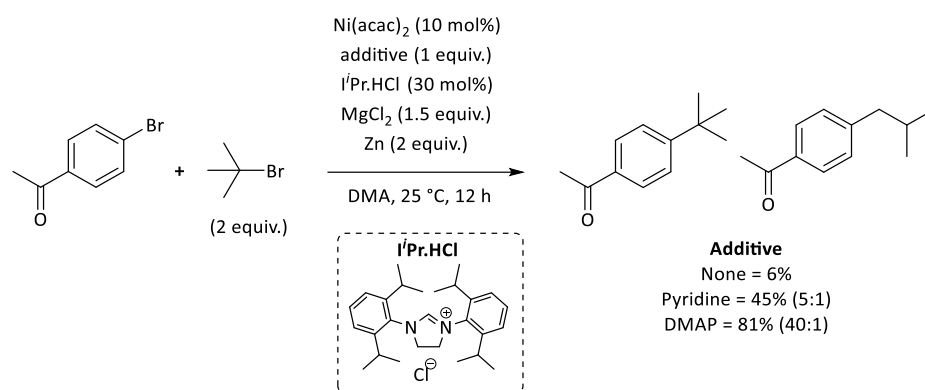
The formation of an organomanganese reagent *in situ* was eliminated as a mechanistic pathway as an organic reducing agent, tetrakis(dimethylamine)ethylene (TDAE), formed a moderate amount of product. The role of dppb is unclear: a drop in product yield of 5% is observed when this is omitted and only 19% conversion is observed when this is used as the

sole ligand in the absence of dtbpy. The following mechanism was proposed: Ni^{II} is reduced to Ni^0 (with Mn^0), oxidative addition of organic halide, reduction of the Ni^{II} intermediate to form $\text{Ni}^{\text{I}}\text{R}$, oxidative addition of the other organic halide to form a Ni^{III} complex (Scheme 3.12).¹⁷⁸ Reductive elimination gives the coupled product and a $\text{Ni}^{\text{I}}\text{X}$ species, which is then reduced to Ni^0 (with Mn^0).¹⁷⁸



Scheme 3.12. Reductive coupling mechanistic pathway proposed by Weix for nickel catalysed coupling of aryl and alkyl halides using manganese.¹⁷⁸

In 2015, Gong expanded on work by Weix, developing the nickel catalysed reductive coupling of aryl bromides with tertiary alkyl halides.¹⁷⁹ During optimisation, it was apparent that either DMAP (4-dimethylaminopyridine) or pyridine as an additive was crucial, with only 6% conversion of $t\text{BuBr}$ and methyl 4-bromobenzoate to coupled products in the absence of either additive (Scheme 3.13).¹⁷⁹ In general, pyridine outperformed DMAP as an additive when electron deficient aryl bromides were used as substrates.¹⁷⁹ Imidazolium salts as additives were found to only slightly increase the yield of coupled product, whereas with DMAP as the additive yields were increased from 75% to 81% in the presence of 1,3-diisopropylimidazolium chloride. The mechanism was not proposed in this study, only the suggestion of radical chemistry involvement due to observations in other nickel catalysed reductive couplings.¹⁷⁹



Scheme 3.13. Nickel catalysed reductive coupling of $t\text{BuBr}$ and methyl 4-bromobenzoate.

Ratios are of the products where quaternary centre is retained/isomerisation.¹⁷⁹

3.2.2. Ligand Properties

A myriad of methods to systematically characterise both the electronic and steric properties of ligands have been developed since the 1970s. The most popular developed by Tolman include the cone angle (steric properties) and TEP (Tolman Electronic Parameter); these were specifically developed for monodentate phosphine ligands but since have been extended to other classes of ligand.¹⁸⁰ These methods described are used for different types of ligand; they are applicable to both phosphine and NHC ligands which are among the most abundant ligands employed within nickel catalysis. However, these methods do not work well for bidentate nitrogen ligands (bipy etc.) which are also commonly employed as ligands in nickel catalysis.

Cone Angles θ

Without the luxury of advanced computer modelling the chemistry world is now accustomed to, Tolman took to modelling complexes with various phosphine ligands and measuring angles involved by hand using a 'ligand angle measuring device' (Figure 3.7).¹⁸¹ Molecular models of several different congested phosphine ligands were constructed and angles measured. With the aim to quantify the size of each ligand, the parameter measures the apex angle of a cone starting from the metal centre and ending on the van der Waals spheres of the outermost atoms. It is noteworthy that the ligand is assumed to be tetrahedral and the metal-phosphorous bond is fixed at 2.28 Å as this distance was observed to be consistent in the metal complexes investigated.^{45,181,182}

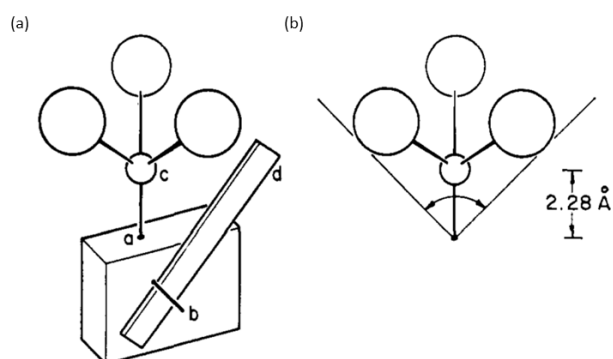


Figure 3.7. (a) Ligand angle measuring device – the ability of ‘d’ to pivot meant this could be set to the outside edges of the cone and the angle to ‘a’ measured with a protractor, these two angles were then added together to get the final cone angle θ . (b) The ligand cone.

To probe the validity of this new technique, competitive binding experiments were carried out with several different nickel complexes bearing a variety of phosphine ligands. Displacement of these ligands with other ligands were used to determine the propensity for ligands to form stable nickel complexes. A good agreement of this so called ‘ligand binding affinity’ with the cone angle was found (Figure 3.8).¹⁸¹ It was observed that once the ideal angle between substituents on a tetrahedral centre was exceeded, the complexes formed are very unstable. At the end of this study, it was concluded that the steric factors have a more significant influence on the stability of the nickel complex formed than electronic properties.¹⁸¹

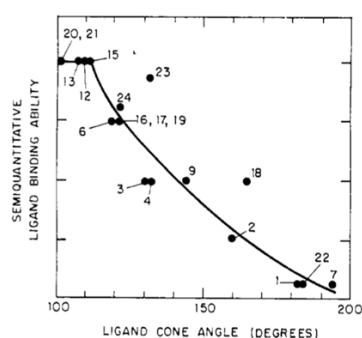


Figure 3.8. Stability of Ni(0) complexes with various phosphine ligands plotted against the cone angle. Displacement studies of $[\text{NiL}_4]$ were conducted to determine which ligands had higher binding affinities, a difference of one unit on the y-axis means that the upper ligand (L) is much more strongly bound than the lower ligand (L') and that the species at equilibrium are $[\text{NiL}_4]$ and $[\text{NiL}_3\text{L}']$.¹⁸¹

This method was later expanded to cover asymmetric phosphine ligands where the R group varies and an average of the three substituents is taken.⁷⁰ In modern times, although this method is still applicable and cone angles from this work are still reliable values, computer programs now allow simulation of new ligands to investigate their steric bulk.

Tolman Electronic Parameter (TEP)

No electronic information can be taken from the NMR spectra of metal-ligand complexes, therefore, it was necessary to quantify the electronic properties of ligands.¹⁸³ It was first shown by Strohmeier that phosphine ligands could be ranked by π acceptor strength through formation of metal carbonyl complexes and measurement of their stretching frequencies in the IR spectrum.^{45,184}

In efforts to quantify the electronic properties of ligands Tolman reacted several phosphorous ligands with $[\text{Ni}(\text{CO})_4]$.¹⁸¹ Initial attempts at ligand exchange with $[\text{Ni}(\text{CO})_4]$ led to mixtures of complexes with different degrees of displacement for different ligands and therefore results could not be compared.¹⁸¹ However, these were the experiments that preceded TEP as we know it today. It is noteworthy that $[\text{Ni}(\text{CO})_4]$ is extremely toxic and has shown to induce severe lung tissue inflammation and is a known carcinogen, and as such needs to be used in a well ventilated area with specialist procedures.¹⁸⁵

TEP determines the electron donor properties of phosphine ligands by displacing a single CO ligand on $[\text{Ni}(\text{CO})_4]$ with the ligand of interest. Data for over 70 different monodentate phosphine ligands were presented in the initial publication.⁵⁸ $[\text{Ni}(\text{L})(\text{CO})_3]$ were not isolated but prepared by reacting $[\text{Ni}(\text{CO})_4]$ with 1 equivalent of ligand and allowed to stand at room temperature for 10 minutes. After this, any remaining $[\text{Ni}(\text{CO})_4]$ was removed under vacuum, and the sample was then diluted and analysed *via* IR spectroscopy. It was clear that more electron withdrawing substituents on the phosphine ligand gave higher CO stretching frequencies, which originates from the Dewar-Chatt-Duncanson (DCD) model.⁵⁸

Dewar first suggested that alkenes could donate π electrons to form bonds that were seen to occur with lone pairs (Figure 3.9(a)).^{186,187} Chatt and Duncanson later investigated the coordination of olefins in organometallic complexes. Using IR spectroscopy, the structure of platinum chloride ethylene was deduced. It was concluded from C-H stretching frequencies that the alkene bond was intact and symmetrically coordinated to Pt. Confirmation that the alkene was bound to Pt was found by the C=C stretching frequency decreasing by 143 cm^{-1} to 1504 cm^{-1} , therefore, a symmetrical alkene structure bound to Pt was deduced (Figure 3.9(b)).¹⁸⁸ These works were combined to give the DCD model that is used to describe the bonding of a metal to alkene, whereby the alkene donates electron density onto the metal and simultaneously the metal donates electron density into the π^* orbital of the alkene (backbonding).

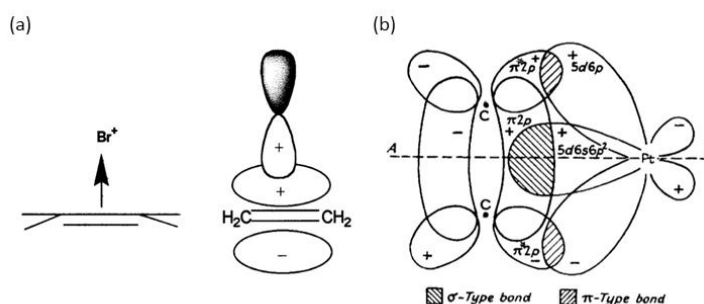


Figure 3.9. (a) Formation of a bromonium ion intermediate illustrated by Dewar.^{186,187} (b)

Orbitals used in combination of ethylene with platinum proposed by Chatt and Duncanson.¹⁸⁸

A similar proposal for the binding of phosphines to metal centres was proposed (Figure 3.10) as an aid in understanding the *trans* effect.^{189,190} In this case, the *trans*-effect refers to the ability of a ligand to weaken the bond *trans* to it (as opposed to those *cis*).¹⁹⁰

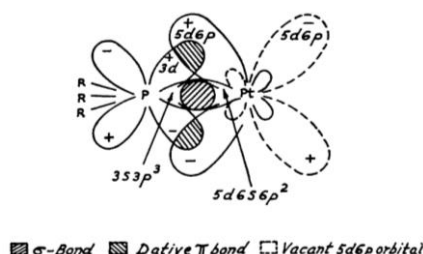


Figure 3.10. A schematic representation of the R_3P -Pt bond.¹⁸⁹

TEP utilising $[Ni(L)(CO)_3]$ complexes exploits the backbonding capability of the CO ligand to determine the σ donor properties of ligand, L. CO differs from the ethene model as CO binds to the metal centre exclusively through the carbon (through donation of the lone pair into an empty d-orbital). A filled metal d-orbital then interacts with the empty π^* orbital on CO, as seen with the ethene model.¹⁸⁸ TEP is determined by measuring ν_{CO} (using IR spectroscopy); free CO $\nu_{CO} = 2143\text{ cm}^{-1}$ and $[Ni(CO)_4]$ $\nu_{CO} = 2057\text{ cm}^{-1}$, better σ donating ligands result in lower CO stretching frequencies (weakening of the C-O bond).

TEP is still the method used to quantify the electronic donor abilities of ligands used in modern organic and organometallic chemistry and is not limited to phosphine ligands. The scope of this parameter has also been expanded to include bidentate ligands but is limited by IR spectrometer resolution (the ability of the spectrometer to separate spectral lines that are very close in wavelength).

Bite Angles

Cone angles (θ) are a valuable and precise way to calculate the size of monodentate ligands. Bite angles are used to quantify the size, specifically the angle at which the phosphine atoms are linked (as opposed to the size of phosphine substituents), of bidentate phosphine ligands. The bite angle of bidentate ligands is described as the ligand-metal-ligand angle.¹⁹¹ The cone angle at each phosphorous atom is the angle between each phosphine atom and metal which are then combined to give the bite angle (Figure 3.11).¹⁹² This angle is strongly dependent on

the backbone of the ligand and depending on the flexibility of this bridge can strongly influence reactivity.^{191,193}

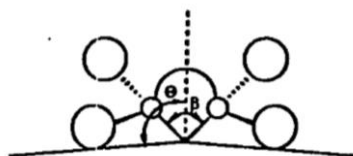


Figure 3.11. Cone angle (θ). Bite angle (β).¹⁹²

Casey later coined the term natural bite angle to describe the bite angle of bidentate ligands that relies only on the rigidity of the backbone and not the metal and used molecular mechanics to calculate these. As with Tolman cone angles, the bite angle is dependent on the M-P distance and was therefore kept constant at 2.30 Å (a typical bond length of Rh-P). It was found that in catalysis, the bite angle deviates away from the natural bite angle and this depends on the flexibility of the backbone.¹⁹²

Potential energy diagrams were calculated for a variety of different ligands and highlighted the range of flexibility in each specific ligand. For comparison, the potential energy diagrams for DIPHOS (1,2-bis(diphenylphosphino)ethane) and DIOP (2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) are given in Figure 3.12.¹⁹² For DIPHOS, which exhibits a steep curve, the minimum (equal to the natural bite angle) is 81.7°. Widening this angle increases the energy by 18 kcal mol⁻¹ while reducing this to 75° increases the energy by only 4 kcal mol⁻¹. This is consistent with crystal structures containing DIPHOS which often have bite angles of less than 90°. In contrast, DIOP has a potential energy curve with a shallow minimum at 103.3°. Bite angles between 90° and 120° only experience small amounts of strain (3 kcal mol⁻¹), which again is consistent with crystal structures where bite angles have a large range between 90° and 107°. ¹⁹²

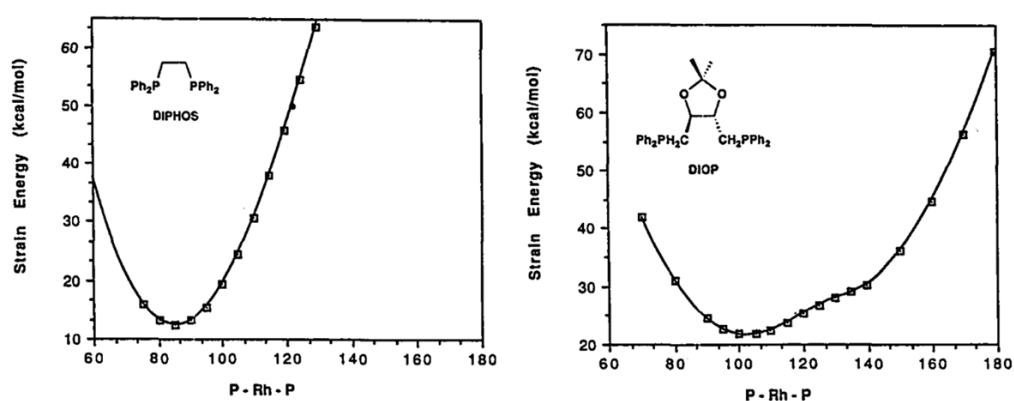


Figure 3.12. Potential energy diagrams for bite angles of DIPHOS and DIOP.

Percentage Buried Volume (%V_{bur})

As monodentate phosphine ligands steric properties are defined by cone angle θ and bidentate ligands by bite angle, Cavallo and Nolan developed a method to quantify the steric properties of NHC ligands.¹⁹⁴ Percentage buried volume (%V_{bur}) is defined as the % of a sphere that is occupied by NHC; this can either be calculated from a crystal structure or by using DFT calculations.¹⁹⁴ This can be calculated for the free NHC, however, this may lead to inaccurate results as the ligand can adopt conformations that would not be possible once complexed. This is why %V_{bur} is often calculated once bound to a metal centre, in a so-called sphere. This sphere has set dimensions, where the metal-ligand bond is set to 2 Å (typical metal-carbene length) and sphere radius of 3.5 Å (typical distance of metal to nitrogen in an NHC) (Figure 3.13).¹⁹⁴ This is the standard method used to define the steric properties of NHC ligands, where the size of a ligand is denoted as the % of the sphere it occupies, %V_{bur}. As with TEP caution needs to be exerted; %V_{bur} can only be compared if complexed to the same metal with same ancillary ligands. Au(NHC)Cl is often used as a benchmark due to its linear structure. Although initially developed to measure the steric bulk of NHC ligands, this is also applicable to other ligand sets (including phosphine ligands).

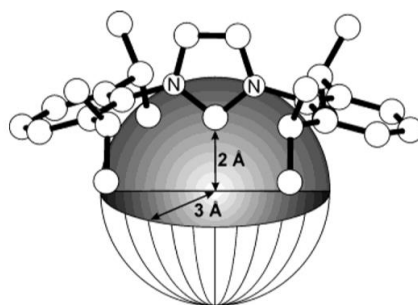
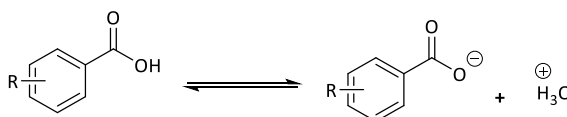


Figure 3.13. Dimensions for determination of (%V_{bur}) from DFT optimised geometries of free ligand.

3.2.3. Hammett Substituent Constants

Hammett substituent constants are the most widely accepted method to assign numeric values to the electronic effect that a substituent has on a molecule. These substituent constants (σ), that are different for both *meta*- and *para*- substituents, reflect the combination of both the inductive and resonance effects for a particular substituent. Hammett first developed this method in the 1930's and found that the dissociation constant (and therefore the pKa) for substituted benzoic acids (in water at 25 °C) could be correlated to the electronic effect of the substituent (Scheme 3.14).^{195,196}



Scheme 3.14. Hydrolysis of substituted benzoic acids developed by Hammett.

The σ value is used to define the electronic effect of a substituent, with electron-donating substituents having negative values and electron-withdrawing substituents having positive values. The σ parameter for a substituent is defined as the difference between the logarithm of dissociation constant (K_X) of substituted benzoic acid and the logarithm of the dissociation constant of benzoic acid (K_H) (Equation 3.1).¹⁹⁶ Parameters can be defined for either *meta*- or *para*- substituents on an aromatic ring, *ortho*- substituents are not defined as steric factors can then have a substantial effect on the rate of reaction. Resonance effects only influence the reaction when in the *ortho*- or *para*- position, meaning σ_m purely has inductive effects. A useful review was compiled in 1991 by Hansch to contain all published σ values and contained

values for 530 different substituents and is widely used to characterise electronic effects for a variety of substituents.¹⁹⁷

Equation 3.1. Equation for Hammett parameter.¹⁹⁷

$$\sigma_X = \log K_X - \log K_H$$

3.3. Introduction from Manuscript

The importance of molecules that contain a large number of sp^3 centers in industries such as pharmaceuticals and agrochemicals is driving much of the reaction discovery and development in the field of nickel catalysis.^{112,113} However, despite recent advances in our mechanistic understanding of nickel catalysis,^{101,198} gaps in this understanding still remain.

This is apparent for the case of the reactions of nickel(0) complexes with alkyl halides, which are quite different from the reactions of nickel(0) complexes with sp^2 organohalides.¹⁹⁹ The reactions of alkyl halides have a greater propensity to involve radical intermediates, and deleterious β -hydride elimination presents further challenges. We have recently focused our attention on the reactions of alkyl halides with nickel(0), with the aim of developing a better understanding of these reactions and thereby underpinning future reaction discovery, development, and understanding.

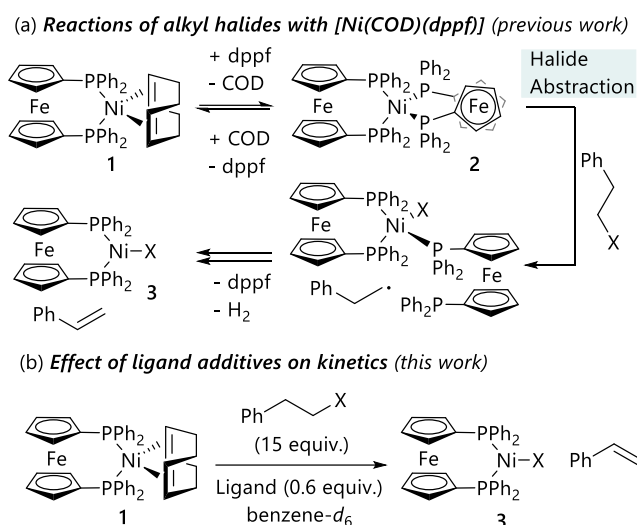
The outcomes of nickel-catalysed reactions can be extremely sensitive to the structure(s) of the ligand(s). For example, Liu *et al.* found that $[\text{Ni}(\text{COD})_2]/\text{dppf}$ was not a competent catalyst for the cross-coupling of phenyl triflate and aniline, but that a modified ligand (1,1'-bis(di(3,5-trifluoromethylphenyl)phosphino)ferrocene) enabled the reaction to achieve almost quantitative conversion.⁹⁰ There are many examples of situations where the mechanisms of nickel-catalysed reactions can also be very sensitive to ligand structure. If the nickel-catalysed Suzuki-Miyaura coupling of benzylic esters is carried out using tricyclohexylphosphine as the ligand the stereochemistry at the benzylic position is retained; however, the use of SIMes produces the stereoinverted product *via* a different mechanistic pathway.²⁰⁰ The size of the NHC ligand in $[\text{Ni}(\text{NHC})_2]$ complexes determines whether $[\text{Ni}(\text{Ar})\text{X}(\text{NHC})_2]$ or $[\text{NiX}(\text{NHC})_2]$ products result from their reactions with aryl halides.^{127,201} The choice of ligand type – bisphosphine or bipyridine – is crucial in the trifluoromethylthiolation reactions of aryl halides.¹³² Changes in phosphine ligand structure

can influence oxidative addition selectivity in the reactions of esters²⁰² or change oxidative addition chemoselectivity entirely.²⁰³

The reactions of alkyl halides with nickel(0) have received relatively little attention compared to reactions of aryl halides and other aryl electrophiles.^{69,73,74,204,205} Baird has studied the reactions of various alkyl halides with $[\text{Ni}(\text{PPh}_3)_4]$ *via* variable temperature ^1H and ^{31}P NMR spectroscopic analyses of reactions *in situ*. The major products from the reactions of iodoalkanes are alkanes and alkenes, with a nickel hydride species obtained as a minor product; this suggests that formal oxidative addition was followed by β -hydride elimination. The alkanes were proposed to arise from the generation of alkyl radicals by halide abstraction, which then abstract the hydride ligand from a nickel hydride complex. The trends observed in the reactivity of alkyl halides followed the stability of the corresponding radicals, consistent with an operative radical mechanism.

We recently published a detailed study of the reactions of the model complex $[\text{Ni}(\text{COD})(\text{dppf})]^{177}$ (**1**) with alkyl halides.⁷⁵ The experimental and computational evidence that was gathered supported a mechanism in which $[\text{Ni}(\text{COD})(\text{dppf})]$ was in equilibrium with $[\text{Ni}(\text{dppf})_2]$ (**2**) (with the additional dppf being a trace impurity in **1**), and that $[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})]$ performed a halide abstraction step to produce $[\text{Ni}(\text{X})(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})]$ plus an alkyl radical (Scheme 3.15(a)); subsequent dppf dissociation and the recombination of the alkyl radical and nickel(I) complex yielded the formal oxidative addition product $[\text{Ni}(\text{X})(\text{R})(\text{dppf})]$, which underwent rapid β -hydride elimination. The final products were $[\text{Ni}(\text{X})(\text{dppf})]$ (**3**) and alkene, with no alkane product observed.

The reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ with alkyl halides relies upon the presence of additional dppf in order to form the three-coordinate species necessary for the halide abstraction step. However, the bidentate nature of dppf means that $[\text{Ni}(\text{dppf})_2]$ is lower in energy than the desired $[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})]$ intermediate. Here, we have examined the use of a range of alternative monodentate ligands and their effects on the rate of stoichiometric and catalytic reactions of alkyl halides (Scheme 3.15(b)).

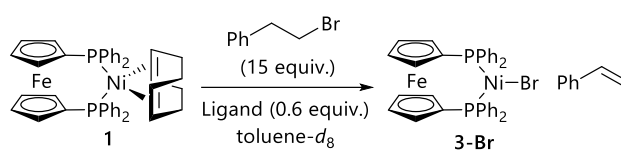


Scheme 3.15. (a) Our previous study of the reactions of [Ni(COD)(dppf)] with alkyl halides.
(b) This work.

3.4. Results and Discussion from Manuscript

3.4.1. Kinetic Studies of Stoichiometric Reactions with Alternative Ligands

Our previous study⁷⁵ established that the rate of reaction between [Ni(COD)(dppf)] (**1**) and alkyl halides was significantly increased by the addition of free dppf ligand, as this shifted the equilibrium between **1** and [Ni(dppf)₂] towards the latter species. For this study, a selection of monodentate group 15 ligands was assembled with a diverse range of steric and electronic properties, and where the Lewis basic atom was nitrogen, phosphorus, arsenic, or antimony. These were all used as additives in the stoichiometric reaction between **1** and (2-bromoethyl)benzene (**4-Br**) which was monitored by ³¹P NMR spectroscopy. All experiments were pseudo-first order in **1**, and the ³¹P NMR spectra confirmed that dppf remained bound to the nickel centre throughout, with no free dppf ligand detected ($\delta_P = -17$ ppm). Data were collected at one or two of three temperatures (263 K, 273 K, or 293 K) depending on how fast the reaction proceeded; the results for reactions with fifteen monodentate ligands, along with previous data for the reaction with added dppf,⁷⁵ are recorded in Scheme 3.16. Pseudo-first order constants are listed in order of largest to smallest. Data span a *ca.* 200-fold range of rate constants.



Ligand	$k_{obs} \times 10^3 \text{ s}^{-1}$			
	263 K	273 K	293 K	k_{rel}
$P(p\text{-C}_6\text{H}_4\text{CF}_3)_3$	2.8(1)			1.00
$P(m\text{-C}_6\text{H}_4\text{Me})_3$	2.4(1)			0.89
$P(p\text{-C}_6\text{H}_4\text{F})_3$	2.4(1)			0.89
$P(p\text{-C}_6\text{H}_4\text{Me})_3$	1.7(1)			0.63
PPh_3	1.40(3)			0.52
$P(p\text{-C}_6\text{H}_4\text{OMe})_3$	1.3(1)	4.4(1)		0.48
$FcPPh_2$		1.80(6)		0.20
$P(n\text{-Bu})_3$		0.87(1)		0.091
dppf		0.50(1)		0.055
PMe_3			3.3(1)	0.030
$AsPh_3$			2.7(1)	0.026
$SbPh_3$			1.8(1)	0.019
PCy_3			0.94(3)	0.008
$P(o\text{-C}_6\text{H}_4\text{Me})_3$		0.04(1)	0.49(2)	0.004
$P(OPh)_3$			0.45(2)	0.004
NEt_3			0.45(2)	0.004

Scheme 3.16. Kinetic studies of the reactions between $[Ni(COD)(dppf)]$ (1) (0.022 mol L^{-1}) and (2-bromoethyl)benzene (4-Br) (0.33 mol L^{-1}) in toluene- d_8 in the presence of various added ligands ($0.0132 \text{ mol L}^{-1}$).

A series of reactions were carried out with different concentrations of triphenylphosphine, confirming that the reaction is first order in added triphenylphosphine (Figure 3.14(a) and (b)); our previous work noted that the reaction was first order in dppf when this was the added ligand.

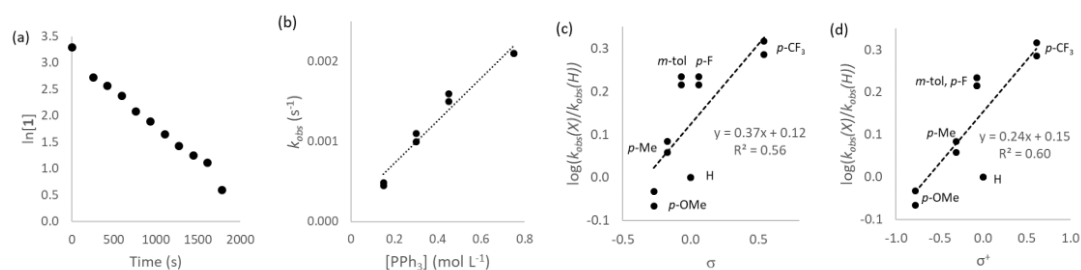


Figure 3.14. (a) Kinetic data for the reaction between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) (0.022 mol L^{-1}) and (2-bromoethyl)benzene (**4-Br**) (0.33 mol L^{-1}) at 263 K in toluene- d_8 in the presence of triphenylphosphine ($0.0132 \text{ mol L}^{-1}$). (b) Plot of k_{obs} versus $[\text{PPh}_3]$. (c) Hammett plot (using substituent constants σ) for the reactions in the presence of substituted triarylphosphines. (d) Hammett plot (using substituent constants σ^+).

The use of diphenylphosphinoferrocene (FcPPh_2) as an additive led to a higher rate of reaction than the corresponding experiment with dppf . This can be rationalized by considering the requirement for (bidentate) dppf to dissociate one phosphine atom from the nickel centre to enable the reaction to occur; the binding of a second FcPPh_2 ligand does not benefit from the chelate effect.

It is apparent that neither the steric nor the electronic properties of the ligand dominate the observed effects on reaction rates; Tolman electronic parameter (TEP) and cone angle data are gathered for some of the ligands deployed in this study (Table 3.1).⁴⁵ It was initially anticipated that electron-rich ligands would generate a more reactive nickel(0) complex, and therefore accelerate halide abstraction. However, the use of tricyclohexylphosphine led to a very slow reaction with no conversion after 45 min at 273 K ($k_{\text{rel}} = 0.008$); reactions in the presence of trimethylphosphine ($k_{\text{rel}} = 0.030$) or tri(*n*-butyl)phosphine ($k_{\text{rel}} = 0.091$) are faster. The reaction with triphenylphosphine as an additive led to a reaction that was faster still ($k_{\text{rel}} = 0.52$), despite being less electron rich.

Table 3.1. Relative rate constants for selected reactions where TEP and cone angle⁴⁵ are known for the corresponding ligand.

Ligand	TEP (cm ⁻¹)	Cone Angle (°)	%V _{bur}	k _{rel}
P(<i>m</i> -C ₆ H ₄ Me) ₃	2067.2	-	-	0.89
P(<i>p</i> -C ₆ H ₄ F) ₃	2071.3	-	31.4	0.89
P(<i>p</i> -C ₆ H ₄ Me) ₃	2066.7	145	31.3	0.63
PPh ₃	2068.9	145	31.2	0.52
P(<i>p</i> -C ₆ H ₄ OMe) ₃	2066.7	-	31.3	0.48
P(<i>n</i> -Bu) ₃	2060.3	132	-	0.31
PMe ₃	2064.1	118	24.0	0.030
PCy ₃	2056.4	170	31.9	0.008
P(<i>o</i> -C ₆ H ₄ Me) ₃	2066.6	194	-	0.004
P(OPh) ₃	2085.3	128	-	0.004

A Hammett plot of $\log(k_{\text{obs(X)}}/k_{\text{obs(H)}})$ versus σ for a set of five triarylphosphines gave a relatively shallow gradient of $\rho = 0.37$ (Figure 3.14(c)).^v A slightly better correlation with $\rho = 0.24$ is obtained using σ^+ parameters for the *para*-substituted triarylphosphines (Figure 3.14(d)),^{vi} but in both cases these show that the reaction is promoted by *electron-poor* triarylphosphines. The relatively simple reaction mechanism that we had initially anticipated – i.e. ligand binding, halide abstraction, ligand dissociation – is too simple to explain the observed trends, and so we turned to computational chemistry for additional insight.

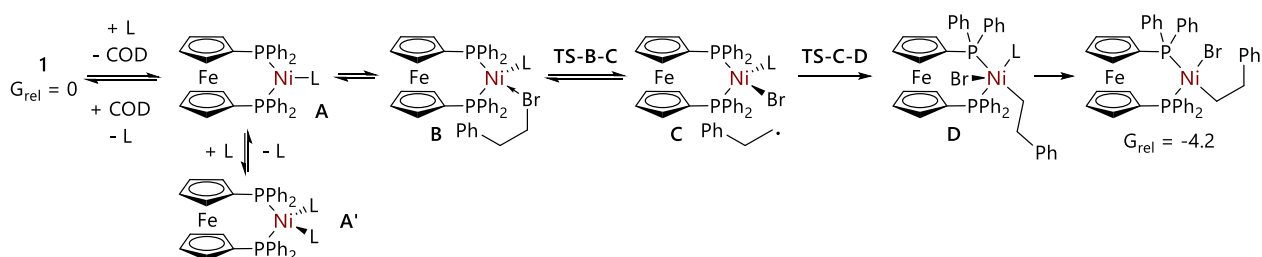
^v We note that triphenylphosphine lies quite far off the line of best fit in each case. These reactions were repeated with freshly recrystallised triphenylphosphine but this did not affect the reaction rate.

^{vi} All six ligands are plotted on the graph but *p*-F and *m*-Me have the same substituent constant and so these are superimposed.

3.4.2. DFT Calculations of the Reaction Mechanism

DFT calculations carried out during our earlier study supported the proposal that the reaction occurs *via* formation of a three-coordinate nickel(0) complex, halide abstraction to form nickel(I) plus a radical, and recombination of these species to form a nickel(II) complex. The nickel(II) complex is then proposed to undergo β -hydride elimination followed by comproportionation to form [NiX(dppf)] (**3**), styrene, and hydrogen. For details of the level of theory used in this study please see the experimental section. Trimethylamine was used as a conformationally less complicated model for triethylamine; we have previously used trimethylphosphine as a model for triethylphosphine.

The reactions of [Ni(COD)(dppf)] (**1**) with (2-bromoethyl)benzene (**4-Br**) in the presence of added ligands were systematically studied. Scheme 3.17 outlines the mechanism, while Table 3.2 records the corresponding data and the overall barrier for the halide abstraction transition state *versus* the lowest energy preceding intermediate. For simplicity, the reactions with the corresponding alkyl chloride and alkyl iodide were not studied here.



Scheme 3.17. Mechanism for the reactions of **1** plus added ligand (L) with (2-bromoethyl)benzene **4-Br**.

In most cases, [Ni(dppf)(L)] had $G_{rel} = -0.6$ to 1.6 kcal/mol, with the exceptions of trimethylamine ($G_{rel} = 14.3$ kcal/mol) and triphenylphosphite ($G_{rel} = -6.1$ kcal/mol). The strong binding of the π -accepting phosphite to the dppf-nickel(0) fragment is not unexpected, given the important role of π -backbonding in the coordination chemistry of organometallic complexes of nickel(0).^{76,206,207} The steric profile of each coordinated ligand in a selection of the corresponding [Ni(dppf)(L)] complexes was evaluated using the percent buried volume ($\%V_{bur}$) metric (see the Supporting Information for the full dataset).^{208–210} This metric has

been widely applied across organometallic chemistry and catalysis. The %V_{bur} value did not vary as much as was anticipated. For example, tricyclohexylphosphine and triphenylphosphine have %V_{bur} that vary by less than one unit (31.9 and 31.2, respectively), despite their vastly different cone angles (170° and 145°, respectively). Trimethylphosphine (24.0), triphenylarsine (22.7), and triphenylstibene (27.7) have a lower %V_{bur} than triarylphosphines (*ca.* 31) in this environment.

Table 3.2. Free energies for the complexes considered during this study, obtained at the M06/6-311+G(d,p),LANL2DZ(d,p)[Sb], SMD(benzene)//B3LYP-D3/6-31G(d),LANL2TZ(f)[Ni,Fe],LANL2DZ(d,p)[Br,As,Sb] level of theory, and quoted relative to [Ni(COD)(dppf)] (1).

Ligand	<i>k</i> _{rel}	G _{rel} (kcal/mol)								
		A	A'	B	TS-B-C	C	TS-C-D	D	ΔG [‡] (HA)	ΔG [‡] (recomb.)
P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	1.00	0.0	4.1	4.3	23.8	20.5			23.8	
P(<i>p</i> -C ₆ H ₄ F) ₃	0.89	1.0	2.9	2.8	22.5	4.5			22.5	
P(<i>p</i> -C ₆ H ₄ Me) ₃	0.63	1.6	5.8	3.8	22.7	18.9			22.7	
PPh ₃	0.52	1.4	5.3	2.5	24.6	17.7	26.4	10.8	24.6	26.4
P(<i>p</i> -C ₆ H ₄ OMe) ₃	0.48	1.0	3.2	4.2	21.4	3.5			21.4	
FcPPh ₂	0.20	0.3	8.0	3.0	24.7	7.2			24.7	
dppf	0.055	-0.2 ^a	- ^b	2.9	24.6	10.1			26.1	
PMe ₃	0.030	0.0	-12.2	5.5	22.2	5.9	4.5	4.1	34.4	16.7
AsPh ₃	0.026	1.4	-5.3	12.1	22.0	9.4			27.3	
SbPh ₃	0.019	0.9	-14.6	9.3	19.0	11.2			33.6	
PCy ₃	0.008	-0.2	- ^c	4.5	26.3	-0.2	31.7	14.6	26.3	31.9
P(OPh) ₃	0.004	-6.1	-21.6	-3.3	18.8	-13.1			40.4	
NMe ₃	0.004	14.3	- ^c	21.1	32.8	15.1			32.8	

It is possible for two monodentate ligands to coordinate the [Ni(dppf)] fragment in most cases; [Ni(dppf)(PMe₃)₂]²¹¹ and [Ni(dppf)(P(OPh)₃)₂] are known species that have been fully

characterized using methods including single crystal X-ray diffraction. The possible formation of these species was also investigated computationally. In the case of trimethylamine and tricyclohexylphosphine, geometry optimization led to the spontaneous decoordination of the second ligand. In all other cases, $[\text{Ni}(\text{dppf})(\text{L})_2]$ complexes could be optimised as minima on the free energy surface. For triphenylarsine, triphenylstibene, trimethylphosphine, and triphenylphosphite the binding of a second ligand is very favourable, and so this increases the barrier to halide abstraction by $[\text{Ni}(\text{dppf})(\text{L})]$; this explains the rather poor performance of these four ligands in the kinetic experiments. The binding of a second diphenylphosphinoferrocene or triarylphosphine ligand is endergonic by a few kcal/mol.

The next step is the formation of $[\text{Ni}(\text{BrCH}_2\text{CH}_2\text{Ph})(\text{dppf})(\text{L})]$, although in many cases the steric environment around nickel precludes short Ni ... Br distances. These are typically slightly higher in energy than $[\text{Ni}(\text{dppf})(\text{L})]$, presumably due to the entropic cost of bringing two molecules together. Halide abstraction takes place subsequently, and forms $[\text{NiBr}(\text{dppf})(\text{L})]$ plus an alkyl radical. Our initial treatment of the data assumed facile ligand dissociation and radical recombination to form $[\text{NiBr}(\text{CH}_2\text{CH}_2\text{Ph})(\text{dppf})]$ (**5**) ($G_{\text{rel}} = -4.2$ kcal/mol) which transpired to be an over-simplification of the reaction mechanism;⁷⁵ the events after halide abstraction but before the formation of **5** will be discussed subsequently.

An initial analysis of the data revealed limited agreement between experimentally-determined rate constants and computationally-determined halide abstraction barriers. FcPPh_2 is a more effective ligand than dppf, and this is reflected in the 1.4 kcal/mol decrease in $\Delta G^\ddagger$. However, the DFT data for triarylphosphines ligands are at odds with the experimental observations, and instead suggest that the reactions with more *electron-rich* ligands should proceed more quickly.

We next considered the possibility that the halide abstraction is in fact reversible, and that a subsequent step in the mechanism might be rate-determining in some or all cases. Experimental evidence suggests that the alkyl radical exists for long enough to undergo unimolecular rearrangement reactions, but the lack of any corresponding alkane or dimerized product suggests that it is captured by the nickel complex relatively quickly.⁷⁵ However, the radical might be captured by the formation of a nickel(II) complex (formation

of a C-Ni bond) or by the abstraction of the halide from the nickel center (C-X reformation), especially within the relatively crowded environment of the nickel center.

Further calculations identified transition states for the combination of the alkyl radical with $[\text{NiBr}(\text{dppf})(\text{L})]$, where L is trimethylphosphine, tricyclohexylphosphine, or triphenylphosphine. In the case of trimethylphosphine, two transition states were characterized: one with approximately trigonal bipyramidal geometry, and one (of lower energy) with distorted square-based pyramidal geometry. For tricyclohexylphosphine and triphenylphosphine pathways only the latter geometry of transition state was located; attempts to locate trigonal bipyramidal transition states were unsuccessful. Geometry optimizations of structures along the reaction coordinate confirmed that the transition states linked the nickel(I) complex and a square-based pyramidal nickel(II) species.

The barrier to recombination varies considerably depending on the identity of the ligand. For tricyclohexylphosphine, the radical capture transition state is significantly higher in energy than the halide abstraction transition state (31.7 *versus* 26.3 kcal/mol), which explains the poor performance of this ligand in the stoichiometric reactions. In contrast, the recombination of the radical with the trimethylphosphine complex presents no significant barrier.

Figure 3.15 displays the free energy profiles for the reactions where trimethylphosphine, tricyclohexylphosphine, and triphenylphosphine are used as additives; these illustrate the three types of behavior that are observed in these reactions. These are discussed in turn.

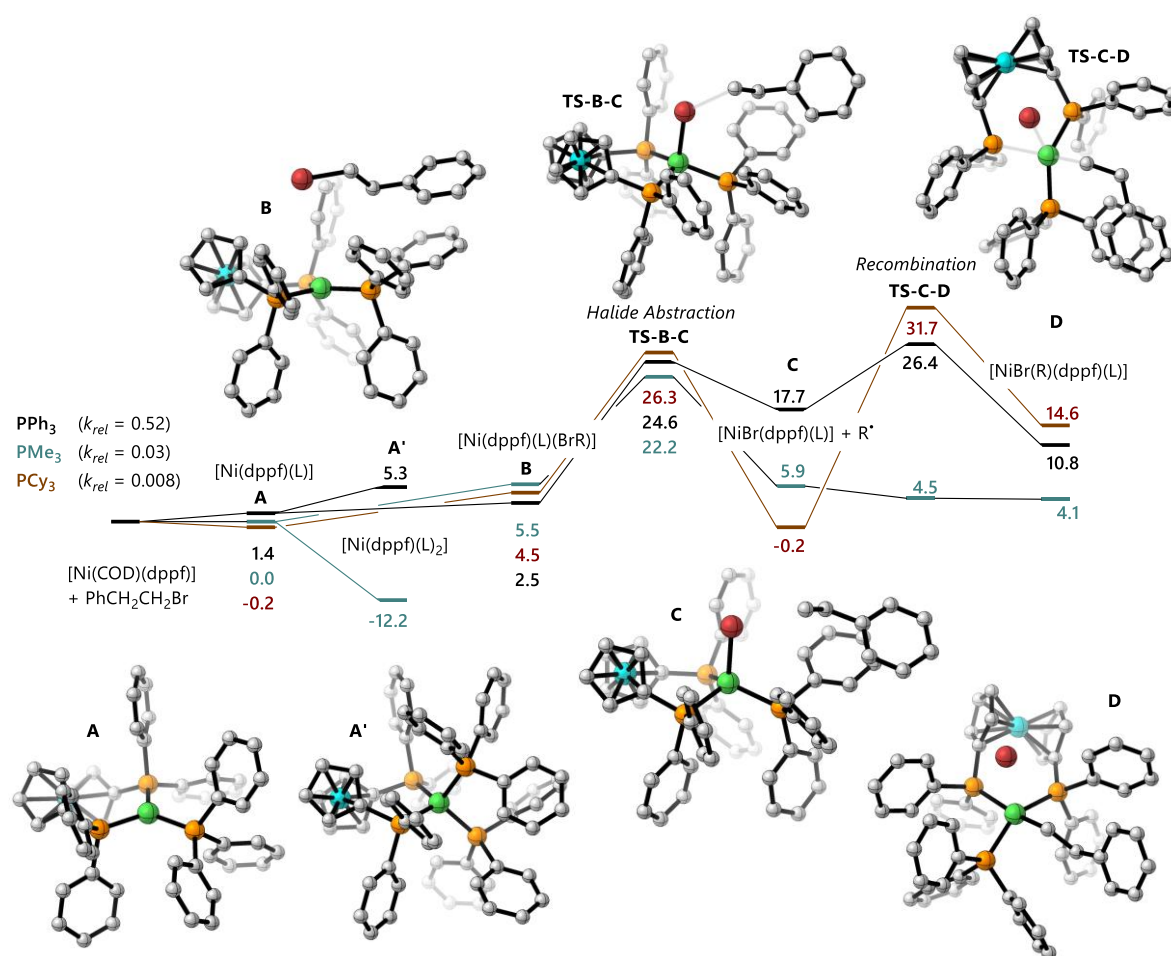


Figure 3.15. Free energy profiles for the reactions of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with (2-bromoethyl)benzene (**4-Br**) in the presence of triphenylphosphine (black), trimethylphosphine (teal), or tricyclohexylphosphine (red). Images represent DFT-derived structures of the relevant intermediates with triphenylphosphine as the added ligand (Ni green, Fe blue, P orange, Br red, C grey) with H atoms omitted for clarity.

In the case of trimethylphosphine, the formation of $[\text{Ni}(\text{dppf})(\text{PMe}_3)_2]$ inhibits the reaction because one of the trimethylphosphine ligands must dissociate before halide abstraction can occur, and this carries a significant energetic penalty. Similar behavior is observed for triphenylphosphite, triphenylarsine, and triphenylstibene.

The reaction in the presence of tricyclohexylphosphine suffers from a large barrier to radical recombination with the nickel(I) intermediate. A structure for $[\text{Ni}(\text{dppf})(\text{PCy}_3)_2]$ could not be obtained because one of the tricyclohexylphosphine ligands dissociated during

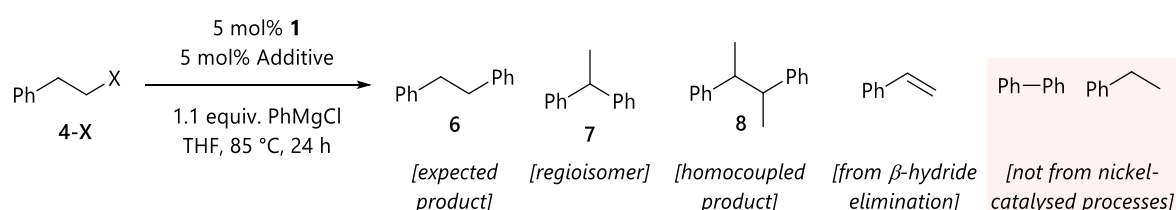
geometry optimization, and so the barrier to halide abstraction is reasonable. However, the radical formed during halide abstraction (**D**) faces a smaller barrier to re-form the C-Br bond (26.5 kcal/mol) than to form a C-Ni bond (31.9 kcal/mol) and so the halide abstraction is reversible.

The reaction in which triphenylphosphine is present faces neither of these issues. The coordination of a second phosphine ($\Delta G = 3.9$ kcal/mol) is less favorable than coordination of the substrate ($\Delta G = 1.1$ kcal/mol) and the transition states for C-Br formation and C-Ni formation are close in energy ($G_{\text{rel}} = 24.6$ and 26.4 kcal/mol), respectively.

The ‘ideal’ added ligand for this process is therefore a ligand that coordinates only once, but that is not sufficiently bulky to interfere with the recombination of the radical with nickel(I).

3.4.3. Relevance to Catalysis

We sought to link our new understanding of the effects of ligands on the halide abstraction step to the outcomes of catalytic reactions of importance to synthetic chemistry. A series of prototypical Kumada-Tamao-Corriu cross-coupling reactions were carried out using (2-haloethyl)benzene substrates (**4-Cl**, **4-Br**, **4-I**) to understand the effects of additives on catalytic reactions (Scheme 3.18). All reactions were catalysed by 5 mol% [Ni(COD)(dppf)] in the presence of 5 mol% of an additional ligand; the same conditions were used in our previous study.⁷⁵

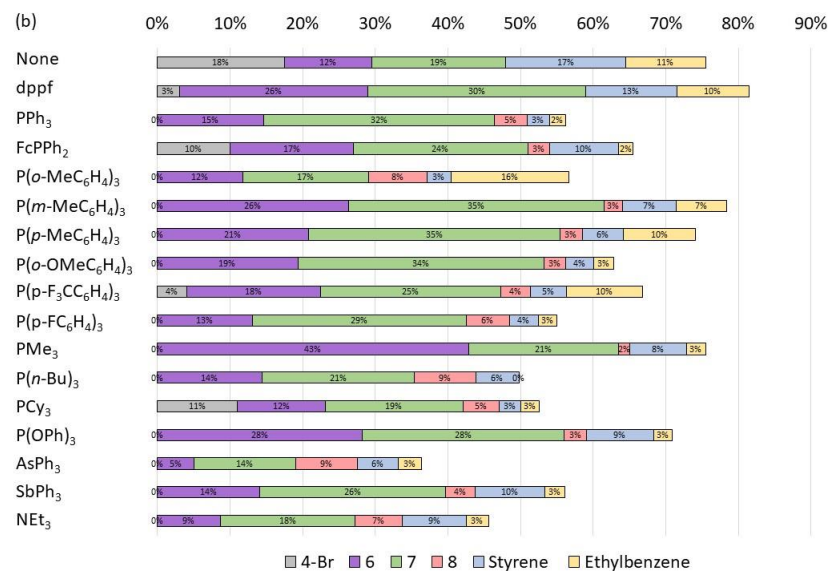
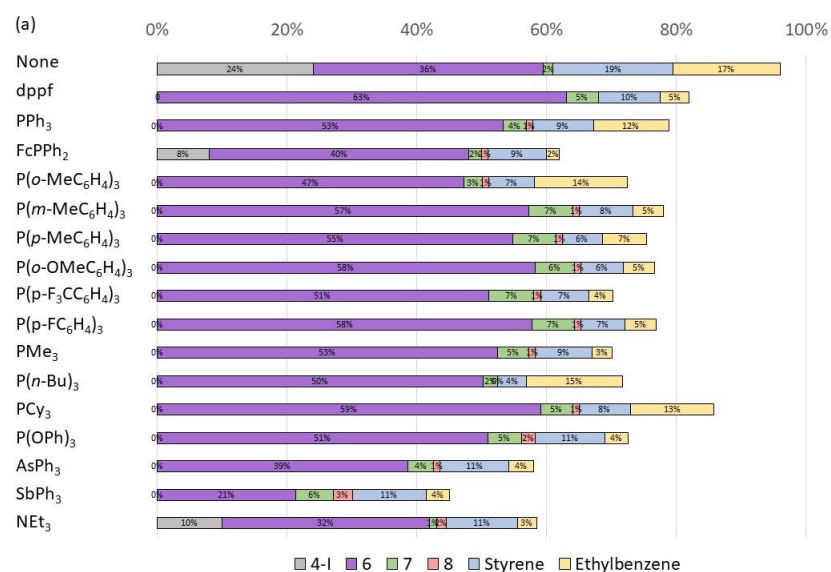


Scheme 3.18. Model Kumada-Tamao-Corriu reactions.

These reactions, and reactions closely analogous to these, have previously been carried out using other nickel catalysts, and typically at temperatures around room temperature. Catalyst systems include 10 mol% Cp*CH₂PPh₂/5 mol% NiCl₂,²¹² 5 mol% of a nickel pincer complex,²¹³ 2.5 mol% of a dinickel(II)/tridentate nitrogen ligand complex,²¹⁴ and 2 mol% of a

diphosphinodithio complex of nickel.²¹⁵ The topics of nickel-catalysed alkyl halide cross-coupling reactions^{216,217} and nickel-catalysed Kumada-Tamao-Corriu reactions have been reviewed.²¹⁸

The reactions undertaken for this study, like those disclosed previously, produced the expected 1,2-diphenylethane product (**6**), the 1,1-diphenylethane regioisomer (**7**), styrene, ethylbenzene, and biphenyl (Figure 3.16). We have shown previously, through the use of control reactions, that ethylbenzene and biphenyl do not arise from nickel-catalysed reactions.⁷⁵ The regioisomer is likely formed from β -hydride elimination followed by migratory insertion to generate the $[\text{NiX}(\text{CH}(\text{Me})\text{Ph})(\text{dppf})]$.⁷⁵ The alkyl halide homocoupling product 2,3-diphenylbutane (**8**) was observed in some reactions, particularly when **4-Cl** was used as the substrate. All reaction outcomes were quantified using GC-FID analysis with an internal standard; the GC-FID was calibrated using authentic pure samples of each analyte. These model reactions proceed poorly in the absence of an added ligand. The reactions of **4-I** are relatively insensitive to the choice of added ligand, although triphenylstibene and triethylamine perform quite poorly. It is likely that the relatively weak carbon-iodine bond strength means that the halide abstraction step is unlikely to be rate-determining in the reactions of alkyl iodides. These reactions significantly favour the expected (linear) product (**6**) over the branched side-product (**7**). The reactions of **4-Br** show more diverse outcomes, and produce mixtures of **6** and **7**. Here, the most effective ligands appear to be trimethylphosphine, tri(*meta*-tolyl)phosphine, and triphenylphosphite. The reactions of **4-Cl** are evidently more challenging, and most reactions had rather poor mass balance and/or did not achieve complete substrate conversion. Once again, tri(*meta*-tolyl)phosphine appears to be the best ligand in terms of enabling complete conversion of the alkyl halide substrate, although the major product is regioisomer **7**.



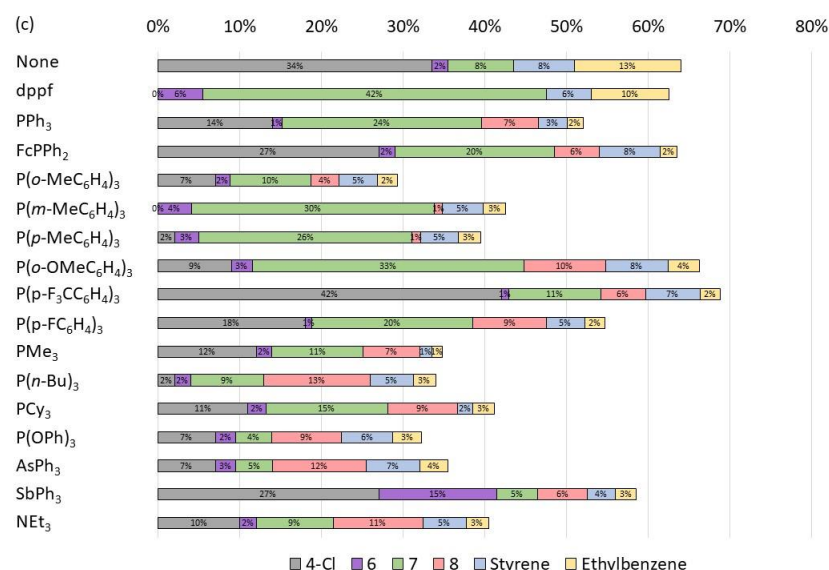


Figure 3.16. Product distributions in model Kumada-Tamao-Corriu cross-coupling reactions using different added ligands. Reactions were conducted with three substrates: (a) (2-iodoethyl)benzene, (b) (2-bromoethyl)benzene, and (c) (2-chloroethyl)benzene.

Despite the 200-fold spread of reaction rates in the stoichiometric halide abstraction reactions, the outcomes of catalysis are generally rather less variable. This suggests that the halide abstraction step is not rate-determining within the overall catalytic cycle and/or that the more forcing conditions used for catalysis mitigate the energetic barrier involved for some ligands. Tri(*meta*-tolyl)phosphine emerges as a ligand that is a good choice for the reactions of any of the three of these substrates. It must be noted that a full optimization of this reaction has not been carried out, but the choice of added ligand represents an important factor that should be considered in these reactions. This added ligand can of course affect steps other than halide abstraction, but an examination of the full catalytic cycle for this reaction is beyond the scope of the present study.

3.5. Extended Discussion

3.5.1. Equilibrium Constants

Attempts to calculate equilibrium constants for a set of monodentate phosphine ligands (PPh₃, P(*p*-tol)₃, P(*m*-tol)₃, P(4-OMeC₆H₄)₃, P(4-CF₃C₆H₄)₃, P(4-FC₆H₄)₃) were undertaken. Addition of 1 equivalent of phosphine to [Ni(COD)(dppf)] (1) plus triphenylphosphine oxide

(1 equivalent) as an internal standard were dissolved in deuterated benzene and a ^{31}P NMR spectrum was obtained. In all cases, singlets corresponding to $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and triphenylphosphine oxide were observed. In addition, there was a third singlet, as opposed to the doublet and a triplet that would be expected for $[\text{Ni}(\text{dppf})\text{L}]$, suggesting rapid exchange of the attached ligand, L. An attempt to resolve this peak (in the case of PPh_3) was made by cooling the sample to $-40\text{ }^\circ\text{C}$, however, this pushed the equilibrium back towards $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and no resolution of the singlet corresponding to $[\text{Ni}(\text{dppf})\text{L}]$ was observed.

3.5.2. Bidentate Ligands

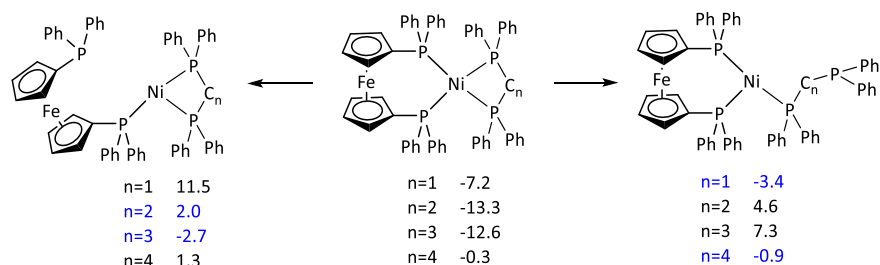
Bidentate ligands were used as additives in both oxidative addition experiments and as additives in Kumada-Corriu-Tamao cross-coupling reactions. Dppm (1,1'-bis(diphenylphosphino)methane), dppe (1,1'-bis(diphenylphosphino)ethane), dppp (1,1'-bis(diphenylphosphino)propane), and dppb (1,1'-bis(diphenylphosphino)butane) were used as additives, and the rates of oxidative addition for these reactions are given in Table 3.3.

Table 3.3. Rates of oxidative addition for when bidentate ligands (plus PPh_3 and $\text{P}(p\text{-C}_6\text{H}_4\text{CF}_3)_3$ for comparison) are used as additives in the reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with 2-bromoethylbenzene (**4-Br**).

Ligand	T (K)	$k_{\text{obs}} (\text{s}^{-1})$	k_{rel}
dppp	293	$8.52(2) \times 10^{-4}$	0.008
dppm	293	$1.11(1) \times 10^{-3}$	0.010
dppe	293	$1.61(2) \times 10^{-3}$	0.014
dppf	273	$0.50(1) \times 10^{-3}$	0.055
dppb	263	$4.31(1) \times 10^{-4}$	0.15
PPh_3	263	$1.4(3) \times 10^{-3}$	0.52
$\text{P}(p\text{-C}_6\text{H}_4\text{CF}_3)_3$	263	$2.8(1) \times 10^{-3}$	1.00

The presence of two triplets in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra during kinetic studies confirmed formation of 4-coordinate tetrahedral complexes during kinetic studies. DFT uncovered the differing reactivity that can occur with bidentate phosphines when compared to

monodentate (Scheme 3.19). In the cases of dppm and dppb, the expected reactivity occurs, where one phosphine of added ligand dissociates to allow for halide abstraction. However, in the cases of dppe and dppp, it is more favourable for one of the phosphine atoms on the dppf to dissociate to generate the vacant site required for halide abstraction.



Scheme 3.19. DFT on ligand dissociation from $[\text{Ni}(\text{dppf})\text{L}]$ when bidentate ligands are used as additives.

Results from cross-coupling reactions are given in Figure 3.17. The bidentate ligands overall perform in a similar way to monodentate phosphine ligands increasing the conversion to products when compared to no additive being used. Dppe does not perform as well when used as an additive in the cross-couplings, which may be due to the differing reactivity implied from DFT calculations. Loss of dppf, as opposed to dppe during oxidative addition may form a species which is be less prone to transmetalation resulting in poor conversion.

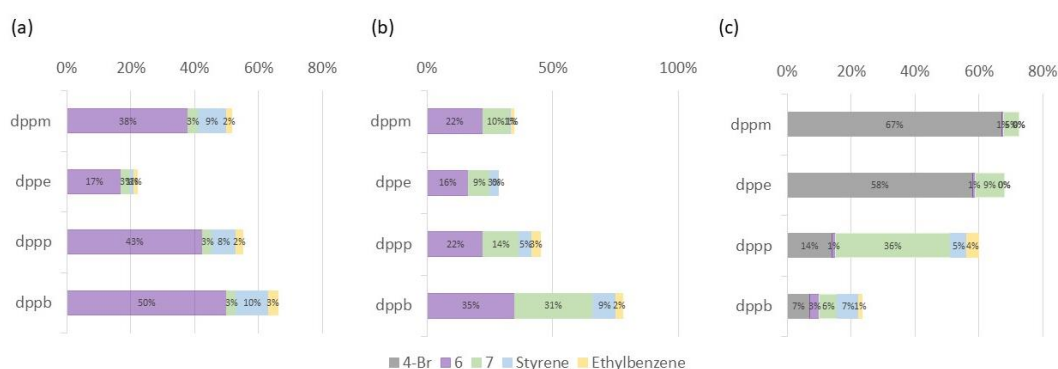


Figure 3.17. Results from Kumada-Corriu-Tamao cross-coupling reactions of alkyl halides with bidentate ligands as additives for (a) 2-iodoethylbenzene (**4-I**), (b) bromoethylbenzene (**4-Br**), (c) chloroethylbenzene (**4-Cl**).

3.5.3. Selectivity

A difference in selectivity for products is observed in cross-coupling reactions depending on which alkyl halide is employed as the substrate. 2-Chloroethylbenzene (**4-Cl**) typically favours the regioisomeric product (**7**) whereas 2-iodoethylbenzene (**4-I**) favours the expected product (**6**), and 2-bromoethylbenzene (**4-Br**) results in a more equal mixture of products. There was not a clear correlation between k_{rel} for oxidative addition and ratio of products (Figure 3.18).

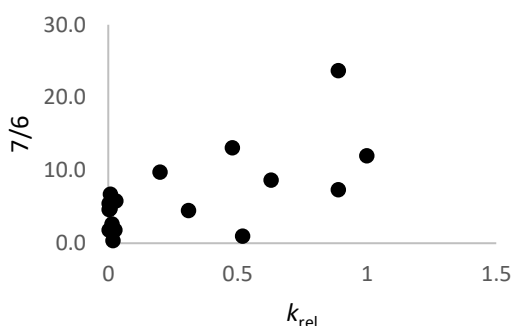


Figure 3.18. A plot of product ratio observed in the cross-coupling of 2-chloroethylbenzene (**4-Cl**) vs k_{rel} for oxidative addition for additives used in this study.

The trend observed is the opposite to what would be expected in this reaction; 2-iodoethylbenzene (**4-I**) has a higher rate of oxidative addition, leading to a higher concentration of styrene which in turn should result in a higher conversion to the regioisomeric product (**7**). This was confirmed experimentally by varying the concentration of styrene added into cross-coupling reactions where 2-chloroethylbenzene (**4-Cl**) was the substrate and dppf used as the additive (Figure 3.19).

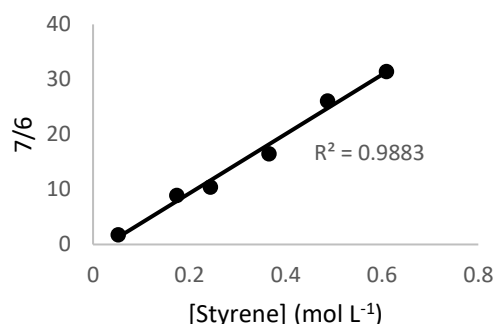


Figure 3.19. Correlation between product ratio and concentration of styrene. Cross-coupling of 2-chloroethylbenzene (**4-Cl**) with PhMgCl, catalysed by 5 mol% of [Ni(COD)(dppf)] (**1**) and dppf.

Attention turned to the transmetalation step, as this could also have an effect on the selectivity of the reaction. Aryl Grignard reagents with various *meta*- and *para*-substituents (*p*-Me, *p*-OMe, *p*-F, *m*-F, *m*-OMe) were synthesised and employed as the transmetalating reagents in the coupling of 2-bromoethylbenzene (**4-Br**). The ratios of products formed was plotted against the σ value for the corresponding substituent (Figure 3.20), but no correlation was observed.¹⁹⁷ This suggests product selectivity does not originate in the transmetalating step of the reaction.

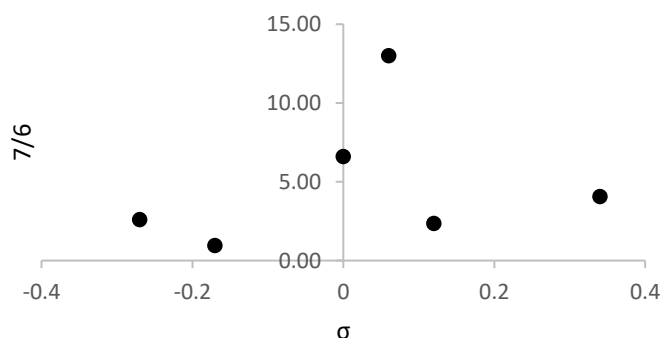


Figure 3.20. Hammett plot for various substituted aryl Grignard reagents vs product ratio.¹⁹⁷ Product ratio from the cross-coupling of 2-bromoethylbenzene with corresponding Grignard reagent, catalysed by 5 mol% [Ni(COD)(dppf)] (**1**) and dppf.

A change in solvent from THF to toluene led to a slight decrease in product ratio (2.1 to 1.6) to indicate a decrease in conversion to regioisomer (**7**). This suggests that once β -hydride elimination has occurred, it is more difficult for the bound styrene to dissociate in toluene.

This may be due to a charged intermediate being formed, which would be more stable in a more polar solvent (THF). Solubility may also play a role, both of nickel complexes involved in cross-coupling and the transmetalating reagents which is a solution in THF.

3.6. Conclusions

This study has established that a range of different added ligands increase the rate of the reaction between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and a model alkyl bromide (**4-Br**), with a *ca.* 200-fold range of rate constants. This is consistent with our current mechanistic model which requires a three coordinate nickel(0) complex that can abstract the halide atom from the alkyl halide substrate. DFT studies have provided further insight into the reaction, identifying that the rate-determining step in the stoichiometric reactions between **1** and **4-Br** can be either the halide abstraction step *or* the recombination of the alkyl radical with the nickel(I) complex formed during halide abstraction.

Studies of a prototypical Kumada-Tamao-Corriu reaction have established that the choice of ligand has relatively little effect for the reactions of **4-I**, but that the reactions in the absence of an added ligand give poor outcomes. The outcomes of the reactions of **4-Br** and **4-Cl** show a more complicated dependence on the structure of the added ligand, but this certainly presents a useful vector for the optimization of these types of cross-coupling reactions.

Chapter 4 - Differences in Reactivity Between Aryl and Vinyl Triflates in Cross-Couplings: A Mechanistic Study

Drafted manuscript – *unpublished*

A drafted manuscript entitled 'Differences in Reactivity Between Aryl and Vinyl Triflates in Cross-Couplings: A Mechanistic Study' with an extended introduction prior to the article and an extended discussion after. The supporting information for this article can be found in the Chapter 7: Experimental.

Contributing authors to this manuscript and their roles are given below:

- Megan E. Greaves – Designed and performed experiments, analysed data, drafted initial manuscript
- Thomas O. Ronson – Helpful discussions as industrial supervisor
- Stephen Sproules – Conducted EPR experiments and analysed the resulting data
- David J. Nelson – Principal Investigator

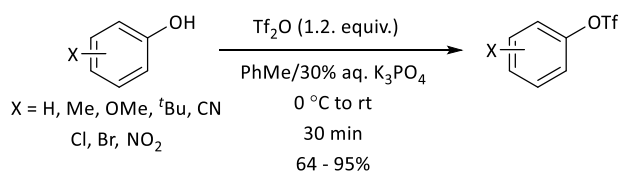
4.1. Abstract from Manuscript

The mechanism of the reactions between $[\text{Ni}(\text{COD})(\text{dppf})]$ and vinyl and aryl triflates has been investigated using kinetic experiments and DFT calculations. The active species $[\text{Ni}(\text{COD})(\text{dppf})]$ can oxidatively add both vinyl and aryl triflates through a three- or five-centered transition state. In general, oxidative addition of vinyl triflates is faster than aryl triflates due to the formation of the preceding η^2 complex (by displacement of COD) being exergonic for vinyl triflates but endergonic for aryl triflates. $[\text{Ni}(\text{COD})(\text{dppf})]$ is a competent catalyst for Kumada-Tamao-Corriu cross-coupling reactions when both vinyl and aryl triflates are employed as substrates.

4.2. Extended Introduction

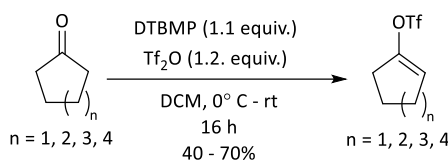
4.2.1. Synthesis

Aryl triflates are easily prepared from widely available and inexpensive phenols, making them an attractive coupling partner in cross-coupling reactions.²¹⁹ Almost quantitative conversions (in most cases) to aryl triflates from the corresponding phenols are observed within 30 minutes when base and triflic anhydride are employed (Scheme 4.1).²¹⁹



Scheme 4.1. Efficient synthesis of aryl triflates from phenols.²¹⁹

The preparation and purification (by distillation) of vinyl triflates is also facile. Use of a bulky base (2,6-di-tert-butyl-4-methylpyridine, DTBMP) and triflic anhydride converts ketones into vinyl triflates at room temperature.²²⁰ This is particularly useful for the synthesis of cyclic vinyl triflates, which then have applications in the pharmaceutical industry (Scheme 4.2).²²¹

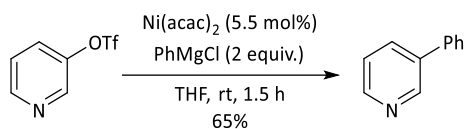


Scheme 4.2. Synthesis of cyclic vinyl triflates from corresponding ketone.²²¹

There are drawbacks associated with aryl and vinyl triflates; the substrates are often oils which are not always completely stable under ambient conditions, with risks of formation of TfOH from residual TfO₂ and water. The cost associated with the synthesis of triflates is also a consideration; 100 g of Tf₂O costs £283 which is expensive compared to TsCl (£32 for 500 g).²²²

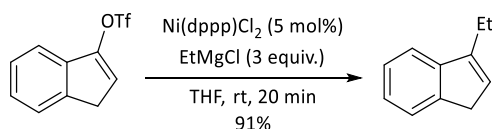
4.2.2. Cross-Coupling

Snieckus *et al.* gave the first example of Ni⁰ catalysed cross-coupling of aryl triflates in Kumada-Tamao-Corriu cross-coupling reactions in 1992 (Scheme 4.3).²²³



Scheme 4.3. Nickel catalysed cross-coupling of pyridin-3-yl triflate with phenylmagnesium chloride.²²³

In addition to the coupling of aryl triflates, there was one single example of cross-coupling a cyclic vinyl triflate.²²³ The scope and limitations of cross-coupling vinyl triflates with alkyl Grignard reagents in Kumada-Tamao-Corriu reactions, with a specific focus on ligand employed was reported by Busacca *et al.* in 1999.²²⁴ Good conversion was achieved with several different vinyl triflates, with reaction times of less than 2.5 hours (Scheme 4.4).



Scheme 4.4. Indanone triflate coupled with EtMgBr utilizing [Ni(dppp)Cl₂] in a high isolated yield in 20 minutes.²²⁴

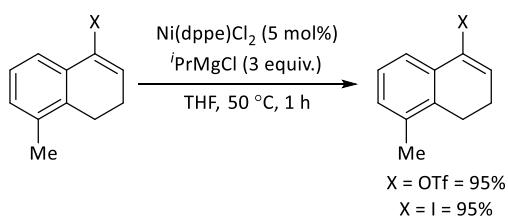
Ligand choice was an important factor to be considered in these cross-coupling reactions. Dppf, dppb and PPh₃ were found to be ineffective (a mixture of unreacted triflate and indene was present), however, dppe and dppp proved effective in most cases.²²⁴ [Ni(acac)₂] which was found to be an effective catalyst in the cross-coupling of triflates with aryl Grignard reagents,²²³ was found to be ineffective in cross-coupling when alkyl Grignard reagents were employed as transmetalating reagents.²²⁴

Dppf was the optimum ligand in the palladium-catalysed cross-coupling of vinyl halides with alkyl Grignard reagents.²²⁵ Dppe performed poorly, with dppp leading to moderate conversions, this order of reactivity was thought to be due to the bite angle (Table 4.1), with dppf aiding in reductive elimination.²²⁵

Table 4.1. Bite angles for dppe, dppp and dppf.²²⁵

Ligand	Bite angle (°)
dppe	85.8
dppp	90.6
dppf	99.1

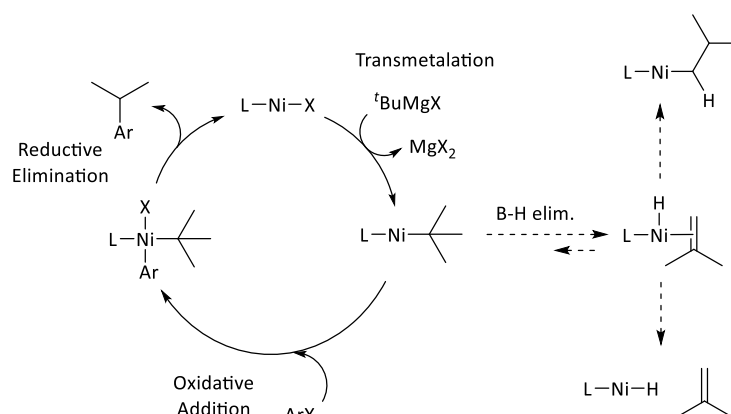
To determine if this observed difference was due to the change from nickel to palladium or a change from vinyl halide to vinyl triflate, a corresponding vinyl iodide was synthesised and employed as the substrate in a cross-coupling reaction (Scheme 4.5). Dppf, acac, dppb and PPh₃ were poor ligands for nickel-catalysed cross-coupling of both vinyl iodide and triflate, whereas dppe gave good conversion for both substrates (Scheme 4.5); only a 40% conversion to product was observed when [Pd(dppe)Cl₂] was used to catalyse the same reaction (for vinyl iodide).



Scheme 4.5. Cross-coupling of vinyl triflate and vinyl iodide with ⁱPrMgCl catalysed by [Ni(dppe)Cl₂].²²⁴

This confirms that in nickel catalysis, when alkyl Grignard reagents are used as the transmetalating reagents for vinyl substrates, bidentate ligands with small bite angles (dppe) are required for good conversion. However, in palladium-catalysed reactions, optimum conditions are obtained when a bidentate ligand with a larger bite angle is used (dppf); this observed difference is due to the metal and is independent of electrophile used.²²⁴

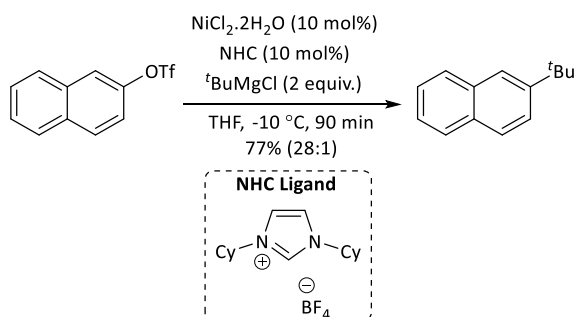
Since the initial development of the cross-coupling of aryl and vinyl triflates, relatively few studies with triflates have been reported, until recently where it seems interest has increased. Cross-couplings that employ tertiary Grignard reagents suffer from formation of isomerised products, due to facile β -hydride elimination (Scheme 4.6). In 2011, Biscoe *et al.* optimised reaction conditions in which facile transmetalation and oxidative addition suppressed the formation of the undesired isomeric product.²²⁶



Scheme 4.6. Catalytic cycle for cross-coupling an aryl (pseudo)halide with $t\text{Bu}$ Grignard reagent, highlighting the formation of isomerised side product.²²⁶

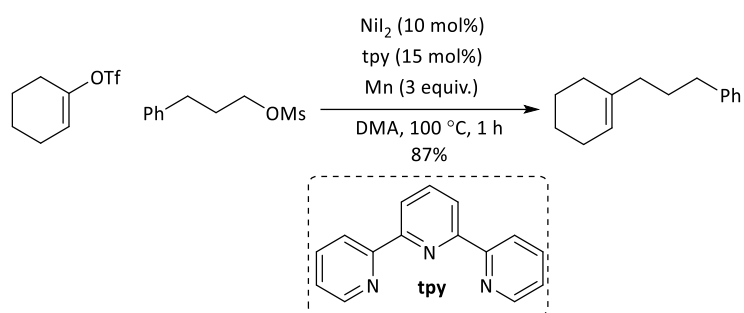
An extensive ligand screen was used to determine the ligand most suitable to suppress deleterious β -hydride elimination and therefore ultimately suppress the formation of isomeric product. Extremely bulky NHCs led to isomerisation, reduction and homocoupled products, whereas less sterically hindered and electron rich NHCs mainly gave the desired cross-coupling product (with little isomerised product present).²²⁶ The reaction was optimised with 4-bromoanisole and $t\text{BuMgCl}$ in which a 90% yield was achieved with a 40:1 ratio of desired: isomerised product. These optimum reaction conditions were applied to a

set of aryl triflates, 2-naphthyltriflate performed particularly well (Scheme 4.7), however, electron rich and sterically hindered aryl triflate performed poorly.²²⁶



Scheme 4.7. Cross-coupling of 2-naphthyl triflate with $t\text{BuMgCl}$ catalysed by $\text{NiCl}_2 \cdot \text{H}_2\text{O}$ and an $\text{ICy} \cdot \text{HBF}_4$ ligand, using previously optimised conditions.²²⁶

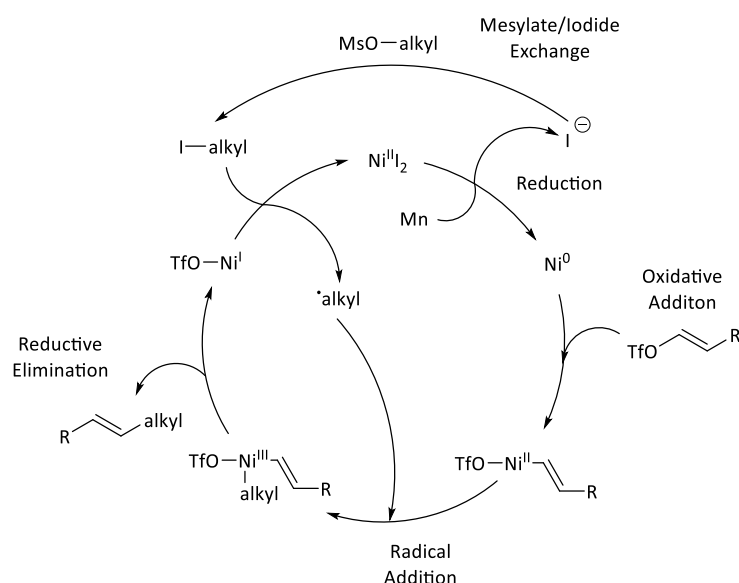
Cycloalkenes are important features in many natural products and pharmaceutical products, and the incorporation of these structural motifs can be achieved with sp^2 - sp^3 couplings of vinyl halides and alkyl transmetalating reagents or *vice versa*.²²⁷ The synthesis and stability of these reactive starting materials is challenging and can often limit the additional functionality that can be incorporated. To overcome this, Shu *et al.* reported the nickel-catalysed coupling of vinyl triflates and alkyl mesylates in a reductive cross-coupling reaction.²²¹ Optimal conditions were found, employing NiI_2 and tpy (terpyridine) catalyst and use of manganese as the reducing agent (Scheme 4.8). Most deviations from these conditions led to reduced alkene and homo-coupled products whilst the alkyl mesylate remained intact.²²¹ To illustrate the application of this reductive cross-coupling, the late-stage functionalisation of several pharmaceutically relevant molecules was carried out.



Scheme 4.8. Optimal conditions for the reductive coupling of vinyl triflates and alkyl mesylates.²²¹

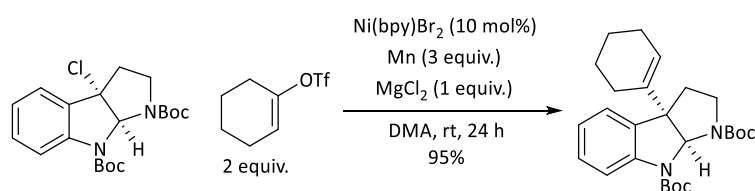
Catalytic amounts of iodide were determined to be an important factor for the success of this reaction, as only trace product was observed when NiBr_2 or NiCl_2 were used as the nickel source. However, the addition of NaI into these reactions did give moderate conversions to the coupled product. The reaction of the mesylate with NaI gave full conversion to the corresponding iodide under the optimum reaction conditions, suggesting that catalytic amounts of iodide are required to activate the mesylate.

A radical mechanism was proposed (Scheme 4.9). As the reaction was inhibited by addition of TEMPO, where only 15% conversion to coupled product was observed. In addition, the use of a cyclopropyl mesylate gave the corresponding ring-opened product. The following mechanism was proposed: (i) reduction of NiI_2 to the Ni^0 active species, (ii) oxidative addition of vinyl triflate (iii) which then reacts with an alkyl radical, (iv) followed by subsequent reductive elimination to give coupled product.²²¹



Scheme 4.9. Proposed mechanism for coupling of vinyl triflates and alkyl mesylates in nickel-catalysed reductive cross-coupling.²²¹

A very similar reductive cross-coupling to specifically form vinyl substituted hexahydropyrrolidinoindolines (Scheme 4.10), that are prominent in natural product synthesis due to interesting bioactive properties, was later developed by Gong *et al.* in 2021.²²⁸ The stereo retentive nature of the reaction was hypothesised to arise from the less congested vinyl-Ni-alkyl intermediate.



Scheme 4.10. Nickel-catalysed reductive coupling of a chloro-hexahydropyrroloindoline with cyclohexenyl triflate.

4.3. Introduction from Manuscript

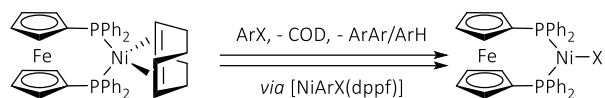
The prevalence of biphenyl motifs in the pharmaceutical, agricultural and materials industries has driven research over the last half a decade.²²⁹ Since the 1970's, triflates have been employed as cross-coupling partners in palladium-catalysed Suzuki-Miyaura, Mizoroki-

Heck and Negishi couplings.²³⁰ The ease of preparation of triflates from cheap and readily available bench stable phenols (aryl triflates) and ketones/alkynes (vinyl triflates) makes them attractive cross-coupling substrates.^{219,221,230,231} The incorporation of alkene moieties has applications in the syntheses of natural products and pharmaceuticals, either by the inclusion of alkenes in the final product or by exploiting the reactivity of alkenes further in the synthetic route.^{232–234} A high prevalence of nickel-catalysed cross-coupling of triflates (particularly recently),^{235–237} where the initial step is an oxidative addition of triflate to a Ni⁰ centre, highlights the importance in understanding the mechanism of this crucial fundamental step.

Relatively little is known about the mechanisms of oxidative addition of vinyl (pseudo)halides to Ni⁰, when compared to aryl and alkyl substrates.^{74,75,103} Fahey investigated the reaction of [Ni(PEt₃)₂(COD)] with chloroprene, confirming successful oxidative addition with the isolation of the *trans*-allylnickel(II) halide complex.⁸¹ The initial coordination of Ni⁰ to the π -system was proposed to be followed by a subsequent rearrangement to yield the observed product. Although the intermediates were not isolated in this case and the mechanism was speculative, similar mechanisms involving ring-walking mechanisms have since been observed with Ni⁰, which support this proposal.^{76,79,80}

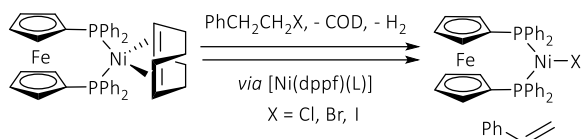
We have previously proposed mechanisms for the oxidative addition of aryl (pseudo)halides and alkyl halides to Ni⁰ based on computational and experimental studies (Scheme 4.11(a), 1(b)).^{72,74–76,155,238} We have typically worked with [Ni(COD)(dppf)] (**1**) for kinetic studies as it is a thermally stable complex that can easily be made on a gram scale, and which has many applications in cross-coupling reactions (dppf = 1,1'-bis(diphenylphosphino)ferrocene, COD = 1,5-cyclooctadiene).¹⁷⁷ We have previously shown that aryl (pseudo)halides react directly with [Ni(COD)(dppf)] (**1**) (*via* a three-centered transition state);⁷⁴ in contrast, alkyl halides react with [Ni(dppf)(L)] complexes (formed *in situ*) *via* a halide abstraction mechanism.^{155,75} This work focuses on the reaction of both aryl and vinyl triflates with [Ni(COD)(dppf)] (**1**) to investigate the mechanism of oxidative addition of triflates and further probe structure/reactivity relationships (Scheme 4.11(c)).^{76,77}

(a) Oxidative addition of aryl halides to $[\text{Ni}(\text{COD})(\text{dppf})]$ (previous work)



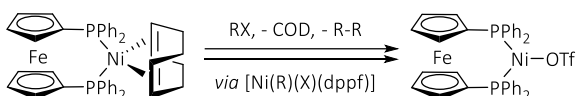
Rate of reaction:
 $\text{I} > \text{Br} > \text{Cl} > \text{OTs} > \text{OCO}_2\text{Et} > \text{OTf} > \text{OCONeEt}_2 > \text{OSO}_2\text{NMe}_2 > \text{OPiv} > \text{OMe} \approx \text{F}$

(b) Reactions of alkyl halides with $[\text{Ni}(\text{COD})(\text{dppf})]$ (previous work)



Halide abstraction and recombination mechanism

(c) Reactions of vinyl and aryl triflates with $[\text{Ni}(\text{COD})(\text{dppf})]$ (this work)

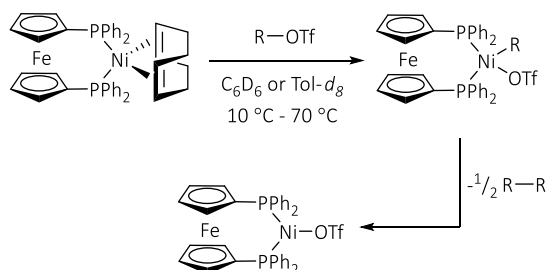


Scheme 4.11. (a) Previous work with aryl (pseudo)halides. (b) Previous work with alkyl halides. (c). This work.

4.4. Results and Discussion from Manuscript

4.4.1. Kinetic Experiments

Stoichiometric reactions between $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and a range of vinyl and aryl triflates showed that the major products were $[\text{Ni}(\text{dppf})(\text{OTf})]$ (**2**) (confirmed by EPR spectroscopy) and the corresponding organic homocoupling product (confirmed by GC-MS) (Scheme 4.12). We have previously observed a $[\text{Ni}(\text{dppf})(\text{Ar})(\text{OTf})]$ oxidative addition product by ^{31}P NMR spectroscopy from the reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with 1-naphthyl triflate.⁷⁴



Scheme 4.12. Product studies for reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with vinyl and aryl triflates.

An *in-situ* sample of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) and cyclohex-1-en-1-yl triflate was analysed by EPR spectroscopy and a spectrum consistent with $[\text{Ni}(\text{dppf})(\text{OTf})]$ (**2**) was obtained (Figure 4.1).

Due to solubility issues with [Ni(dppf)(OTf)] (**2**) in toluene- d_8 , THF was used for the *in-situ* EPR analysis so that the sample remained homogeneous. The observed g_{iso} value was similar to that obtained for [Ni(dppf)Cl] (2.173 vs 2.172);⁷⁴ however, the larger hyperfine coupling constant in this case is consistent with a smaller oxygen donor. We have previously reported EPR data from this complex derived from the reaction of **1** with $p\text{-F}_3\text{CC}_6\text{H}_4\text{OTf}$.⁷⁴

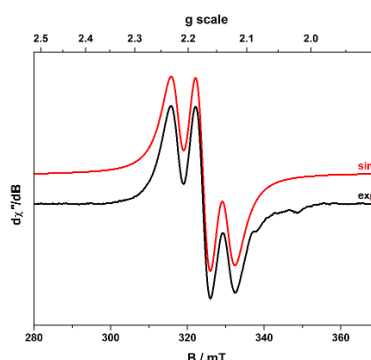


Figure 4.1. X-band EPR spectrum of [Ni(OTf)(dppf)] (**1**) and cyclohex-1-en-1-yl triflate recorded in THF solution at 293 K (experimental conditions: frequency, 9.8593 GHz; power, 6.3 mW; modulation, 0.6 mT). Experimental spectrum is shown as the black line, simulation as the red trace: $g_{iso} = 2.1733$; $A_{iso} = 65 \times 10^{-4} \text{ cm}^{-1}$.

Kinetic experiments were performed using our previously published methodology;^{74–76,155} full details can be found in the Supporting Information. The substrate and complex **1** were combined in benzene- d_6 or toluene- d_8 the decay of **1** was monitored by $^{31}\text{P}\{^1\text{H}\}$ analysis at time points. All kinetic experiments were pseudo-first order with respect to [Ni(COD)(dppf)] (**1**), first-order in substrate, and were inhibited when COD was added, An Eyring-Polanyi treatment of data at multiple temperatures yielded activation parameters. The plots obtained for cyclo-hept-1-en-1-yl and phenyl triflate are shown in Figure 4.2; the full dataset is provided in the Supplementary Information. The vinyl and aryl substrates will be discussed separately.

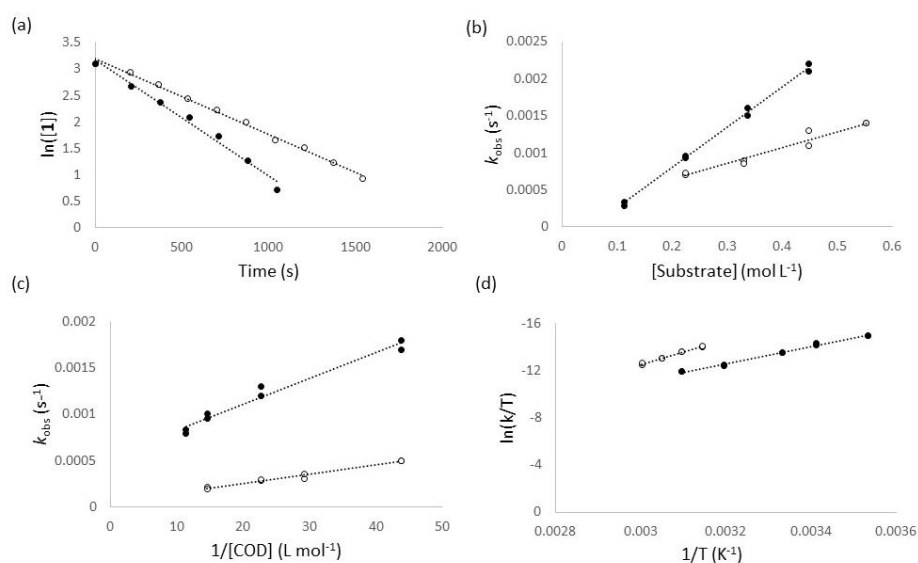
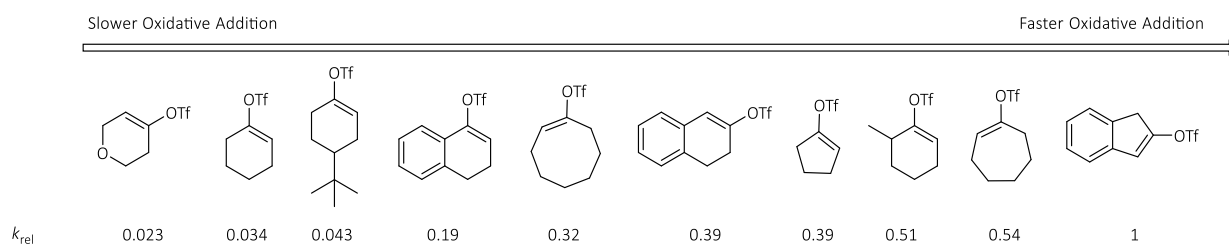


Figure 4.2. Kinetic data from the reactions of [Ni(COD)(dppf)] (**1**) (22 mmol L⁻¹) in benzene-d₆ with 0.44 mol L⁻¹ cyclo-hept-1-en-1-yl triflate (circles) and phenyl triflate (open circles) at 323 K and 333 K respectively: (a) pseudo-first-order behaviour; (b) first-order in substrate; (c) inhibition by COD; (d) Eyring-Polanyi treatment.

Vinyl

The reactions of cyclic vinyl substrates were studied initially to understand the effect ring size (5, 6, 7 and 8) had on the rate of reaction; acyclic vinyl triflates are much more synthetically challenging to access. The oxidative addition rates decrease in the order 7 > 5 > 8 >> 6 (Scheme 4.13, Table 4.2). The rather puzzling low reactivity of cyclohex-1-en-1-yl triflate was further investigated by synthesis of an analogue with a 4-*tert*-butyl substituent to lock the conformation of the six-membered ring, in order to determine whether the low reactivity could be attributed to a conformational change. However, this had very little effect on the rate of oxidative addition (Scheme 4.13). The incorporation of a heteroatom in the cyclohexyl ring also had little impact on the rate of oxidative addition.



Scheme 4.13. Reactivity scale for vinyl triflates.

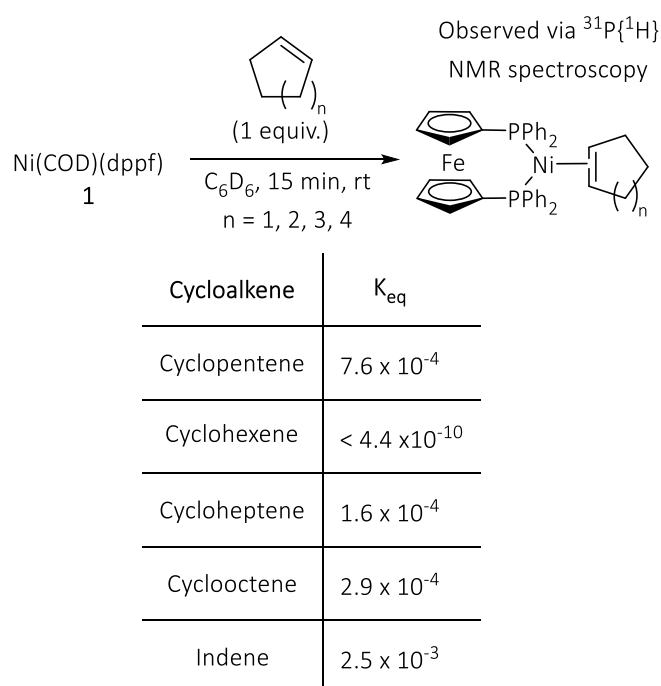
Table 4.2. Rate constants and k_{rel} for reactions of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with 20 equivalents of vinyl triflates at 283 – 343 K. Reactions were performed in benzene- d_6 (below 343 K) and toluene- d_8 (at 343 K). Reactions were carried out in duplicate and the average rate constants are quoted here; all rate constants can be found in the Supporting Information.

Substrate	T (K)	k_{obs}	k_{rel}
1H-Inden-2-yl	323	$4.1(1) \times 10^{-3}$	1
Cyclohept-1-en-1-yl	323	$2.2(1) \times 10^{-3}$	0.54
6-Methylcyclohex-1-en-1-yl	323	$2.1(1) \times 10^{-3}$	0.51
Cyclopent-1-en-1-yl	323	$1.61(1) \times 10^{-3}$	0.39
3,4-Dihydronaphthalen-2-yl	323	$1.6(3) \times 10^{-3}$	0.39
Cyclooct-1-en-1-yl	323	$1.2(1) \times 10^{-3}$	0.32
3,4-Dihydronaphthalen-1-yl	323	$7.6(2) \times 10^{-4}$	0.19
4-(<i>t</i> -Butyl)cyclohex-1-en-1-yl	343	$2.0(1) \times 10^{-3}$	0.043
Cyclohex-1-en-1-yl	343	$1.6(1) \times 10^{-3}$	0.034
	323	$1.4(2) \times 10^{-4}$	
3,6-Dihydro-2H-pyran-4-yl	343	$1.1(1) \times 10^{-3}$	0.023

Experiments were conducted to measure equilibrium constants for cycloalkenes. Cycloalkenes were reacted with $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**), in a 1:1 ratio to determine if initial binding of the triflate was responsible for the observed order in reactivity, these are given in Scheme 4.14. In contrast to the other cycloalkenes, the addition of cyclohexene to $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) afforded no detectable $[\text{Ni}(\text{dppf})(\eta^2\text{-cyclohexene})]$ in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum. Therefore, it is proposed that initial binding of the vinyl triflates, to form an η^2

complex, enhances reactivity and the inability of cyclohexene to displace COD explains the low rate of oxidative addition for cyclohex-1-en-1-yl triflate. When vinyl substrates are employed as substrates, they are affected less by the addition of excess COD because they can better compete for coordination to dppf-Ni^0 ; 1 equivalent of COD added to the reaction of cyclohept-1-en-1-yl with $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) led to a 20% decrease in the rate, compared to a 60% decrease when phenyl triflate was used as the substrate (*vide infra*), further supporting this initial binding of the alkene being a key event.

The inclusion of a fused aryl ring to the vinyl triflate increases reactivity, as shown by use of 1*H*-inden-2-yl and 3,4-dihydronaphthalen-1-yl triflates (Scheme 4.13). The 3,4-dihydronaphthalen-2-yl triflate was found to have a higher rate of oxidative addition than 3,4-dihydronaphthalen-1-yl triflate, which may be due to steric hinderance at the alkene in the latter substrate. The equilibrium constant measured (Scheme 4.14) by addition of indene to a sample of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) indicates a stronger binding affinity for fused aryl substrates, with a 3-fold increase in K_{eq} observed (compared to cyclopentene).



Scheme 4.14. Equilibrium constants measured for $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) (22.2 mmol L^{-1}) plus cycloalkenes (22.2 mmol L^{-1}) in C_6D_6 at 300 K.

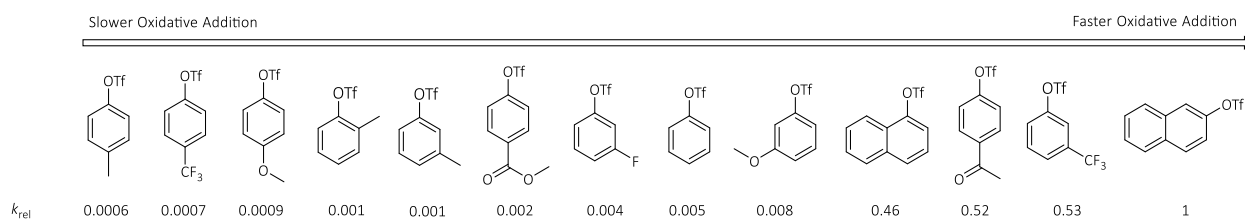
Activation parameters (Table 4.3) were obtained by monitoring the reactions of [Ni(COD)(dppf)] (**1**) with 20 equivalents of vinyl triflate at a range of temperatures; the corresponding plots are provided in the Supporting Information. As noted previously,⁷⁴ the displacement of COD by vinyl triflate is involved in the overall reaction meaning that $\Delta S^\ddagger$ is the sum of the entropy change for the initial ligand exchange and the entropy of activation of the subsequent oxidative addition. Generally, an increased rate of reaction is accompanied with a decrease in $\Delta H^\ddagger$ and a decrease in $\Delta S^\ddagger$; similar parameters were obtained for cyclopent-1-en-1-yl and cyclooct-1-en-1-yl triflate which accounts for their comparable rates of reaction. The oxidative addition of the cyclohex-1-en-1-yl triflate substrate has a somewhat larger entropy of activation.

Table 4.3. Activation parameters and k_{rel} obtained for vinyl triflates.

Triflate	ΔH (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)	k_{rel}
Cyclohept-1-en-1-yl	14	-26	0.54
Cyclopent-1-en-1-yl	17	-18	0.39
Cyclooct-1-en-1-yl	17	-20	0.32
Cyclohex-1-en-1-yl	21	-9	0.034

Aryl

In general, the oxidative addition reactions of vinyl substrates were found to be faster than those of aryl substrates due to the favourable binding of the alkenes as shown in Scheme 4.14. A series of aryl triflates were synthesized; an excess of each of these substrates was added to [Ni(COD)(dppf)] (**1**) and the reactions were monitored using ³¹P{¹H} NMR spectroscopy. The rate constants for these reactions are provided in Table 4.4 and a reactivity series in Scheme 4.15. The use of naphthalenyl triflates, in a similar vein to 3,4-dihydronaphthalenyl substrates, led to an increase in the rate of reaction when compared to phenyl triflate, which was attributed to an increase binding affinity.²³⁹ As expected due to ring-walking, a process where the nickel centre (with a high binding affinity to ketones) initially binds to the ketone before ‘walking’ around a conjugated system to the site of oxidative addition, the acetophenone triflate reacted rapidly with [Ni(COD)(dppf)] (**1**).^{76,77}



Scheme 4.15. Reactivity scale for aryl triflates.

Table 4.4. Rate constants for reactions of [Ni(COD)(dppf)] (**1**) with 20 equivalents of aryl triflates at 283 – 343 K. Reactions were performed in benzene- d_6 (below 343 K) and toluene- d_8 (at 343 K). Reactions were performed out in duplicate with average rate constants quoted here; all rate constants can be found in the Supporting Information.

Triflate	T (K)	k_{obs}	k_{rel}
Naphthalen-2-yl	283	$3.4(1) \times 10^{-3}$	1
4-Acetylphenyl	293	$3.7(1) \times 10^{-3}$	0.40
Naphthalen-1-yl	293	$3.3(1) \times 10^{-3}$	0.36
3-(Trifluoromethyl)phenyl	283	$3.2(2) \times 10^{-4}$	0.094
	293	$8.5(8) \times 10^{-4}$	
Pyridin-2-yl	293	$9.50(2) \times 10^{-4}$	0.010
3-Methoxyphenyl	293	$9.9(2) \times 10^{-5}$	0.011
	323	$6.5(5) \times 10^{-4}$	
Phenyl	323	$4.0(1) \times 10^{-4}$	6.6×10^{-3}
3-Fluorophenyl	323	$3.4(4) \times 10^{-3}$	5.6×10^{-3}
4-Methylester	323	$1.5(2) \times 10^{-4}$	2.5×10^{-3}
	343	$1.8(1) \times 10^{-3}$	
<i>m</i> -Tolyl	343	$1.2(1) \times 10^{-3}$	2.5×10^{-4}
<i>o</i> -Tolyl	343	$1.1(1) \times 10^{-3}$	2.3×10^{-4}
4-Methoxyphenyl	343	$8.3(4) \times 10^{-4}$	1.7×10^{-4}
4-(Trifluoromethyl)phenyl	343	$6.56(1) \times 10^{-4}$	1.4×10^{-4}
<i>p</i> -Tolyl	343	$5.4(1) \times 10^{-4}$	1.1×10^{-4}

A series of *para*- and *meta*- substituted aryl triflates were synthesised for oxidative addition studies with $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**). A Hammett analysis was carried out using the rate data for substrates with the following substituents: *p*-CF₃, *p*-OMe, *p*-Me, *p*-COOMe, *m*-F and *m*-OMe. The resultant plot (Figure 4.3) has two distinct regions; for electron-rich substrates the reaction constant $\rho = 3.0$ while the opposite trend is observed for electron-poor substrates ($\rho = 6.7$). This is consistent with a change in rate-determining step as with our previous study on the oxidative addition of pseudo-halides to $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**), however gradients for ArCl substrates are much shallower than this ($\rho = 1.2$).⁷⁴ We propose that for electron-rich substrates, the rate-determining step is displacement of COD whereas, for electron-poor substrates (when displacement of COD occurs more readily) the rate-determining step is oxidative addition. It was confirmed in our previous study⁷⁴ that electron-rich substrates are more sensitive to the addition of COD than electron-poor substrates, supporting a change in rate-determining step.

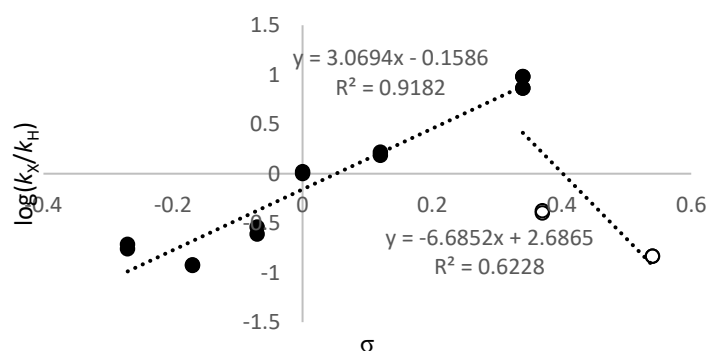


Figure 4.3. Hammett treatment for the oxidative addition of various *para*- and *meta*-substituted aryl triflates (0.44 mol L⁻¹) to $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) (22.2 mmol L⁻¹) in C₆D₆, 323 – 343 K (depending on substrate). Each experiment was performed twice and each duplicate is plotted as an individual point.

Activation parameters were also obtained for phenyl triflate (Figure 4.2): $\Delta H^\ddagger = 21 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -9 \text{ cal mol}^{-1} \text{ K}^{-1}$. Identical values were obtained for cyclohex-1-en-1-yl triflate and this is reflected in the similar rate constants obtained in kinetic experiments with these substrates ($1.4(2) \times 10^{-4} \text{ s}^{-1}$ for phenyl and $4.0(1) \times 10^{-4} \text{ s}^{-1}$ for cyclohex-1-en-1-yl at 323 K). This further supports the inability of cyclohex-1-en-1-yl triflate to effectively displace COD prior to oxidative addition.

4.4.2. DFT Calculations

We have previously optimised DFT calculations for systems involving $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**),⁷⁵ therefore, data reported here was obtained using the same level of theory. All calculations were performed using Gaussian16 (Rev. C.03) software. Geometries were optimised using the B3LYP functional with Grimme D3 corrections, with no solvation model, with the 6-31G(d) basis set for all atoms except Ni and Fe, for which LANL2TZ(f) was used. Energies were refined using single points at the M06/6-311+G(d,p) level of theory in benzene solvent (SMD model).

The conformations of the cycloalkenes were considered carefully. The cyclopent-1-en-1-yl triflate adopts an envelope conformation. The cyclohex-1-en-1-yl triflate substrate might adopt a chair or a boat conformation, but only the former could be located. The cyclohept-1-en-1-yl triflate substrate can adopt chair or boat conformations, while cyclooct-1-en-1-yl triflate can adopt four different conformations;²⁴⁰ pathways for each of these conformers were examined to identify the lowest energy pathway for each substrate.

Free energy profiles for the reactions of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with cyclohept-1-en-1-yl triflate and phenyl triflate are provided in Figure 4.4; data is provided in Table 4.5 and 4.6 for other aryl and vinyl triflates where DFT calculations were carried out.

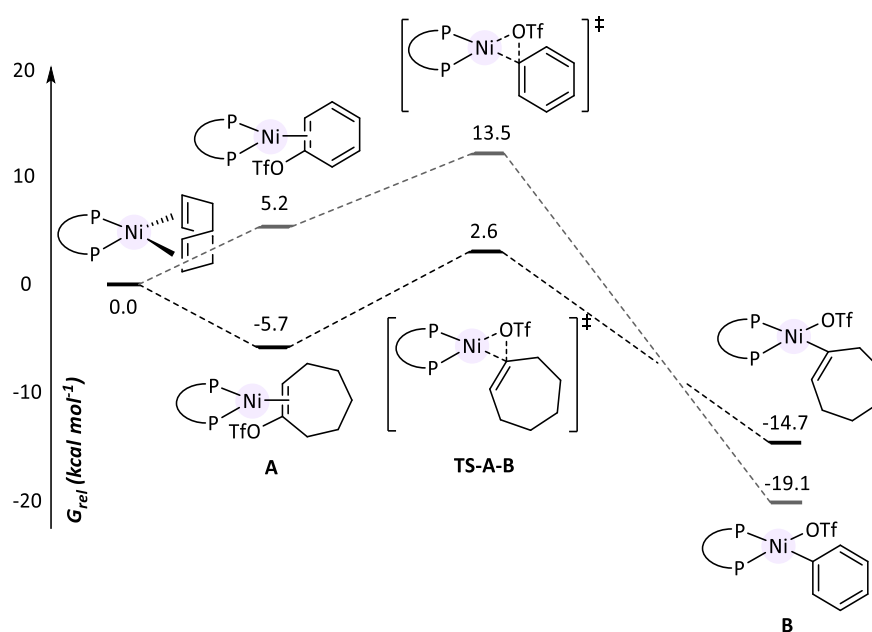


Figure 4.4. Free energy profiles for the reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) with cyclohept-1-en-1-yl triflate (black) and phenyl triflate (grey).

The DFT data highlight the major differences in reactivity when comparing aryl and vinyl triflates. As previously shown experimentally (Scheme 4.14), displacement of COD with vinyl triflates (except for cyclohex-1-en-1-yl triflate) to form the corresponding η^2 -complex is exergonic (-6.1 to -11.8 kcal/mol) compared to an endergonic reaction with phenyl triflate (5.2 kcal/mol). Incorporation of a fused aryl ring to phenyl triflate makes formation of the η^2 complex favourable (-0.6 kcal/mol for naphthalen-2-yl and -0.5 kcal/mol for naphthalen-1-yl triflate). Similarly, with the incorporation of a fused phenyl ring on cyclohex-1-en-1-yl triflate (3,4-dihydronaphthalen-1-yl triflate), the displacement of COD becomes more exergonic (-5.0 to -7.4 kcal/mol). The use of 3,4-dihydronaphthalen-2-yl triflate further decreases the barrier for formation of the η^2 -complex, in agreement with the experimentally observed k_{rel} .

Three-centred transition states for oxidative addition were found to be lower in energy for vinyl triflates (0.3 – 6.7 kcal/mol) than aryl triflates (9.2 – 13.5 kcal/mol), further supporting the observed higher rate of reaction. Five-centre transition states were located for aryl triflates but were higher in energy, e.g. 14.4 kcal/mol vs 13.5 kcal/mol for phenyl triflate. Further work is currently underway to investigate five-centered transition states for the vinyl halide substrates.

DFT calculations for cyclohex-1-en-1-yl triflate do not account for the low rate of reaction observed as formation of the η^2 complex was found to be exergonic (-5.0 kcal/mol). However, experimentally it has been shown that cyclohexene is unable to displace COD, in contrast to other cycloalkenes.

Table 4.5. Free energies for the reaction of aryl triflates relative to [Ni(COD)(dppf)] (**1**).

Geometries obtained at the B3LYP-D3/6-31G(d)+LANL2TZ(f) level of theory and energies obtained at the M06/6-311+G(d,p), SMD(benzene) level of theory.

Triflate	k_{rel}	G_{rel} (kcal/mol)		
		A	TS-A-B (3c)	B
Naphthalen-2-yl	1	-0.6	9.2	-19.3
Naphthalen-1-yl	0.46	-0.5	9.2	-23.1

Table 4.6. Free energies for the reaction of vinyl triflates relative to [Ni(COD)(dppf)] (**1**). Geometries obtained at the B3LYP-D3/6-31G(d)+LANL2DZdp+LANL2TZf and energies obtained at the M06/6-311+G(d,p), SMD(benzene) level of theory.

Triflate	k_{rel}	G_{rel} (kcal/mol)		
		A	TS-A-B (3c)	B
3,4-Dihydronaphthalen-2-yl	0.39	-11.8	1.4	-20.3
Cyclopent-1-en-1-yl	0.39	-6.4	6.7	-9.8
Cyclooct-1-en-1-yl	0.34	-6.1	0.3	-13.1
3,4-Dihydronaphthalen-1-yl	0.19	-7.4	4.8	-20.5
Cyclohex-1-en-1-yl	0.034	-5.0	3.0	-17.5

4.4.3. Catalysis

Both vinyl and aryl triflates were employed in typical Kumada-Tamao-Corriu cross-couplings catalysed by [Ni(COD)(dppf)] (**1**) (Scheme 4.16). Only cross-coupled product was observed in these reactions; no homocoupling of the starting material was detected by GC-FID. Particularly in the case of cyclopent-1-en-1-yl triflate (it may also occur with other vinyl substrates but to a lesser extent), product may be lost due to cleavage of the C-OTf bond; however, cyclopentene is too volatile to be observed in the GC.

$$\text{R-OTf} \xrightarrow[\text{THF, 85 } ^\circ\text{C, 24 h}]{\text{Ni(COD)(dppf) (5 mol\%), PhMgCl (1.1 equiv.)}} \text{R-Ph}$$

Triflate	Unreacted Triflate (%)	Cross-Coupled Product (%)
Cyclopent-1-en-1-yl	5	50
Cyclohex-1-en-1-yl	0	85
Cyclohept-1-en-1-yl	0	87
Cyclooct-1-en-1-yl	0	96
4-(Trifluoromethyl)phenyl	10	79

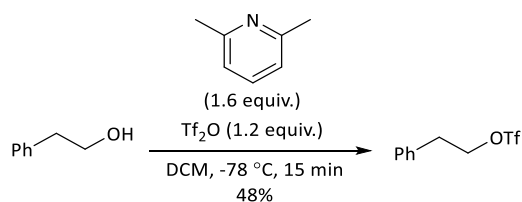
Scheme 4.16. Kumada-Tamao-Corriu cross-coupling reactions. Conducted with 0.25 mmol triflate, 5 mol% [Ni(COD)(dppf)] (**1**) and 1.1 equivalents of PhMgCl in 1 mL THF. All reactions were carried out in duplicate and can be found in the Supplementary Information.

4.5. Extended Discussion

4.5.1. Synthesis of Other Triflates

Alkyl

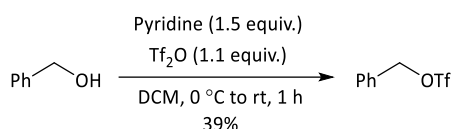
A sample of 2-phenylethyl triflate was prepared according to a literature procedure (Scheme 4.17).²⁴¹ However, heating a sample of triflate in C₆D₆ in an NMR tube at 70 °C led to decomposition of the triflate, therefore, rate data could not be obtained.



Scheme 4.17. Synthesis of 2-phenylethyl triflate from 2-phenylethanol.

Benzyl

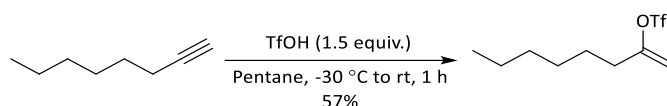
Benzyl triflate was synthesised from benzyl alcohol according to a literature procedure (Scheme 4.18).²⁴² The addition of benzyl triflate to a sample of [Ni(COD)(dppf)] (**1**) at room temperature gave an immediate colour change (from orange to green) indicative of formation of Ni^{II}, suggesting impurities within the sample of benzyl triflate, and so rate data was not collected.



Scheme 4.18. Synthesis of benzyl triflate from benzyl alcohol.

Acyclic

Attempts to synthesise sufficiently clean samples of acyclic vinyl triflates were unsuccessful. The most promising preparation was of 2-octenyl triflate, synthesised following a literature preparation (Scheme 4.19).²⁴³ Rate data obtained for this substrate (when 20 equivalents was added to [Ni(COD)(dppf)] (**1**)) was zero-order with respect to [Ni(COD)(dppf)] (**1**). GC-MS analysis of 2-octenyl triflate showed trace amounts of starting alkyne remaining in the product. Displacement of COD with alkyne before oxidative addition explains the zero-order dependence on [Ni(COD)(dppf)] (**1**) observed. Therefore, suitable rate data could not be obtained for 2-octenyl triflate to allow comparison with the other substrates.



Scheme 4.19. Synthesis of 2-octenyl triflate from 1-octyne.

4.5.2. Pyridin-2-yl Triflate

Oxidative Addition

The corresponding triflate was synthesised from 2-hydroxypyridine and reacted with [Ni(COD)(dppf)] (**1**) in a kinetic experiment. A 26-fold rate enhancement was observed for pyridine-2-yl triflate when compared to phenyl triflate (Table 4.7).

Table 4.7. Rate data for the oxidative addition of pyridin-2-yl triflate to [Ni(COD)(dppf)] (**1**) in comparison with other triflates used in this study.

Triflate	T (K)	k_{obs}	k_{rel}
Naphthalen-2-yl	283	$3.4(1) \times 10^{-3}$	1
3-(Trifluoromethyl)phenyl	293	$8.5(8) \times 10^{-3}$	0.53
4-Acetylphenyl	293	$3.7(1) \times 10^{-3}$	0.52
Naphthalen-1-yl	293	$3.3(1) \times 10^{-3}$	0.46
Pyridin-2-yl	293	$9.50(2) \times 10^{-4}$	0.13
3-Methoxyphenyl	323	$6.5(5) \times 10^{-4}$	0.008
Phenyl	323	$4.0(1) \times 10^{-4}$	0.005

A crystal structure was obtained after oxidative addition of pyridin-2-yl triflate to [Ni(COD)(dppf)] (**1**) (Figure 4.5), where the nickel centre is bound to the nitrogen and adjacent carbon which an outsphere triflate present. A scaled-up reaction confirmed that the major product from this reaction is that shown in Figure 4.5.

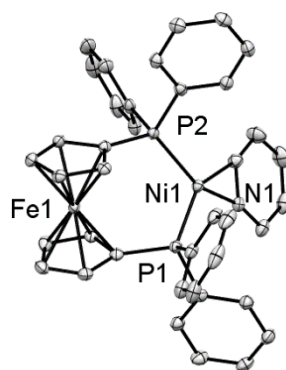


Figure 4.5. Crystal structure obtained from the reaction of [Ni(COD)(dppf)] (**1**) and pyridine-2-yl triflate.

Similar crystal structures were obtained by Rull *et al.* in the reaction of (IⁱPr)Ni⁰ pre-catalysts with 2-chloropyridines, where the chloride remains bound to the nickel centre (Figure 4.6).²⁴⁴

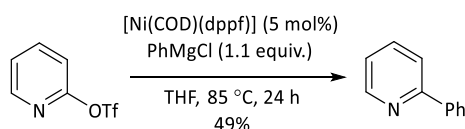


Figure 4.6. Crystal structure obtained from the reaction of [(IⁱPr)Ni(η⁶-toluene)] and 2-chloro-6-*tert*-butylpyridine.²⁴⁴

This work will be included in a larger study of reactions of pyridine substrates with [Ni(COD)(dppf)] (**1**).

Cross-coupling Reaction

Conversion of pyridin-2-yl triflate in Kumada-Tamao-Corriu cross-couplings was moderate when compared to the cross-coupling of other vinyl and aryl triflates (Scheme 4.20). This is thought to be due to a more difficult transmetalation step due to the oxidative addition product (Figure 4.5).



Scheme 4.20. Cross-coupling of pyridin-2-yl triflate with PhMgCl.

4.5.3. Other Electrophiles

The phenyl tosylate, mesylate and nonaflate were synthesised following literature procedures from phenol.^{74,245,246} The substrates were reacted in excess with [Ni(COD)(dppf)] (**1**) and kinetic data was obtained (Table 4.8).

Table 4.8. Rate of oxidative addition of various phenyl substrates to [Ni(COD)(dppf)] (**1**) at 333 K in C₆D₆.

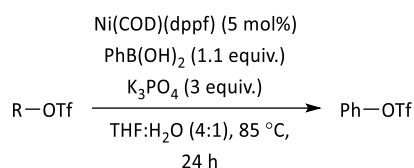
Substrate	k_{obs} (s ⁻¹)
-----------	-------------------------------------

Phenyl triflate	$1.3(1) \times 10^{-3}$
Phenyl nonaflate	$1.45(2) \times 10^{-3}$
Phenyl tosylate	$9.38(1) \times 10^{-4}$
Phenyl mesylate	$9.5(4) \times 10^{-4}$

A slight enhanced rate was observed for phenyl triflate and nonaflate *versus* phenyl tosylate and mesylate thought to be due to incorporation of fluorine in triflate and nonaflate functional groups.

4.5.4. Cross-Coupling Reactions

Suzuki-Miyaura cross-coupling reactions were initially carried out in this study and a difference in reactivity was observed between aryl and vinyl triflates. Aryl triflates converted to product well under standard Suzuki-Miyaura conditions (Scheme 4.21), whereas vinyl triflates showed no conversion.



Scheme 4.21. Suzuki-Miyaura cross-coupling conditions used in this study.

Upon addition of a halide source, tetrabutylammonium iodide (TBAI), low levels of conversion of vinyl triflate to product were observed (Table 4.9). Overall, results obtained from Suzuki-Miyaura cross-coupling reactions were somewhat irreproducible which initiated a change to Kumada-Tamao-Corriu couplings. Kumada-Tamao-Corriu are also more convenient cross-coupling reactions for following with ^{31}P NMR spectroscopy if required, due to the homogeneous nature of the reactions.

Table 4.9. Results from multiple repeats of Suzuki-Miyaura cross-couplings.

Triflate	Conversion to Product (%)			
	Run 1	Run 2	Run 3	Run 4

<i>p</i> -CF ₃ phenyl	61	77	31	33
Cyclopentyl	6	8	3	4

As the addition of a halide source (TBAI) did increase conversion of vinyl triflates, this may suggest that the triflate is too weakly coordinating for transmetalation to be successful. Reproducibility may be attributed to the amount of variables in a Suzuki-Miyaura cross-coupling reactions and the lack of robustness observed with nickel complexes (as previously eluded to). A full study into the optimisation (DOE, design of experiments) of these reactions may help increase conversion of vinyl triflates in Suzuki reactions.

4.6. Conclusions

We have conducted a comprehensive study of the reaction of vinyl and aryl triflates with [Ni(COD)(dppf)] (**1**) and can propose an mechanism for oxidative addition. We propose an initial η^2 complex, where COD is displaced by the organotriflate substrate prior to oxidative addition, which subsequently proceeds through a three-centered transition state; further investigation is required to understand if and when a five-centre transition state may be more favourable. The enhanced reactivity of vinyl triflates compared to aryl triflates is due to a favorable formation of η^2 complexes in the case of vinyl triflates, as shown experimentally and *via* DFT calculations.

[Ni(COD)(dppf)] (**1**) has been shown to be a competent catalyst in Kumada-Tamao-Corriu cross-coupling reactions, with good conversion for vinyl and aryl triflates. Loss of product is observed in the case of cyclopent-1-en-1-yl triflate, which is thought to be due to formation of cyclopentene which is too volatile to be analysed by GC.

Chapter 5 - Quantitative Assessment of Nickel(0) Precursors for Cross-Coupling Reactions

Drafted manuscript - *unpublished*

A drafted manuscript entitled 'Quantitative Assessment of Nickel(0) Precursors for Cross-Coupling Reactions' with an extended introduction prior to the article and an extended discussion after. The supporting information for this article can be found in the Chapter 7: Experimental.

Contributing authors to this manuscript and their roles are given below:

- Megan E. Greaves – Designed and performed experiments, analysed data, drafted initial manuscript
- Thomas O. Ronson – Helpful discussions as industrial supervisor
- Alan R. Kennedy – X-ray Crystallographer

- David J. Nelson – Principal Investigator

5.1. Abstract from Manuscript

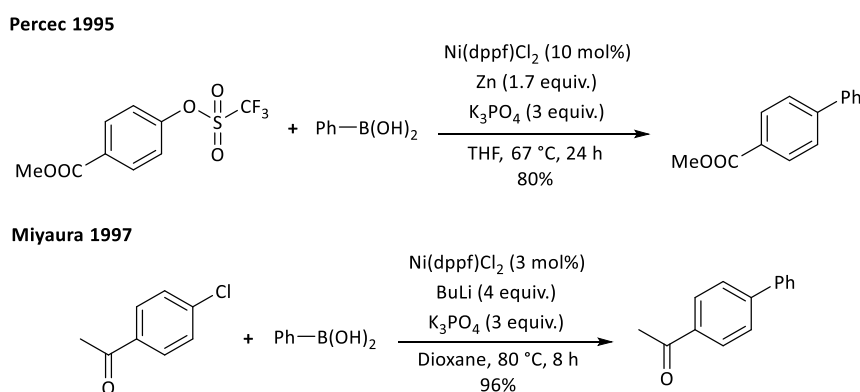
Several different $[\text{Ni}(\text{dppf})\text{L}]$ complexes have been synthesised through various methods. To determine the effect the ancillary ligand has on oxidative addition, these complexes have been reacted with an aryl halide and rate data obtained. The data collected during this study will prove vital in the choice of pre-catalysts used for catalytic reactions in the future.

5.2. Extended Introduction

Nickel sources typically come in two forms (Ni^{II} or Ni^0) and are typically derived from $[\text{NiCl}_2 \cdot x\text{H}_2\text{O}]$, $\text{Ni}(\text{OAc})_2$, or $[\text{Ni}(\text{COD})_2]$. Once functionalised with various ligands, Ni^{II} pre-catalysts then must typically undergo reduction to active Ni^0 species *in situ* to catalyse cross-coupling reactions.²⁴⁷ These pre-catalysts are bench stable and can be stored under air for months or even years. This advantage coupled with the low cost of $[\text{NiCl}_2 \cdot 6\text{H}_2\text{O}]$ (£37 per mol) means these are prevalent in the literature for carbon-carbon bond formation.²⁴⁸ These well-defined pre-catalysts can be employed to carry out a variety transformations including but not limited to Suzuki-Miyaura cross-coupling reactions and C-H arylation.^{77,249} Many synthetic transformations rely on the use of $[\text{Ni}(\text{COD})_2]$ as the source of Ni^0 , as this is the most widely available and reliable commercially available Ni^0 source. As a result, it is used on a multi-tonne scale for the polymerisation of butadiene and ethylene.²⁵⁰ The lability of COD allows

for the relatively facile substitution of this ligand with other functionalised ligands such as phosphines or NHCs, enabling several transformations in catalytic systems. Having states this, there are significant drawbacks associated with $[\text{Ni}(\text{COD})_2]$. Most obvious is the extremely air-sensitive nature of this complex, meaning that all manipulations and storage of $[\text{Ni}(\text{COD})_2]$ require a glovebox and/or Schlenk techniques. The complex is also temperature sensitive and will degrade at ambient temperature in the solid state, and therefore requires to be stored in a glovebox freezer. This effectively restricts the use of this reagent to researchers with regular access to a glovebox with adjacent freezer and would make large scale reactions difficult in standard synthetic laboratories.

In the efforts to find catalysts that are air-stable to replace $[\text{Ni}(\text{COD})_2]$, many different forms of Ni^{II} have been developed to do a variety of cross-coupling reactions.²⁵¹ To highlight one class of examples, $[\text{Ni}(\text{dppf})\text{X}_2]$ (where X = halide), have been developed from the mid-1990's to enable the coupling of aryl sulfonates (Percec) and aryl chlorides (Miyaura) with aryl boronic acids (Scheme 5.1).^{252,253} In these cases, zinc or butyllithium was used as the reductant to generate the active Ni^0 species. This then creates a new issue: the generation of the Ni^0 active species can take several steps in some cases and the side products generated in doing so can then be problematic under reaction conditions.²⁵¹

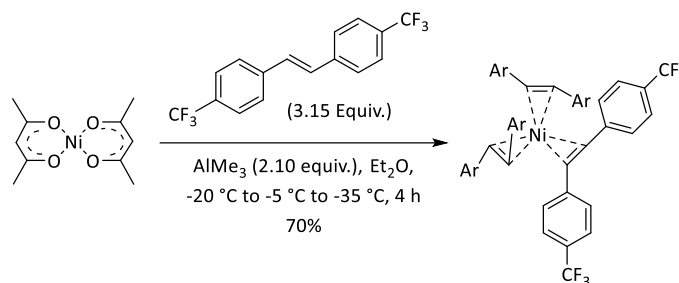


Scheme 5.1. Advances in developing air-stable alternatives to $[\text{Ni}(\text{COD})_2]$ during the 1990's.^{252,253}

5.2.1. $[\text{Ni}(\text{Fstb})_3]$

Structure, Synthesis and Stability

Cornella developed a 16-electron Ni^0 -olefin complex, $[\text{Ni}(\text{}^{\text{F}}\text{stb})_3]$ ($\text{}^{\text{F}}\text{stb}$ = (*E*)-4,4'-bis(trifluoromethyl)stilbene). In contrast to other Ni^0 sources, it is air-stable for months without decomposition (in the solid state).¹² It can be synthesised from $[\text{Ni}(\text{COD})_2]$ and $\text{}^{\text{F}}\text{stb}$ giving a moderate yield of 46% but this does not eliminate the need to use the air-sensitive $[\text{Ni}(\text{COD})_2]$ compound. Alternatively, it can be made from the reduction of $\text{Ni}(\text{acac})_2$ (air stable and inexpensive) in the presence of $\text{}^{\text{F}}\text{stb}$ to give the desired complex in a higher 70% yield and can be made on a >20 g scale (Scheme 5.2). The resulting complex is stable in the freezer under air for several months. However, it can only be manipulated at ambient temperature for days before degradation is observed and therefore is stored at $-18\text{ }^\circ\text{C}$.¹²



Scheme 5.2. Synthesis of $[\text{Ni}(\text{}^{\text{F}}\text{stb})_3]$ from reduction of air-stable $[\text{Ni}(\text{acac})_2]$ in the presence of $\text{}^{\text{F}}\text{stb}$.¹²

The structure of the $[\text{Ni}(\text{}^{\text{F}}\text{stb})_3]$ was confirmed *via* X-ray crystallography and showed a distorted trigonal planar geometry with the phenyl rings on the $\text{}^{\text{F}}\text{stb}$ in a staggered orientation (Figure 5.1). The elongated alkene bond in $[\text{Ni}(\text{}^{\text{F}}\text{stb})_3]$ confirm backbonding as observed in $[\text{Ni}(\text{COD})_2]$.¹²

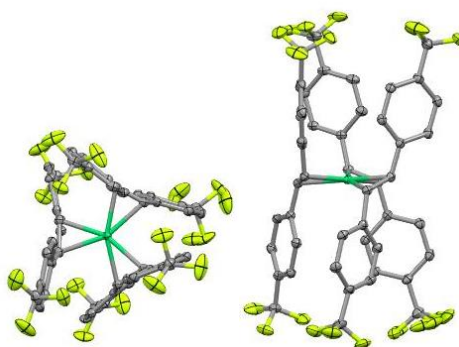
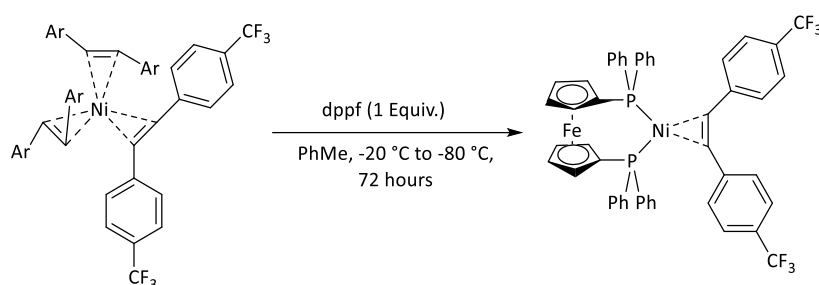


Figure 5.1. Crystal structure of $[\text{Ni}(\text{}^{\text{F}}\text{stb})_3]$.¹²

Ligand Exchange

Due to the 16-electron count of $[\text{Ni}(\text{Fstb})_3]$, ligand exchange is facile with a number of ligands regularly used in nickel catalysed reactions including phosphines and amines. Taking dppf as an example, $[\text{Ni}(\text{Fstb})_3]$ can be dissolved with dppf in toluene and the bisphosphine ligand displaces two of the Fstb ligands. The resultant complex, $[\text{Ni}(\text{Fstb})(\text{dppf})]$, crystallises from solution which enables isolation (Scheme 5.3). However, due to the rapid dissociation of Fstb from $[\text{Ni}(\text{Fstb})_3]$ in solution, reactions with other ligands are typically performed at $-80\text{ }^\circ\text{C}$ and held at these low temperatures for several days (requiring specialist equipment).¹²



Scheme 5.3. Synthesis of $[\text{Ni}(\text{dppf})(\text{Fstb})]$.¹²

In contrast to $[\text{Ni}(\text{COD})(\text{dppf})]$, $[\text{Ni}(\text{dppf})(\text{Fstb})]$, has all electron density from the Ni^0 delocalised onto one carbon-carbon double bond, as evident from the elongated bond in the Fstb in the crystal structure (Figure 5.2). $[\text{Ni}(\text{COD})(\text{dppf})]$ has a different electron count and tetrahedral geometry in contrast to $[\text{Ni}(\text{dppf})(\text{Fstb})]$; 16-electrons and trigonal planar. Similar results were observed when using bipy or PPh_3 for ligand exchange.¹²

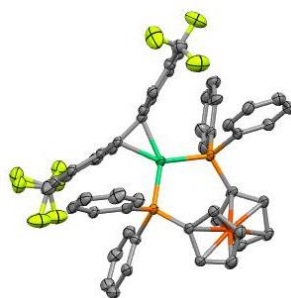
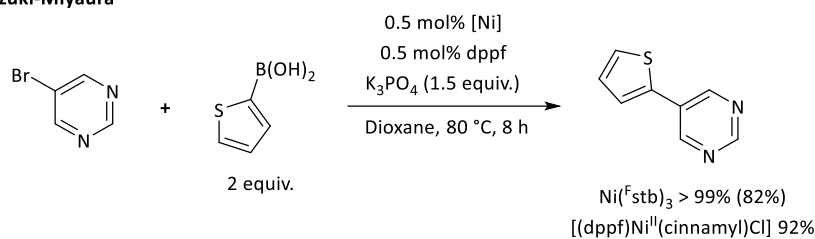


Figure 5.2. Crystal structure of $[\text{Ni}(\text{dppf})(\text{Fstb})]$.¹²

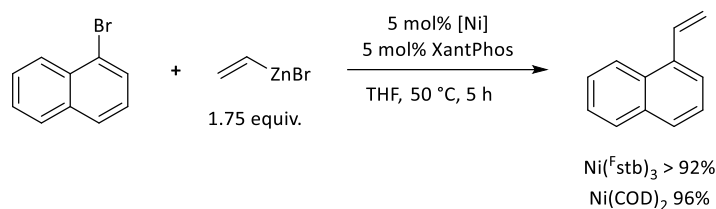
Catalytic Properties

The catalytic properties of $[\text{Ni}(\text{Fstb})_3]$ were also investigated; Cornella and his team compared this complex to traditional nickel sources including Ni^{II} pre-catalysts and $[\text{Ni}(\text{COD})_2]$. Several examples of different transformations were investigated and these included Suzuki-Miyaura, Negishi, Buchwald-Hartwig, Heck and Kumada-Corriu-Tamao cross-coupling reactions. A priority of this work was the Suzuki-Miyaura cross-coupling reaction due to its abundant use in the chemical industry.²⁵⁴ As these reactions often employ Ni^{II} pre-catalysts due to their bench-stable nature, $[\text{Ni}(\text{Fstb})_3]$ carried out the same transformation and results were compared to the analogous $[(\text{dppf})\text{Ni}(\text{cinnamyl})\text{Cl}]$ pre-catalyst (Scheme 5.4).²⁵⁵ $[\text{Ni}(\text{Fstb})_3]$ was found to have competitive activity to the Ni^{II} precursor (92%), with an almost quantitative conversion and a high isolated yield of 82%.¹² It is noteworthy that this cross-coupling reaction was carried out with a sample of $[\text{Ni}(\text{Fstb})_3]$ that had been kept under air and in a regular freezer for 6 months before being employed in this transformation, highlighting its unparalleled stability when compared to $[\text{Ni}(\text{COD})_2]$.¹² A Negishi cross-coupling reaction between 1-bromonaphthalene and vinylzinc bromide was also carried out using $[\text{Ni}(\text{Fstb})_3]$ with XantPhos as the additional ligand, to compare this to a $[\text{Ni}(\text{COD})_2]$ system (Scheme 5.4).²⁵⁶ Again, the yield of cross-coupled product was comparable at 92% conversion (measured using GC-FID analysis with an internal standard). It is evident from the extensive range of cross-coupling reactions carried out that $[\text{Ni}(\text{Fstb})_3]$ is a competitive catalyst that could eventually replace $\text{Ni}(\text{COD})_2$. $[\text{Ni}(\text{Fstb})_3]$ removes the need to choose between a catalyst that is air-stable (Ni^{II} pre-catalysts) or a formally Ni^0 catalyst.

Suzuki-Miyaura



Negishi



Scheme 5.4. Suzuki-Miyaura and Negishi cross-coupling reactions carried out with $[\text{Ni}(\text{F}^{\text{stb}})_3]$ and then compared to either a Ni^{II} pre-catalyst or $[\text{Ni}(\text{COD})_2]$. The value in brackets relates to isolated yield.^{12,255,256}

5.2.2. $[\text{Ni}(\text{tBu}^{\text{stb}})_3]$

Structure, Synthesis and Stability

To address the unstable nature of $[\text{Ni}(\text{F}^{\text{stb}})_3]$ in solution and at ambient temperatures, a second generation of nickel-stilbene complexes was reported by Cornella.²⁵⁷ The replacement of CF_3 groups with tBu groups on the stilbene yielded $[\text{Ni}(\text{tBu}^{\text{stb}})_3]$ (Figure 5.3) using the same synthetic method as for $[\text{Ni}(\text{F}^{\text{stb}})_3]$ (Scheme 5.3).

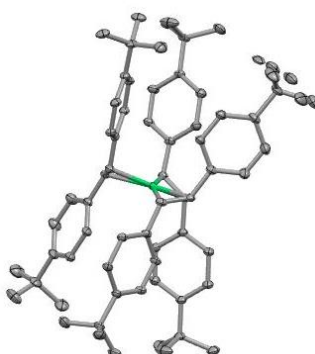
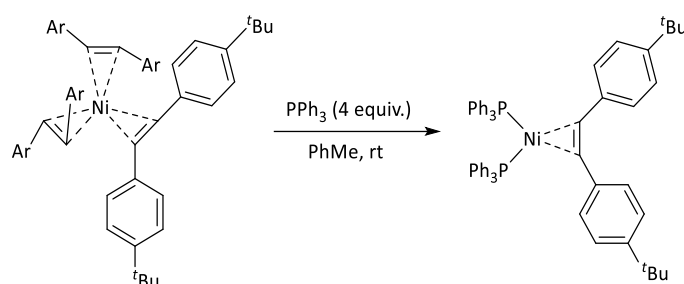


Figure 5.3. Crystal structure of $[\text{Ni}(\text{tBu}^{\text{stb}})_3]$.²⁵⁷

$[\text{Ni}(\text{tBu}\text{stb})_3]$ is remarkably stable to temperature, where degradation is only observed at 60 °C after 1 hour, meaning it can be stored under air on the benchtop (as opposed to -18 °C required for $[\text{Ni}(\text{Fstb})_3]$). The complex is also highly stable in solution with no decomposition observed in a variety of solvents.²⁵⁷

Ligand Exchange

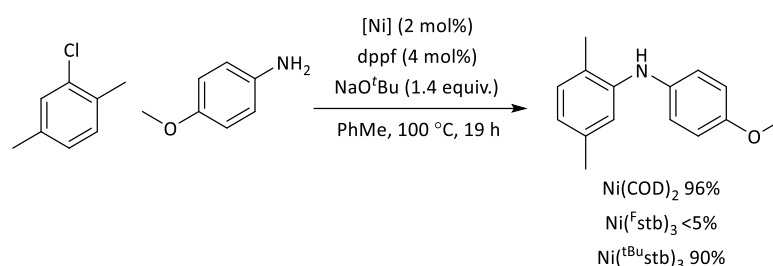
Addition of 4 equivalents of PPh_3 to $[\text{Ni}(\text{tBu}\text{stb})_3]$ afforded quantitative conversion to $[\text{Ni}(\text{tBu}\text{stb})(\text{PPh}_3)_2]$ (Scheme 5.5) as evidenced by equal concentrations of $[\text{Ni}(\text{tBu}\text{stb})(\text{PPh}_3)_2]$ and PPh_3 in the ^{31}P NMR spectra.



Scheme 5.5. Quantitative conversion of $[\text{Ni}(\text{tBu}\text{stb})_3]$ to $[\text{Ni}(\text{tBu}\text{stb})(\text{PPh}_3)_2]$ on addition of PPh_3 .

Catalytic Properties

The catalytic activity of $[\text{Ni}(\text{tBu}\text{stb})_3]$ combined with appropriate ligands was compared to both $[\text{Ni}(\text{COD})_2]$ and $[\text{Ni}(\text{Fstb})_3]$ in typical cross-coupling reactions and industrially relevant reactions.²⁵⁷ In examples where $[\text{Ni}(\text{Fstb})_3]$ had proved unsuccessful in the desired transformations, the more electron rich $[\text{Ni}(\text{tBu}\text{stb})_3]$ was employed and comparable conversions to $[\text{Ni}(\text{COD})_2]$ were observed (Scheme 5.6).



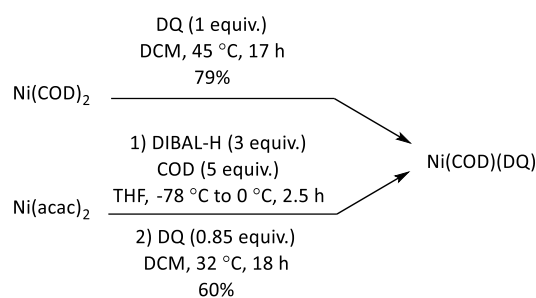
Scheme 5.6. Cross-coupling of 2-chloro-1,4-dimethylbenzene and *p*-anisidine catalysed by different Ni⁰ sources.²⁵⁷

5.2.3. [Ni(COD)(DQ)]

Structure, Synthesis and Stability

As early as the 1960's Ni⁰ complexes using duroquinone (DQ) as a ligand were being synthesised and their properties were being investigated.^{258,259} The earliest mention of such a complex was bis(duroquinone)nickel which was obtained as a crystalline red solid in a good yield. Remarkably, as a Ni⁰ source, it was air stable and stable under (non-oxidising) acidic conditions. In contrast to [Ni(^Fstb)₃], it was found to be stable at ambient temperature and decomposition was only observed when heated to 205 °C.²⁵⁸ Stress tests were also performed by Engle, which demonstrated the unusual stability of [Ni(COD)(DQ)]. Notably, this was stable on silica gel (using MeOH and DCM as eluent), highlighting the ease of purification.²⁶⁰

The optimal synthesis of [Ni(COD)(DQ)] is from [Ni(COD)₂] (79% yield). While synthesis from [Ni(acac)₂] is also possible, the yield is considerably lower (60%) and the first step is *in-situ* generation of [Ni(COD)₂] (Scheme 5.7). Although [Ni(COD)(DQ)] is an air-stable source of Ni⁰, the synthesis of this complex does not eliminate the drawbacks encountered with use of [Ni(COD)₂] as it is either used as a starting material or generated *in-situ*.



Scheme 5.7. Synthetic routes to $[\text{Ni(COD)(DQ)}]$.¹³

After the discovery of nickel-duroquinone complexes, in 1965, Dahl and Glick investigated the structure and bonding found in $[\text{Ni(COD)(DQ)}]$. They obtained crystals of $[\text{Ni(COD)(DQ)}]$ and were able to determine the molecular structure using X-ray crystallography (Figure 5.4(a)).²⁶¹ As expected, the nickel was sandwiched between a boat form of COD and DQ and the 2 sets of parallel double bonds in COD and DQ were found to be perpendicular. This resulted in a tetrahedral geometry at the nickel centre. Interestingly, it was also found that there was deformation of the carbonyl groups in DQ, as they were pointing away from the nickel centre; in contrast, the methyl groups were bent towards the nickel.²⁶¹ Engle confirmed these observations with a more recent crystal structure (Figure 5.4(b)). From the IR stretching frequency of 1553 cm^{-1} in $[\text{Ni(COD)(DQ)}]$ (free DQ = 1687 cm^{-1}), it was evident that π -backbonding from the nickel to DQ was in operation.²⁶⁰

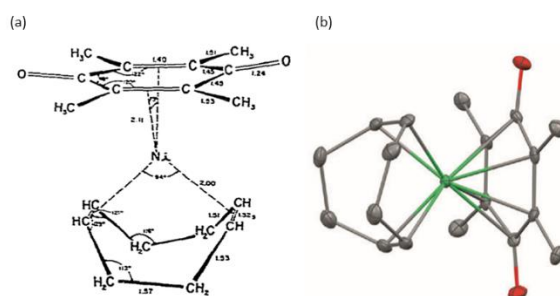
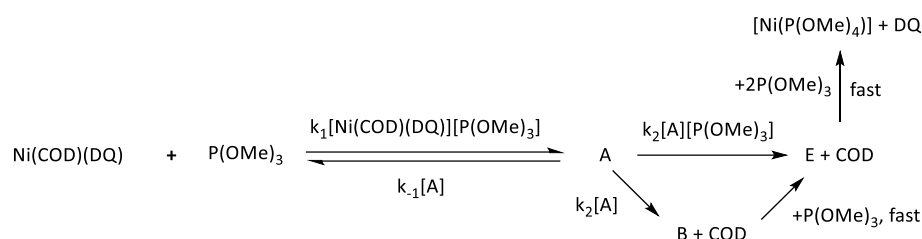


Figure 5.4. Crystal structures of Ni(COD)(DQ) . (a) Dahl and Glick 1965. (b) Engle 2020.^{260,261}

Ligand Exchange

IR spectroscopy was used to follow the displacement of COD with PBU_3 in $[\text{Ni}(\text{COD})(\text{DQ})]$ in hydrocarbon solvents.²⁶² $[\text{Ni}(\text{COD})(\text{DQ})]$ was characterised with a $\nu(\text{CO})$ of 1553 cm^{-1} . Over time, this peak disappeared with a simultaneous appearance of a peak at 1540 cm^{-1} , characterised as $[\text{Ni}(\text{PBU}_3)(\text{DQ})]$. There was a lack of free DQ due to the absence of a peak at 1687 cm^{-1} . The spectra remained unchanged over a 48 hour period.²⁶² This data proved that COD could be displaced with other ligands to form different Ni^0 complexes. This was also confirmed *via* ^1H spectroscopy, where the olefinic protons intensified over time to suggest liberation of free COD.²⁶² With the aim to gather kinetic data on this system *via* UV-Vis spectroscopy, the concentration was lowered (0.1 mM). However, degradation of $[\text{Ni}(\text{PBU}_3)(\text{DQ})]$ was observed, presumed to be due to the oxidation of the complex (due to its extreme air-sensitive nature) and therefore kinetic data was not reproducible and this study was abandoned.²⁶²

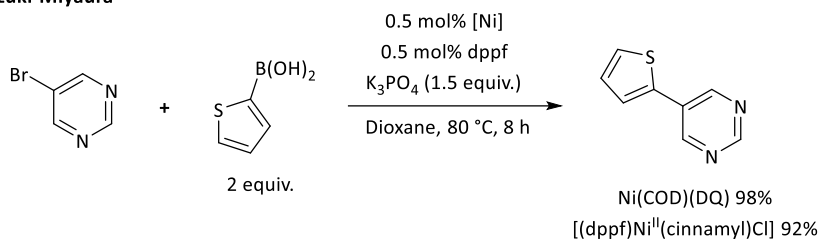
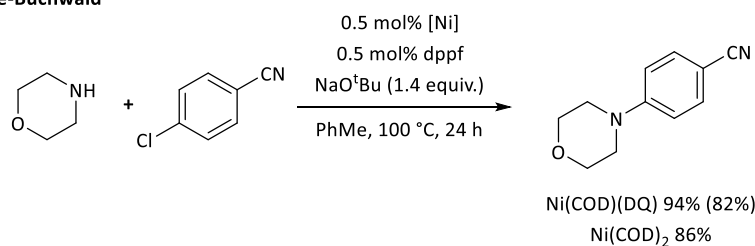
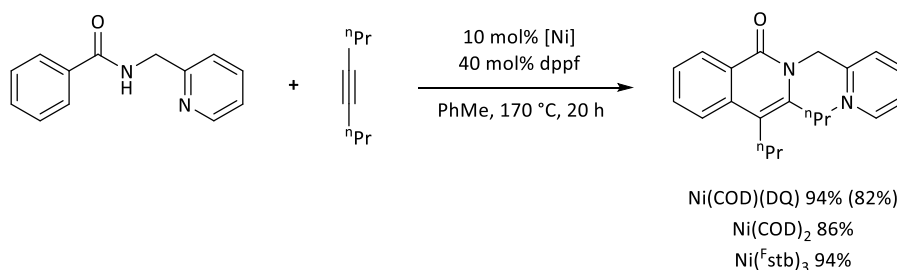
Attention then turned to using trimethylphosphite as an alternative ligand for these reactions to allow for the collection of kinetic data. These reactions showed no degradation of any products and showed the replacement of COD only, showing the olefin to be a better leaving group than DQ. It was found that the displacement of DQ was 20 times slower than the displacement of COD. Another interesting observation was difference in $\nu(\text{CO})$ between $[\text{Ni}(\text{COD})(\text{DQ})]$ (1553 cm^{-1}) and $[\text{Ni}(\text{DQ})_2]$ (1580 cm^{-1}), suggesting a more strongly bound DQ in $[\text{Ni}(\text{COD})(\text{DQ})]$.²⁶² Binding of the olefin to nickel was found to weaken on approach of the nucleophile and was found to have a high activation energy. The subsequent displacement of COD with the incoming nucleophile was found to be rapid and was not a rate-determining step.²⁶² The mechanism of the reaction between $[\text{Ni}(\text{COD})(\text{DQ})]$ and trimethylphosphite is given in Scheme 5.8. Intermediates are most likely to have the following structures: E, $[\text{Ni}(\text{DQ})(\text{P}(\text{OMe})_3)]$, A $[\text{Ni}(\text{COD})(\text{DQ})]$ (where the COD is bound in a mondentate fashion) and B unsaturated $[\text{Ni}(\text{DQ})(\text{P}(\text{OMe})_3)_2]$.



Scheme 5.8. Proposed mechanism for the reaction of [Ni(COD)(DQ)] with trimethylphosphite.²⁶²

Catalytic Properties

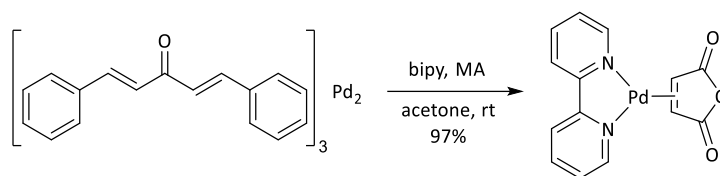
The catalytic activity of [Ni(COD)(DQ)] had not previously been investigated, Engle hypothesised a similar activity (to [Ni(COD)₂], [Ni(^Fstb)₃] or common Ni^{II} precatalysts) could be achieved with [Ni(COD)(DQ)] plus ligand (phosphines, NHCs or amines).²⁶⁰ To enable comparison to [Ni(^Fstb)₃], a Suzuki-Miyaura reaction was carried out under the same conditions (Scheme 5.9). [Ni(COD)(dppf)] was found to be as competent as [Ni(^Fstb)₃] and the original Ni^{II} pre-catalyst, giving almost quantitative conversions to product. Similarly, using [Ni(COD)(DQ)] as a pre-catalyst with dppf as a ligand in the amination of aryl chlorides gave excellent conversions, both inside and outside of the glovebox (Scheme 5.9).²⁶⁰ To challenge [Ni(COD)(DQ)] further, Engle carried out a C-H activation reaction, developed by Chatani, to compare to both [Ni(COD)₂] and [Ni(^Fstb)₃]. This newly developed area of nickel catalysed reactions still faces challenges and work is still underway to fully optimise these reactions. However, [Ni(COD)(DQ)] gave a comparable conversion to both [Ni(COD)₂] and [Ni(^Fstb)₃].^{12,260,263}

Suzuki-Miyaura**Wolfe-Buchwald****Chatani**

Scheme 5.9. Suzuki-Miyaura, Buchwald and C-H activation reactions carried out with [Ni(COD)(DQ)] and then compared to either a Ni^{II} pre-catalyst, [Ni(COD)₂] and [Ni(Fstb)₃]. The value in brackets relates to a repeat reaction using Schlenk techniques outside of the glovebox.^{255,260,263,264}

5.2.4. [DMPDAB-Pd-MAH]**Structure and Stability**

Palladium(II) precatalysts are often employed in cross-coupling reactions, and the Pd(0) active species is generated *insitu*, however multiple reduction pathways can lead to inactive Pd(I) or unreactive dimers.²⁶⁵ [Pd₂dba₃] (dba = dibenzylideneacetone) is a Pd(0) source commonly used in catalyst screening as it is air-stable and eliminates the requirement for an initial reduction step (Scheme 5.10).^{265–267} However, the resultant complexes, although stable in crystalline form under air were insoluble in common organic solvents, except chloroform in which degradation occurred.²⁶⁶



Scheme 5.10. Displacement of dba with 2,2-bipyridine (bipy) and maleic anhydride (MA) to form the corresponding Pd(0) complex.²⁶⁶

Use of $[\text{Pd}_2\text{dba}_3]$ as a Pd(0) source has limitations including poor solubility, has reproducibility issues and has been shown to decompose to palladium nanoparticles.²⁶⁵ As such, the Leitch group have reported a new Pd(0) precursor; $[\text{DMPDAB-Pd-MA}]$ (Figure 5.5) ($\text{DMPDAB} = \text{N,N'}$ -bis(2,6-dimethylphenyl)ethan-1,2-diimine).²⁶⁵ Several advantages are offered with $[\text{DMPDAB-Pd-MA}]$ when compared to $[\text{Pd}_2\text{dba}_3]$ including good solubility (in solvents including THF), solution stability (stable for 48 hours in THF, acetone and chloroform) and clean displacement of DMPDAB in the presence of catalytically relevant phosphine ligands (including dppf).²⁶⁵

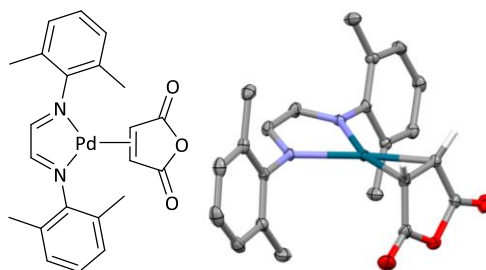
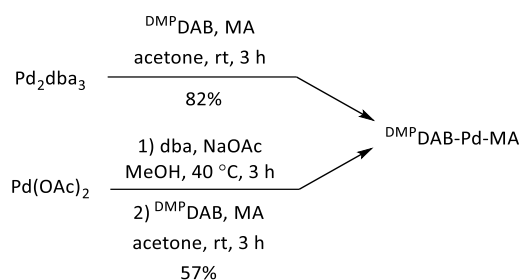


Figure 5.5. $[\text{DMPDAB-Pd-MA}]$.²⁶⁵

$[\text{DMPDAB-Pd-MA}]$ can be synthesised from either $[\text{Pd}_2\text{dba}_3]$ (250 mg scale, 82% yield) or $[\text{Pd}(\text{OAc})_2]$ (3.6 g scale, 57% yield) (Scheme 5.11). When synthesised via either method, the product is obtained as a red solid of high purity without the requirement for recrystallisation.²⁶⁵



Scheme 5.11. Synthetic routes to [DMPDAB-Pd-MA].²⁶⁵

Ligand Exchange

Stirring [DMPDAB-Pd-MA] with phosphine ligand (in THF) at ambient temperature for 1 hour gave full conversion to a single phosphine-containing species, [PR₃-Pd-MA]. Several examples including (but not limited to) complexes containing dppp, dppf (Figure 5.6), XantPhos, and BrettPhos were isolated in moderate to good yields and crystals suitable for X-Ray diffraction studies were obtained.²⁶⁵

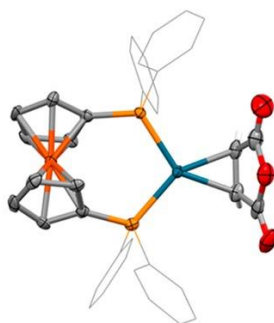
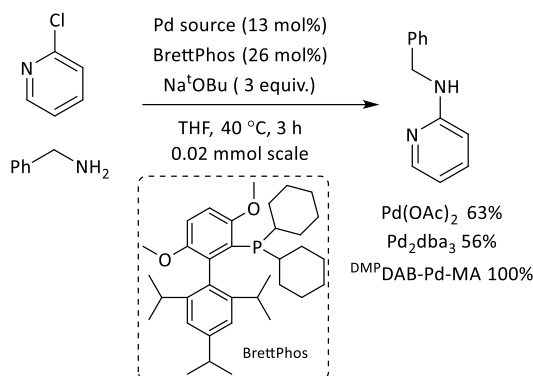


Figure 5.6. Crystal structure of [Pd(dppf)(MA)].²⁶⁵

Catalytic Properties

High throughput screens were carried out to access the effectiveness of [DMPDAB-Pd-MA] in catalytic reactions compared to other palladium sources.²⁶⁵ Six different screens were carried out to cover an array of C-N, C-C and C-O cross-coupling reactions employing 13 mol% of palladium and 26 mol% of phosphine ligand. Conversions were determined by HPLC (high-performance liquid chromatography). In a coupling of 2-chloropyridine and benzylamine (Scheme 5.12), [DMPDAB-Pd-MA] (plus BrettPhos) was a superior catalyst when compared to [Pd(OAc)₂] and [Pd₂dba₃]. A subsequent scaled-up reaction (4.5 mmol) was successfully

catalysed by 0.25 mol% [^{DMP}DAB-Pd-MA] and 0.5 mol% BrettPhos to give a 91% isolated yield.²⁶⁵



Scheme 5.12. Cross-coupling of 2-chloropyridine with benzylamine with different palladium sources.²⁶⁵

5.2.5. [Ni(dppf)(Ph₂CO)]

New methodology (unpublished) for the synthesis of [Ni(dppf)(Ph₂CO)] from [Ni(dppf)Cl₂] has been developed within the Nelson group.

5.3. Introduction from Manuscript

Nickel catalysis is an exciting area of modern synthetic organic chemistry and has received significant recent attention.¹¹⁶ Research in this area has focussed on developing new suites of reactions and new reactivity manifolds such as tandem photocatalysis/cross coupling^{268,269} and reductive electrophile coupling.¹⁰¹ While some reactions are conducted using a nickel(II) source such as [NiX₂(DME)] or [NiCl(*o*-tol)(TMEDA)]^{270,271} and a ligand, or using well-defined pre-catalysts such as [NiCl(Ar)(PR₃)₂] or [NiCl(Ar)(bisphosphine)]²⁷², a very large number of reactions rely on the *in situ* formation of an active catalyst from [Ni(COD)₂] and free ligand. The reliance of this chemistry on [Ni(COD)₂] inevitably introduces a number of limitations. [Ni(COD)₂] is expensive, being approximately half the cost of PdCl₂ (per mol), is thermally unstable and oxidises readily in air, even in the solid state. The release of one equivalent of COD can also decrease the rate of reaction as COD will compete with the reaction substrate for coordination to the metal centre.¹³¹ These limitations make it difficult for non-specialists

– most of whom will not have ready access to a glovebox – to deploy this chemistry, and increases the cost and complexity of industrial-scale applications of nickel catalysis.

Two research groups have made advances in overcoming this key limitation of nickel catalysis by preparing, characterising, and testing alternative sources of nickel(0). Nattman *et al.* prepared $[\text{Ni}(\text{Fstb})_3]$ ($\text{Fstb} = (E)\text{-4,4'-bis(trifluoromethyl)stilbene}$) which is a formally Ni^0 16-electron complex that is air-stable in the solid state but decomposes at room temperature in solution, even under anaerobic conditions; it was shown that different classes of ligand readily react with this precursor to form $[\text{Ni}(\text{L})(\text{Fstb})]$ species. A second generation of 16-electron complex, $[\text{Ni}(\text{tBuStb})_3]$ ($\text{tBuStb} = (E)\text{-4,4'-bis(tert-butyl)stilbene}$), was later developed by Nattman *et al.* and showed improved stability both in the solid state and in solution.²⁵⁷

In contrast, Tran *et al.* utilised $[\text{Ni}(\text{COD})(\eta^6\text{-DQ})]$ which is a formally Ni^0 18-electron complex that appears to show solution and solid state stability, but for which the coordination chemistry is relatively unexplored (DQ = duroquinone). Nickel(0) precursors would be expected to produce species that will feature on-cycle or off-cycle in the reactions for which they are used as a catalyst, and so we were motivated to explore the reactivity of these putative intermediates in a quantitative and qualitative fashion using dppf as a model ligand (dppf = 1,1'-bis(diphenylphosphino)ferrocene); here we document our studies of coordination chemistry and oxidative addition reactions to aryl halides using these new nickel(0) sources.

5.4. Results and Discussion from Manuscript

5.4.1. Synthesis and Characterisation of Complexes

A series of $[\text{Ni}(\text{dppf})(\text{L})]$ complexes were targeted for this work. We have worked extensively with $[\text{Ni}(\eta^2\text{-COD})(\text{dppf})]$, which is readily prepared from the reaction of $[\text{Ni}(\text{COD})_2]$ with one equivalent of dppf. $[\text{Ni}(\text{dppf})(\eta^2\text{-ethene})]$ was prepared from the reaction of a slurry of $[\text{Ni}(\eta^2\text{-COD})(\text{dppf})]$ in diethyl ether with an excess of ethene;²⁷³ ethene is a monodentate ligand that is capable of escaping the solution phase, although this process is not necessarily rapid,²⁷⁴ and so is included as an interesting comparison. Single crystal X-ray diffraction analysis confirmed the molecular structure of this species to be $[\text{Ni}(\text{dppf})(\eta^2\text{-ethene})]$ (Figure 5.7a).

The reactions of $[\text{Ni}(\eta^2\text{-Fstb})_3]$ have been explored using a series of prototypical ligands, including dppf, but for this work $[\text{Ni}(\text{dppf})(\eta^2\text{-Fstb})]$ and $[\text{Ni}(\text{dppf})(\eta^2\text{-tBuStb})]$ were

prepared from the reaction of $[\text{Ni}(\text{dppf})(\text{benzophenone})]$, MeMgCl and the corresponding stilbene ligand. All complexes were found to have analytical data consistent with the relevant literature reports and single crystal X-ray diffraction analysis confirmed the molecular structures of these species (Figure 5.7b and 5.7c).^{12,273}

In the case of $[\text{Ni}(\eta^2, \eta^2\text{-COD})(\eta^6\text{-DQ})]$, it was anticipated that reaction with dppf might form either $[\text{Ni}(\eta^2, \eta^2\text{-COD})(\text{dppf})]$ or $[\text{Ni}(\text{dppf})(\eta^6\text{-DQ})]$. Somewhat surprisingly, the reaction of this nickel precursor with 1 equiv. of dppf led to no reaction whatsoever at room temperature in benzene- d_6 , even over extended periods of time (12 h). The ligands are clearly very strongly bound, and so duroquinone was added to $[\text{Ni}(\eta^2, \eta^2\text{-COD})(\text{dppf})]$ to probe whether the issue was simply an equilibrium in favour of $[\text{Ni}(\text{COD})(\text{DQ})]$ plus dppf ; this reaction yielded a rapid colour change from yellow to dark red, and the singlet for $[\text{Ni}(\text{COD})(\text{dppf})]$ on the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum was replaced by two doublets, consistent with the formation of $[\text{Ni}(\text{dppf})(\eta^2(\text{CO})\text{-DQ})]$. Single crystals of the product were obtained by diffusion ($\text{C}_6\text{D}_6/\text{hexane}$), and single crystal X-ray diffraction analysis revealed the molecular structure of this species to be $[\text{Ni}(\text{dppf})(\eta^2(\text{CO})\text{-DQ})]$ (Figure 5.7d).

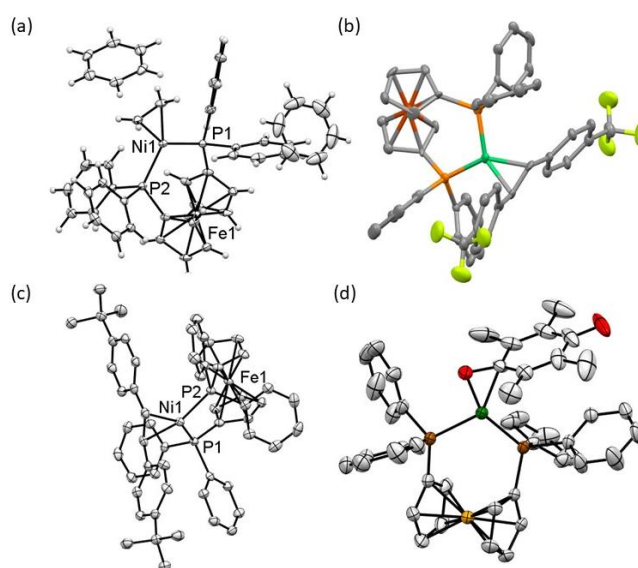


Figure 5.7. Crystal structures; (a) $[\text{Ni}(\text{dppf})(\eta^2\text{-ethene})]$, (b) $[\text{Ni}(\text{dppf})(\eta^2\text{-Fstb})]$, (c) $[\text{Ni}(\text{dppf})(\eta^2\text{-tBuStb})]$ and (d) $[\text{Ni}(\text{dppf})(\eta^2(\text{CO})\text{-DQ})]$.

5.4.2. Kinetic Experiments

[Ni(dppf)(ethene)] reacts with aryl halides in a reaction that is *pseudo*-first order with respect to nickel and first order in substrate (Figure 5.8). As expected (due to the favoured displacement of COD by ethene) the oxidative addition of 4-bromobenzotrifluoride (20 equivalents) is 5 times faster with [Ni(COD)(dppf)] when compared to [Ni(dppf)(ethene)].⁷⁴

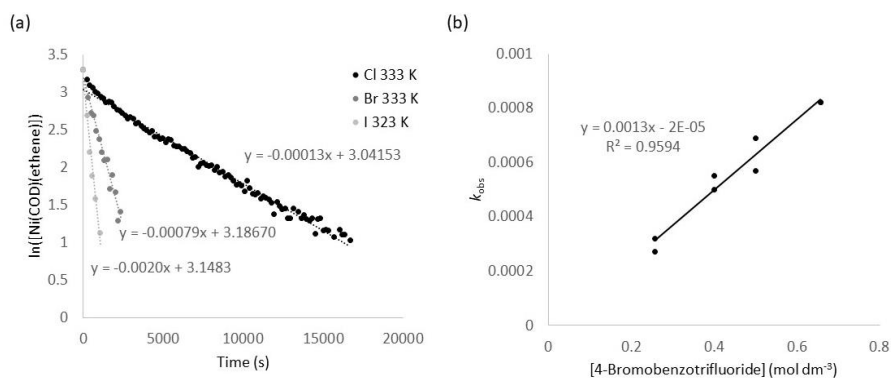


Figure 5.8. (a) Pseudo-first order plot for the reaction of [Ni(dppf)(ethene)] (27.1 mmol dm⁻³) with 4-iodo, 4-bromo and 4-chlorobenzotrifluoride (0.54 mol dm⁻³) in C₆D₆. (b) Plot of k_{obs} vs concentration of 4-bromobenzotrifluoride in the oxidative addition of substrate to [Ni(dppf)(ethene)] at 333 K in C₆D₆.

No reaction took place between [Ni(dppf)(DQ)] and 4-bromobenzotrifluoride after 4 hours at 70 °C. Reactions between [Ni(dppf)(^tstb)] and 4-bromobenzotrifluoride were irreproducible and shows deviation from first-order behaviour (Figure 5.9).

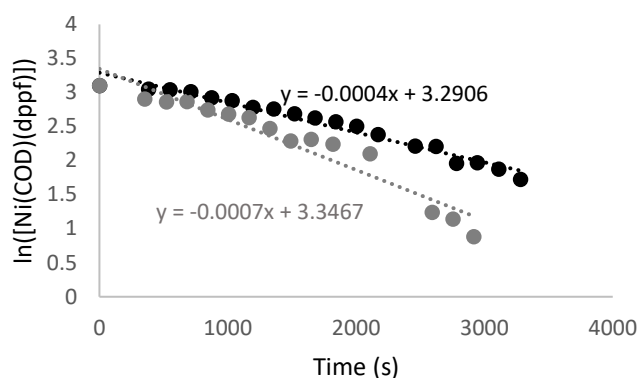


Figure 5.9. Plot of $\ln[\text{Ni}(\text{dppf})(^{\text{Fstb}})]$ vs time for the reaction of $[\text{Ni}(\text{dppf})(^{\text{Fstb}})]$ ($17.2 \text{ mmol dm}^{-3}$) with 4-bromobenzotrifluoride (0.34 mol dm^{-3}) at 343 K containing data from duplicate runs.

A crystalline sample of $[\text{Ni}(\text{dppf})(\text{Ph}_2\text{CO})]$ was isolated and reacted with 4-bromobenzotrifluoride, the reaction was *pseudo*-first order with respect to $[\text{Ni}(\text{dppf})(\text{Ph}_2\text{CO})]$ (Figure 5.10). Only a slight decrease in rate was observed ($k_{\text{obs}} = 3.0 \times 10^{-4} \text{ s}^{-1}$ at 323 K) when compared to the analogous reaction of $[\text{Ni}(\text{COD})(\text{dppf})]$ with 4-bromobenzotrifluoride, $k_{\text{obs}} = 6.9 \times 10^{-4} \text{ s}^{-1}$ at 323 K.

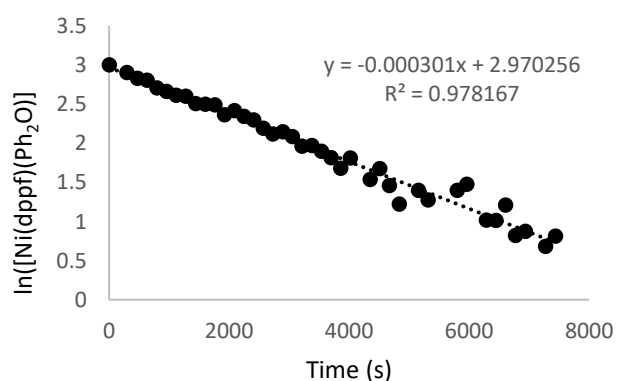


Figure 5.10. Plot of $[\text{Ni}(\text{dppf})(\text{Ph}_2\text{CO})]$ vs time for the reaction of $[\text{Ni}(\text{dppf})(\text{Ph}_2\text{CO})]$ ($20.1 \text{ mmol dm}^{-3}$) and 4-bromobenzotrifluoride (0.40 mol dm^{-3}) at 323 K.

Reaction of $[\text{Ni}(\text{dppf})(\text{Ph}_2\text{O})]$, $\text{PhB}(\text{OH})_2$ and diphenylacetylene (DPA) yielded the $[\text{Ni}(\text{dppf})\text{DPA}]$ as the product, and crystals suitable for X-Ray diffraction were obtained (Figure 5.11).

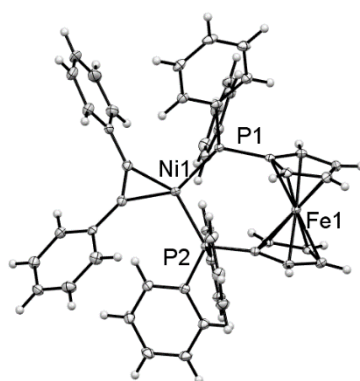


Figure 5.11. Crystal structure of $[\text{Ni}(\text{dppf})\text{DPA}]$.

The reaction of $[\text{Ni}(\text{dppf})\text{DPA}]$ with 4-bromobenzotrifluoride showed *pseudo-zero* order dependence on Ni^0 , while the addition of 1 equivalent of diphenylacetylene decreased the rate of reaction; this remained *pseudo-zero* order (Figure 5.12).

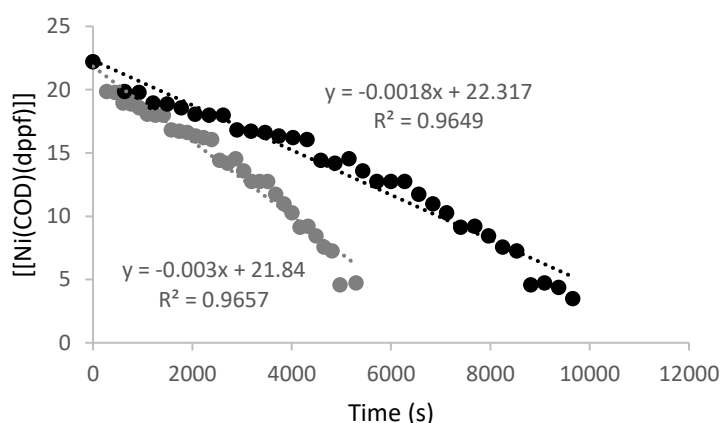
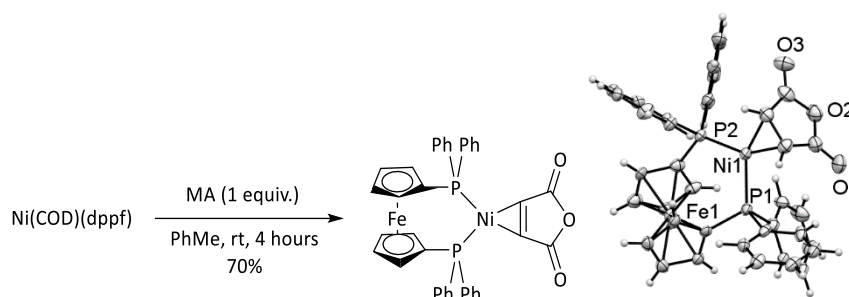


Figure 5.12. Plot of $[\text{Ni}(\text{dppf})(\text{DPA})]$ vs time for the reaction of $[\text{Ni}(\text{dppf})(\text{DPA})]$ ($20.2 \text{ mmol dm}^{-3}$) and 4-bromobenzotrifluoride (0.40 mol dm^{-3}); (grey) without added diphenylacetylene (black) with added diphenylacetylene ($20.2 \text{ mmol dm}^{-3}$).

COD was fully displaced by maleic anhydride when added to a sample of $[\text{Ni}(\text{COD})(\text{dppf})]$ (1:1), generating a clean sample of $[\text{Ni}(\text{dppf})(\text{MA})]$ (Scheme 5.13). Crystals were obtained that were suitable for X-Ray diffraction studies (Scheme 5.13). $[\text{Ni}(\text{dppf})(\text{MA})]$ was sufficiently soluble in toluene to allow for kinetic studies. No reaction was observed (at 70°C over 4 hours) after addition of 4-bromobenzotrifluoride (20 equivalents) to a sample of $[\text{Ni}(\text{dppf})(\text{MA})]$ in toluene- d_8 .



Scheme 5.13. Synthesis and crystal structure of $[\text{Ni}(\text{dppf})(\text{MA})]$.

5.4.3. Computational Studies

All calculations were carried out using Gaussian16, at the B3LYP-D3 level of theory. For optimisation, the 6-31G(d) basis set was used for hydrogen, carbon, oxygen, and fluorine, the LANL2DZ(dp) basis set was used for bromide, and the LANL2TZ(f) basis set was used for nickel. The energies were then refined using single point calculations with the 6-311+G(d,p) basis set on all atoms.

The optimisation of the structure of $[\text{Ni}(\text{dppf})(\text{DQ})]$ was attempted from several starting points, including three isomers with an η^6 -bound DQ ligand, one with an $\eta^2(\text{CC})$ -bound DQ ligand, and one with an $\eta^2(\text{CO})$ -bound DQ ligand. The former four starting points all converged on structurally and energetically very similar $\eta^2(\text{CC})$ -bound DQ complexes, suggesting that an η^6 -bound species is unlikely to be stable; however, the $\eta^2(\text{CO})$ -isomer was lower in energy, consistent with the crystal structure obtained (Figure 5.7(d)). The optimisation of $[\text{Ni}(\eta^2, \eta^2\text{-COD})(\text{dppf})]$, $[\text{Ni}(\eta^2\text{-ethene})(\text{dppf})]$, and $[\text{Ni}(\text{dppf})(\eta^2\text{-stb-CF}_3)]$ was unproblematic.

5.5. Extended Discussion

5.5.1. $[\text{Ni}(\text{dppf})(\text{ethene})]$ and Alkyl Halides

In contrast to $[\text{Ni}(\text{COD})(\text{dppf})]$, oxidative addition reactions of 2-haloethylbenzene substrates to $[\text{Ni}(\text{dppf})(\text{ethene})]$ were *pseudo*-first order in nickel without addition of dppf (Figure 5.14).⁷⁵ This suggests that $[\text{Ni}(\text{dppf})(\text{ethene})]$ is the active species in this reaction, as opposed to *insitu* formation of the active species, $[\text{Ni}(\text{dppf})_2]$, in the case of $[\text{Ni}(\text{COD})(\text{dppf})]$. As observed in the reaction of $[\text{Ni}(\text{dppf})(\text{ethene})]$, this reaction was much slower than that of $[\text{Ni}(\text{COD})(\text{dppf})]$ and alkyl halides.⁷⁵

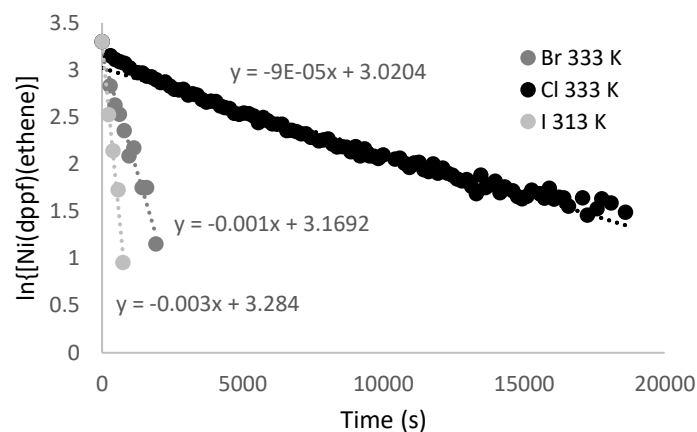


Figure 5.14. Pseudo-first order plot for the reaction of $[\text{Ni(dppf)(ethene)}]$ ($27.1 \text{ mmol dm}^{-3}$) with 2-iodo, 2-bromo and 2-chloroethylbenzene (0.54 mol dm^{-3}) in C_6D_6 .

5.6. Conclusions

Ligands used within this study readily displace COD in $[\text{Ni(COD)(dppf)}]$ to form the corresponding complex, meaning that the resultant complexes are less-prone to oxidative addition than $[\text{Ni(COD)(dppf)}]$. Samples of $[\text{Ni(dppf)L}]$ are usually contaminated with other phosphine-containing species meaning kinetic studies are unreliable.

Use of air-stable nickel(0) sources plus ligand have been shown to catalyse reactions successfully through in-situ formation of $[\text{Ni(dppf)L}]$ species but isolation of these remains challenging. Work is ongoing in the Nelson group to find useful ways to synthesise these complexes cleanly to allow for kinetic analysis.

Chapter 6 - Conclusions and Outlook

Previously within the Nelson group, the mechanism of oxidative addition of aryl halides to $[\text{Ni}(\text{COD})(\text{dppf})]$ has been proposed.⁷⁴ The aim of this PhD project was to expand understanding in the mechanisms involved in the oxidative addition of alkyl and vinyl substrates to. A separate conclusion has been made at the end of each chapter, here the PhD project has been summarised as a whole.

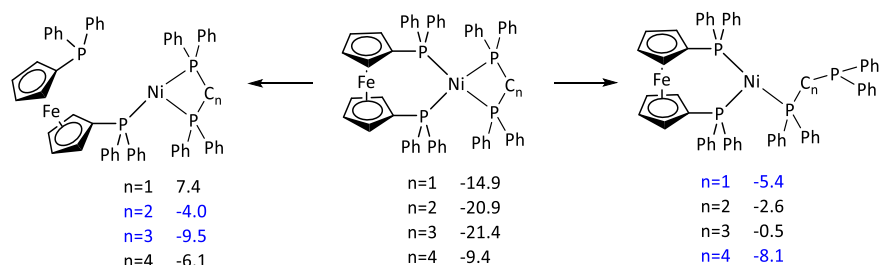
Studies into other electrophiles were limited during this study, the corresponding alkyl carbamate was synthesised and appeared to operate *via* a different mechanism. The mechanism in operation was not probed any further and it would benefit from further study. Other electrophiles would also be of interest, these could include carbonate, phosphate, tosylate, mesylate, nonaflate. It would be interesting to see if different electrophiles operate in the same way to alkyl halides or to the carbamate. The alkyl triflate was synthesised for Chapter 4 and was found to be unstable at temperatures required to monitor oxidative addition.

Chapter 2 explores the reaction of alkyl halides with, where oxidative addition was found to proceed through a $[\text{Ni}(\text{dppf})_2]$ active species, formed *insitu* from free dppf remaining from the synthesis of $[\text{Ni}(\text{COD})(\text{dppf})]$.⁷⁵ $[\text{Ni}(\text{dppf})_2]$ is proposed to abstract a halide from the alkyl halide, followed by a radical recombination to form the formal oxidative addition product. β -H elimination yields styrene and the corresponding nickel hydride complex. Comproportionation of $[\text{Ni}(\text{dppf})\text{HX}]$ with $[\text{Ni}(\text{COD})(\text{dppf})]$ eliminates H_2 and forms $[\text{Ni}(\text{dppf})\text{X}]$ as the ultimate nickel-containing product (confirmed by EPR).⁷⁵

This reaction was expanded to a number of $[\text{Ni}(\text{dppf})\text{L}]$ complexes in Chapter 3, which were found to react via the same mechanism as $[\text{Ni}(\text{dppf})_2]$. Addition of monodentate phosphine ligands, where $[\text{Ni}(\text{dppf})\text{PR}_3]$ was the active species, allowed determination of trends in behaviour. Ligands too sterically demanding (e.g. $\text{P}(o\text{-tol})_3$) and too electron rich (e.g. PCy_3) caused significant decreases in reactivity.

The use of bidentate ligands (dppm, dppe, dppp) as additives in the reactions of $[\text{Ni}(\text{dppf})\text{L}]$ with alkyl halides gave a wide span of rate constants. DFT calculations uncovered the unexpected reactivity of dppe and dppp, where dissociation of the added ligand (as

opposed to dppf) was favourable to generate the required vacant site of oxidative addition (Scheme 6.1). It would be interesting to analyse other bidentate phosphine ligands to understand if there is a trend of reactivity, this could also be expanded to include bidentate phosphine ligands.



Scheme 6.1. DFT on ligand dissociation from $[\text{Ni}(\text{dppf})\text{L}]$ when bidentate ligands are used as additives.

With regards to the Kumada-Tamao-Corriu cross-couplings of alkyl halides carried out during both studies in Chapters 1 and 2, the route of selectivity was not elucidated. 2-Iodoethylbenzene was shown to favour the desired (linear) product, 2-bromoethylbenzene gave an equal mixture of desired (linear) and regioisomeric (branched) products and 2-chloroethylbenzene favoured the regioisomeric (branched) product. There was no correlation between selectivity and the rates of oxidative addition (k_{obs}). The type of Grignard reagent employed was also investigated; change of the halide and substitution of the aryl ring gave no correlations with selectivity. This work would benefit from further studies into selectivity, the reductive elimination step has not been investigated. Synthesis of model complexes to represent stages in the catalytic cycle may be helpful to determine the step responsible for the unexpected selectivity observed.

Vinyl triflates were found to be more reactive than aryl triflates in Chapter 4. Mechanistic similarities were observed when studying their oxidative addition to $[\text{Ni}(\text{COD})(\text{dppf})]$; a concerted three- or five- centred mechanism (dependent on substrate) is proposed for both sets of substrates.⁷⁴ An initial η^2 coordination of the alkene in the reactions of vinyl triflates is thought to be responsible for the observed enhanced reactivity of these substrates.

Work is currently underway within the Nelson to fully understand the reaction of pyridine substrates with dppf-Ni⁰ complexes which will include the unusual crystal structure obtained in the reaction of 2-pyridinyl triflate with [Ni(COD)(dppf)] (Figure 6.1). The work will include N-heteroaryl substrates (pyridines, quinolines, pyrimidines etc.) of halides and oxygen electrophiles (triflates, tosylates, mesylates etc.) to fully understand their differing reactivity compared to aryl (*pseudo*)halides.

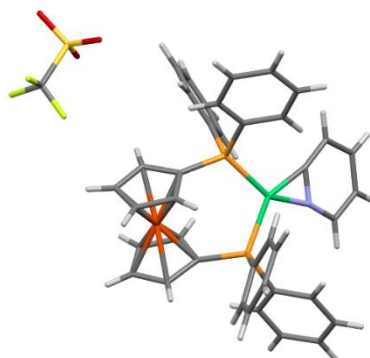


Figure 6.1. Crystal structure obtained from the reaction of [Ni(COD)(dppf)] (**1**) and pyridine-2-yl triflate.

Chapter 5 aims to quantify the effect of the ancillary on rates of oxidative addition of aryl halides to [Ni(dppf)L]. Issues arose with obtaining sufficiently clean samples suitable for kinetic experiments. Complexes that were isolated cleanly, [Ni(dppf)(ethene)] and [Ni(dppf)(Ph₂CO)] were used in reactions with 4-bromobenzotrifluoride and rates of oxidative addition were slower than for [Ni(COD)(dppf)].

Extensive work is still necessary with regards to synthesis of these [Ni(dppf)L] species to be used in oxidative addition kinetic studies. New methodology (unpublished) developed within the Nelson group to synthesise [Ni(dppf)(Ph₂CO)] will hopefully then allow access to clean samples of [Ni(dppf)L] species. A full set of these complexes will need to be synthesised cleanly and their reactivity with aryl (and alkyl) halides studied to draw meaningful conclusions about the effect the ancillary ligand has on the rates of oxidative addition.

Chapter 7 - Experimental

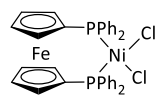
7.1. General

Anhydrous toluene, THF and hexane were obtained from Inert Technology PureSolv apparatus; regular Karl-Fisher analyses ensured that water content was always below 10 ppm. Substrates used in kinetic experiments and cross-coupling reactions were obtained from commercial sources and used as supplied. Any substrates prepared are detailed below, as are synthesis of nickel complexes used. $[\text{Ni}(\text{COD})_2]$ (96% purity) was obtained from Alfa Aesar and was stored in the glovebox freezer at $-40\text{ }^{\circ}\text{C}$. 1,1'-Bis(diphenylphosphino)ferrocene (dppf) was obtained from Fluorochem and stored in the glovebox. Alkyl halides, phenols, ketones, benzyl alcohol and ligands used as additives were all commercially available and used without purification. $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) was synthesised according to a literature procedure.²⁷⁵ Any manipulations of air-sensitive nickel complexes were carried out under nitrogen or argon using Schlenk techniques, or in an argon-filled glovebox (≤ 0.1 ppm oxygen and water). All deuterated solvents were obtained from commercial sources and dried over $4\text{ \AA}$ molecular sieves overnight before use.

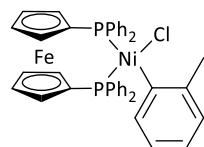
NMR spectroscopy was performed using Bruker spectrometers, either: an AV3-400 equipped with a liquid nitrogen cryoprobe; an AV3-400Nano equipped with a BBFO-z-ATMA probe and temperature control; an AV3-500HD equipped with a smartprobe and temperature control; or an AVII-600 equipped with a BBO-z-ATMA probe and temperature control. All kinetic experiments were carried out on the latter instrument. ^1H NMR chemical shifts are reported relative to residual solvent signals.¹³⁹ $^{13}\text{C}\{^1\text{H}\}$ NMR chemical shifts are reported relative to the deuterated solvent signal.¹³⁹ ^{19}F and ^{31}P NMR chemical shifts are reported relative to external standards. GC-MS analyses were carried out using an Agilent 7890A gas chromatograph fitted with a RESTEK RXi-5Sil column (30 m x 0.32 mm I.D. x 0.25 μm) and an Agilent 5975C MSD running in EI mode. GC-FID analyses were carried out using an Agilent 7890A gas chromatograph fitted with an Agilent HP5 column (30 m x 0.25 mm I.D. x 0.25 μm).

7.2. Experimental Data for Chapter 2

7.2.1. Synthesis of Compounds



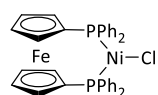
[Ni(dppf)Cl₂]. Prepared according to the literature procedure.²⁷⁶ NiCl₂·6H₂O (400 mg, 1.2 mmol) and EtOH (50 mL) were charged to a 100 mL RBF and sealed with septum. Solution was sparged with N₂ for 15 min, septum removed and dppf (677 mg, 1.2 mmol) charged in one portion, flask fitted with condenser and heated to 80 °C. After 30 min, flask cooled to room temperature then cooled in ice bath for 10 min. Solid collected by vacuum filtration and washed with EtOH (2 x 20 mL). Solid dried under vacuum to yield product as dark green powder (741 mg, 90%). As [Ni(dppf)Cl₂] is paramagnetic and not soluble in organic solvents, no NMR data is reported.



[Ni(dppf)(o-tol)Cl]. Prepared according to the literature procedure.²⁷⁶ Ni(dppf)Cl₂ (400 mg, 0.58 mmol) was charged to an oven dried RBF and sealed with septum. Anhydrous THF (40 mL) added and solution cooled in ice bath, o-tolylmagnesium chloride (0.48 mL of 1.2 M solution, 0.58 mmol) was added dropwise. Colour change of solution from green to yellow was observed. After complete addition, solution left to stir in ice bath for 15 min. Solution evaporated to dryness under reduced pressure. MeOH added (10 mL) and sonicated until suspension was obtained. Suspension was cooled in ice bath and yellow precipitate collected under vacuum filtration, then washed with cold MeOH (2 x 5 mL). Collected solid was dried under vacuum to yield product as yellow powder (346 mg, 81%).

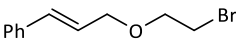
³¹P{¹H} NMR (162 MHz): δ 11.52 (*J*_{PP} = 25.2 Hz), 29.51 (*J*_{PP} = 23.3 Hz).

NMR is consistent with the literature.²⁷⁵



[Ni(dppf)Cl]. Ni(dppf)Cl₂ (248 mg, 0.4 mmol) was added to a flame-dried Schlenk flask which was backfilled with argon. Anhydrous THF (10 mL) was added. In a different flame-dried Schlenk flask, Ni(COD)(dppf) (289 mg, 0.4 mmol) was added in an argon filled glovebox. This flask was removed from the glovebox and the complex was dissolved in anhydrous toluene (10 mL). The Ni(dppf)Cl₂ solution was transferred into the flask containing the Ni(COD)(dppf) solution *via* cannula. The reaction was stirred at room temperature overnight, during which time the product precipitated from solution. The solid

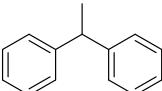
was recovered by cannula filtration, washed with anhydrous hexane, and dried under high vacuum for 3 hours. The final product was recovered as a pale-yellow solid (213 mg, 82%). As [Ni(dppf)Cl] is paramagnetic, no NMR is reported. [Ni(dppf)Cl] was confirmed by EPR analysis and was consistent with the literature.⁷⁶

 **(E)-(3-(2-bromoethoxy)prop-1-en-1-yl)benzene.** Prepared following the literature procedure.²⁷⁷ A 100 mL RBF was charged with cinnamyl alcohol (1 g, 7.5 mmol), 2-bromoethanol (1.6 mL, 22.4 mmol), 1 M aqueous HCl (1.3 mL, 0.75 mmol), and acetonitrile (40 mL). The reaction was heated at reflux (80 °C) for 24 hours. Once the reaction had cooled to room temperature, it was washed with sat. sodium bicarbonate solution (50 mL). The organic layer was dried over MgSO₄, filtered, and then concentrated under reduced pressure. The crude mixture was purified using column chromatography (hexane:Et₂O 85:15) to give the desired compound as a colourless oil (0.1 g, 6 %).

¹H NMR (400 MHz, CDCl₃): δ 3.53 (t, 2H, ³J_{H-H} = 6.2, CH₂Br), 3.84 (t, 2H, ³J_{H-H} = 6.2, OCH₂), 4.25 (dd, 2H, ³J_{H-H} = 6.0, ⁴J_{H-H} = 1.3, OCH₂), 6.32 (dt, 1H, ³J_{H-H} = 15.9, ⁴J_{H-H} = 6.0, CHCHCH₂), 6.66 (d, 1H, ³J_{H-H} = 15.9, PhCCH₂), 7.24 – 7.30 (m, 1H, aryl), 7.31 – 7.38 (m, 2H, aryl), 7.39 – 7.45 (m, 2H, aryl).

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 30.0 (CH₂Br), 69.5 (CH₂O), 71.2 (OCH₂), 125.0 (CHCH₂O), 126.1 (CHPh), 126.3 (aryl CH), 127.4 (aryl CH), 128.1 (aryl CH), 132.5 (aryl CH), 136.0 (C).

NMR data consistent with literature.¹⁰²

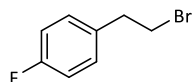
 **1,1-Diphenylethane.** Diphenylethylene (1 mL, 5.7 mmol) was added to a RBF with Pd/C (5 wt%, 1.2 g), which was then sealed with septum and evacuated and backfilled with nitrogen. Propanol (20 mL) was added and the flask was evacuated and backfilled again. A balloon of hydrogen was attached to the flask *via* a needle. The reaction was then stirred at room temperature for 24 h. The balloon was removed, the Pd/C was filtered off and the solvent was removed under reduced pressure to give 1,1-diphenylethane as a colourless oil (0.6 g, 59%).

¹H NMR (400 MHz, CDCl₃): δ 1.70 (d, 3H, ³J_{H-H} = 6.9, CH₃CH), 4.20 (q, 1H, ³J_{H-H} = 6.9, CH₃CH), 7.21 – 7.35 (m, 10H, aryl).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 21.4 (CH_3), 44.3 (CHCH_3), 125.5 (aryl CH), 127.2 (aryl CH), 127.9 (aryl CH), 145.9 (aryl C).

GC-MS ($\text{C}_{14}\text{H}_{14}$) m/z : 182.1

NMR data consistent with the literature.²⁷⁸



1-(2-Bromoethyl)-4-fluorobenzene. 2-(4-Fluorophenyl)ethan-1-ol (1.3

mL, 10 mmol) was stirred in PhMe (5 mL). PBr_3 (0.9 mL, 10 mmol) was added dropwise and the solution heated to 100 °C then allowed to cool. Once cooled, ice water (10 mL) was added and washed with Na_2CO_3 (10 mL). The aqueous phase was extracted with PhMe (3 x 10 mL). Organic extracts dried over MgSO_4 , filtered and concentrated. Pentane added (50 mL) and cooled, white precipitate filtered and solution concentrated to yield 1-(2-bromoethyl)-4-fluorobenzene (340 mg, 17%) as a yellow oil.

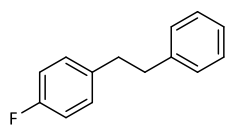
^1H NMR (400 MHz, CDCl_3): δ 3.16 (t, 2H, $^3J_{\text{H-H}} = 7.6$), 3.57 (t, 2H, $^3J_{\text{H-H}} = 7.6$), 7.01-7.06 (m, 2H), 7.19-7.22 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 32.5, 37.9, 114.9 (d, $J_{\text{CF}} = 18.5$), 129.7 (d, $J_{\text{CF}} = 8.2$), 134.1 (d, $J_{\text{CF}} = 3.6$), 161.2 (d, $J_{\text{CF}} = 244.1$).

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -115.9.

GC-MS ($\text{C}_8\text{H}_8\text{BrF}$) m/z : 201.9.

NMR data consistent with the literature.¹⁵²



1-Fluoro-4-phenethylbenzene. Prepared according to a literature procedure.²⁷⁹ Benzyltriphenylphosphonium chloride (4 g, 10 mmol) and

LiOH (0.5 g, 13 mmol) was stirred in propanol (50 mL) for 20 mins at room temperature. 4-Fluorobenzaldehyde (1 mL, 9.3 mmol) was added and the solution refluxed for 16 h. Once cooled, EtOAc (75 mL) and brine (75 mL) were added and the organic phase separated. The organic layer was dried over MgSO_4 , filtered and concentrated. The solid was recrystallised from EtOH to yield 4-fluorostilbene (0.5 g) as a white solid, this was used in the next step without further purification.

4-Fluorostilbene (0.5 g, 2.5 mmol) was added to a RBF with Pd/C (10 wt%, 50 mg), which was then sealed with septum and evacuated and backfilled with nitrogen. Propanol (20 mL) was added and the flask was evacuated and backfilled again. A balloon of hydrogen was attached to the flask *via* a needle. The reaction was then stirred at room temperature for 24 h. The balloon was removed, the Pd/C was filtered off and the solvent was removed under reduced pressure to give 1-fluoro-4-phenethylbenzene (86 mg, 22%), as a white solid.

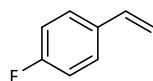
^1H NMR (400 MHz, CDCl_3): δ 2.82 (s, 4H), 6.85-6.89 (m, 2H), 7.01-7.14 (m, 5H), 7.18-7.22 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 37.1, 38.0, 115.0 (d, $J_{\text{CF}} = 21.1$), 126.0, 128.4 (d, $J_{\text{CF}} = 12.3$), 129.8 (d, $J_{\text{CF}} = 8.2$), 141.5, 160.2, 162.4.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz): δ -117.6.

GC-MS ($\text{C}_{14}\text{H}_{13}\text{F}$) m/z : 200.1.

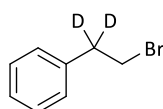
NMR data consistent with the literature.²⁸⁰



4-Fluorostyrene. Prepared according to a literature procedure.²⁷⁹

Methyltriphenylphosphonium bromide (3.7 g, 10 mmol) and LiOH (0.5 g, 13 mmol) was stirred in propanol (50 mL) at room temperature for 20 mins. 4-Fluorobenzaldehyde (1 mL, 9.3 mmol) was added and the solution refluxed for 16 h. Once cooled, EtOAc (75 mL) and brine (75 mL) were added and the organic phase separated. The organic layer was dried over MgSO_4 , filtered and concentrated. A Kugelrohr was used to separate 4-fluorostyrene from starting material and triphenylphosphine oxide. The product remained impure, however was able to determine the ^{19}F chemical shift of 4-fluorostyrene, all that was necessary in this case.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz): δ -114.2.



(2-Bromoethyl-1,1- d_2)benzene. Synthesised according to literature procedures.^{150–152}

Phenyl acetic acid (1 g, 7.3 mmol) was dissolved in anhydrous THF (10 mL) and stirred at -78°C . BuLi (8.8 mL, 2.5 M, 21.9 mmol) was added dropwise and stirred for 1 hour at -78°C . The reaction was warmed to 0°C and quenched with D_2O (20 mL). The reaction mixture was acidified with HCl (10 mL, 6 M) and

extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and concentrated to yield deuterated phenyl acetic acid (0.9 g), this was used in the next step without further purification.

LiAlH₄ (0.3 g, 7.8 mmol) was suspended in anhydrous THF (6 mL) and cooled in ice bath. Deuterated phenyl acetic acid from the previous step (0.9 g, 6.5 mmol) was added dropwise as a solution in THF (10 mL), the reaction mixture was stirred for 1 hour at room temperature. The reaction was quenched with HCl (20 mL, 0.5 M) and extracted with EtOAc (3 x 20 mL). The organic layers were combined and washed with H₂O (50 mL) and brine (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to yield the product (0.6 g), this was used in the next step without further purification.

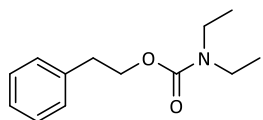
Deuterated phenylethanol from the previous step (0.6 g, 4.8 mmol) and CBr₄ (1.8 g, 5.3 mmol) were dissolved in DCM (10 mL). PPh₃ (1.4 g, 5.3 mmol) was added in portions and the reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure and petroleum ether (20 mL) added. The precipitate was filtered and washed with petroleum ether (100 mL), the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography to yield the product (0.4 g, 32%, 60% deuteration) as a colourless oil.

¹H NMR (400 MHz, CDCl₃): δ 3.59 (d, ³J_{H-H} = 7.7 Hz, 2H), 7.24 – 7.37 (m, 5H).

²H NMR (61 MHz, CDCl₃): δ 3.15.

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 32.3, 38.6 (t, J_{CD} = 20.0 Hz), 126.5, 128.1, 128.2, 138.5.

NMR data consistent with the literature.²⁸¹



Phenethyl diethylcarbamate. Under anhydrous/inert conditions, 2-phenylethanol (2 mL, 16.7 mmol), NEt₃ (2.8 mL, 20.0 mmol), diethylcarbomyl chloride (2.3 mL, 18.4 mmol) and anhydrous DCM

(50 mL) were charged to a 100 mL RBF. The solution was refluxed for 16 h. After cooling, NaOH (1 M, 50 mL) was added and layers separated. The aqueous phase was extracted with DCM (3 x 20 mL), the combined organic phases were washed with HCl (1 M, 50 mL), brine (50 mL) and dried over MgSO₄. The solution was filtered and concentrated to give crude product.

The product was purified *via* column chromatography (hexane: EtOAc 10:1) to yield phenethyl diethylcarbamate (1.7 g, 45%) as a yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 1.10 (br, 6H), 2.97 (t, 2H, $^3J_{\text{H-H}} = 6.7$ Hz), 3.26 (br, 4H), 4.31 (t, 2H, $^3J_{\text{H-H}} = 6.7$), 7.22-7.39 (m, 5H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 13.2 (d, $J = 35.7$ Hz), 35.2, 40.9 (d, $J = 49.1$ Hz), 65.1, 125.9, 127.9, 128.5, 137.9, 155.4.

GC-MS ($\text{C}_{13}\text{H}_{19}\text{NO}_2$) m/z : 104.1 (PhEt^+)

7.2.2. Kinetic Experiments

All kinetic plots can be found online in the supplementary information at ACS Catal., 2020, 10, 10717 - 10725. Kinetic data was obtained in the same manner as that used previously in the Nelson group by following the decay of starting Ni^0 complex.⁷⁴

In an argon-filled glovebox, a septum-fitted NMR tube was charged with a solution of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) (8 mg, 0.011 mmol, except in Table S5) and any solid additives in dry benzene- d_6 or toluene- d_8 (0.5 mL). Once dissolved, any liquid additives (or stock solutions of additives) were then added. This sample was used to tune, match, lock and shim the spectrometer, and to set the receiver gain. A spectrum was acquired to check the integrity of the sample. The aryl halide (5-25 equiv.) was added to start the reaction and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra (16 scans/spectrum; interpulse delay = 2 s) were acquired at intervals until >87% conversion ($3t_{1/2}$) was achieved. All experiments were performed in duplicate.

In each case, the absolute integral for **1** in each spectrum was normalised to that of the initial spectrum in order to obtain concentrations for those reactions that were zero order in **1** (Table 7.1). In all other reactions, which were pseudo-first order in **1**, rate constants were obtained by plotting the natural log of the integral for **1** *versus* time.

Table 7.1. Rates obtained from plotting the concentration of Ni^0 versus time. These kinetic experiments were carried out without extra dppf added into the reactions. Substrates are 2-haloethylbenzene, halide specified in table.

Entry	Halide	[RX] (mol L ⁻¹)	Additive	[Additive] (mmol L ⁻¹)	Solvent	T (K)	k_{obs} (mol L ⁻¹ s ⁻¹)
1a	Cl	0.33	None	-	C ₆ D ₆	323	0.017
1b	Cl	0.33	None	-	C ₆ D ₆	323	0.016
2a	Br	0.33	None	-	C ₆ D ₆	303	0.015
2b	Br	0.33	None	-	C ₆ D ₆	303	0.013
3a	I	0.33	None	-	C ₆ D ₆	293	0.024
3b	I	0.33	None	-	C ₆ D ₆	293	0.023
4a	Br	0.33	Ni(dppf)Cl ₂	22	C ₆ D ₆	303	0.034
5a	Br	0.33	Ni(dppf)Cl	22	C ₆ D ₆	303	0.012
5b	Br	0.33	Ni(dppf)Cl	22	C ₆ D ₆	303	0.013
6a	Br	0.33	dppf	22	C ₆ D ₆	303	$t_{1/2} < 300 \text{ s}$
7a	Br	0.0022	None	-	C ₆ D ₆	303	1.8×10^{-3}
7b	Br	0.0022	None	-	C ₆ D ₆	303	1.8×10^{-3}
8a	Br	0.011	None	-	C ₆ D ₆	303	3.3×10^{-3}
8b	Br	0.011	None	-	C ₆ D ₆	303	3.3×10^{-3}
9a	Br	0.022	None	-	C ₆ D ₆	303	4.4×10^{-3}
9b	Br	0.022	None	-	C ₆ D ₆	303	4.2×10^{-3}
10a	Br	0.044	None	-	C ₆ D ₆	303	6.5×10^{-3}
10b	Br	0.044	None	-	C ₆ D ₆	303	6.6×10^{-3}
11a	Br	0.11	None	-	C ₆ D ₆	303	0.012
11b	Br	0.11	None	-	C ₆ D ₆	303	0.010
12a	Br	0.22	None	-	C ₆ D ₆	303	0.015
12b	Br	0.22	None	-	C ₆ D ₆	303	0.013

13a	Br	0.44	None	-	C ₆ D ₆	303	0.014
13b	Br	0.44	None	-	C ₆ D ₆	303	0.013
14a	Br	0.56	None	-	C ₆ D ₆	303	0.017
14b	Br	0.56	None	-	C ₆ D ₆	303	0.013
15a	Br	0.33	COD	56	C ₆ D ₆	303	7.2 x 10 ⁻³
15b	Br	0.33	COD	56	C ₆ D ₆	303	7.4 x 10 ⁻³
16a	Br	0.33	COD	78	C ₆ D ₆	303	6.2 x 10 ⁻³
16b	Br	0.33	COD	78	C ₆ D ₆	303	5.3 x 10 ⁻³
17a	Br	0.33	COD	111	C ₆ D ₆	303	4.8 x 10 ⁻³
17b	Br	0.33	COD	111	C ₆ D ₆	303	4.3 x 10 ⁻³
18a	Br	0.33	COD	133	C ₆ D ₆	303	4.3 x 10 ⁻³
18b	Br	0.33	COD	133	C ₆ D ₆	303	3.8 x 10 ⁻³
19a	Br	0.33	COD	167	C ₆ D ₆	303	2.6 x 10 ⁻³
19b	Br	0.33	COD	167	C ₆ D ₆	303	1.7 x 10 ⁻³
20a	Br	0.33	BHT	22	C ₆ D ₆	283	1.0 x 10 ⁻³
20b	Br	0.33	BHT	22	C ₆ D ₆	283	1.1 x 10 ⁻³

Table 7.2. Rates obtained from plotting the natural log of the concentration of Ni⁰ versus time (first-order dependence). All reactions used dppf as an additive (0.3 equivalents with respect to nickel, 6.6 mmol L⁻¹). Rates obtained from plotting the natural log of the integral of Ni⁰ versus time. Substrates are 2-haloethylbenzene, halide specified in table.

Entry	Halide	[RX] (mol L ⁻¹)	Additive	[Additive] (mmol L ⁻¹)	Solvent	T (K)	<i>k</i> _{obs} (s ⁻¹)
1a	Cl	0.33	None	-	C ₆ D ₆	318	1.8 x 10 ⁻³
1b	Cl	0.33	None	-	C ₆ D ₆	318	1.6 x 10 ⁻³
2a	Br	0.33	None	-	C ₆ D ₆	283	1.3 x 10 ⁻³
2b	Br	0.33	None	-	C ₆ D ₆	283	1.3 x 10 ⁻³
3a	I	0.33	None	-	C ₆ D ₅ CD ₃	273	3.4 x 10 ⁻³
3b	I	0.33	None	-	C ₆ D ₅ CD ₃	273	3.7 x 10 ⁻³

4a	Br	0.33	BHT	330	C ₆ D ₆	283	1.3 x 10 ⁻³
4b	Br	0.33	BHT	330	C ₆ D ₆	283	1.1 x 10 ⁻³
5a	Br	0.11	None	-	C ₆ D ₆	283	4.5 x 10 ⁻⁴
5b	Br	0.11	None	-	C ₆ D ₆	283	4.6 x 10 ⁻⁴
6a	Br	0.22	None	-	C ₆ D ₆	283	9.7 x 10 ⁻⁴
6b	Br	0.22	None	-	C ₆ D ₆	283	1.1 x 10 ⁻³
7a	Br	0.44	None	-	C ₆ D ₆	283	1.6 x 10 ⁻³
7b	Br	0.44	None	-	C ₆ D ₆	283	1.7 x 10 ⁻³
8a	Br	0.55	None	-	C ₆ D ₆	283	1.8 x 10 ⁻³
8b	Br	0.55	None	-	C ₆ D ₆	283	1.9 x 10 ⁻³
9a	Br	0.33	COD	41	C ₆ D ₆	283	6.4 x 10 ⁻⁴
9b	Br	0.33	COD	41	C ₆ D ₆	283	6.2 x 10 ⁻⁴
10a	Br	0.33	COD	49	C ₆ D ₆	283	4.3 x 10 ⁻⁴
10b	Br	0.33	COD	49	C ₆ D ₆	283	4.2 x 10 ⁻⁴
11a	Br	0.33	COD	81	C ₆ D ₆	283	3.2 x 10 ⁻⁴
11b	Br	0.33	COD	81	C ₆ D ₆	283	3.2 x 10 ⁻⁴
12a	Br	0.33	COD	98	C ₆ D ₆	283	2.5 x 10 ⁻⁴
12b	Br	0.33	COD	98	C ₆ D ₆	283	2.5 x 10 ⁻⁴
13a	Br	0.33	COD	114	C ₆ D ₆	283	2.4 x 10 ⁻⁴
13b	Br	0.33	COD	114	C ₆ D ₆	283	2.4 x 10 ⁻⁴
14a	Cl	0.33	None	-	C ₆ D ₆	303	1.8 x 10 ⁻⁴
14b	Cl	0.33	None	-	C ₆ D ₆	303	2.0 x 10 ⁻⁴
15a	Cl	0.33	None	-	C ₆ D ₆	308	4.2 x 10 ⁻⁴
15b	Cl	0.33	None	-	C ₆ D ₆	308	4.4 x 10 ⁻⁴
16a	Cl	0.33	None	-	C ₆ D ₆	313	8.7 x 10 ⁻⁴
16b	Cl	0.33	None	-	C ₆ D ₆	313	8.1 x 10 ⁻⁴
17a	Cl	0.33	None	-	C ₆ D ₆	323	3.8 x 10 ⁻³
17b	Cl	0.33	None	-	C ₆ D ₆	323	3.4 x 10 ⁻³

18a	Br	0.33	None		C ₆ D ₅ CD ₃	273	2.7 x 10 ⁻⁴
18b	Br	0.33	None		C ₆ D ₅ CD ₃	273	2.9 x 10 ⁻⁴

Table 7.3. The order in dppf was investigated by varying the amounts of dppf added to each reaction. Rates obtained from plotting the natural log of the integral of Ni⁰ versus time. Substrates are 2-haloethylbenzene, halide specified in table.

Entry	Halide	[RX] (mol L ⁻¹)	Additive	[Additive] (mmol L ⁻¹)	Solvent	T (K)	<i>k</i> _{obs} (s ⁻¹)
1a	Br	0.33	dppf	2.2	C ₆ D ₆	283	6.1 x 10 ⁻⁴
1b	Br	0.33	dppf	2.2	C ₆ D ₆	283	4.9 x 10 ⁻⁴
2a	Br	0.33	dppf	4.4	C ₆ D ₆	283	9.3 x 10 ⁻⁴
2b	Br	0.33	dppf	4.4	C ₆ D ₆	283	9.1 x 10 ⁻⁴
3a	Br	0.33	dppf	5.5	C ₆ D ₆	283	1.2 x 10 ⁻³
3b	Br	0.33	dppf	5.5	C ₆ D ₆	283	1.1 x 10 ⁻³
4a	Br	0.33	dppf	6.6	C ₆ D ₆	283	1.3 x 10 ⁻³
4b	Br	0.33	dppf	6.6	C ₆ D ₆	283	1.3 x 10 ⁻³
5a	Br	0.33	dppf	8.8	C ₆ D ₆	283	1.9 x 10 ⁻³
5b	Br	0.33	dppf	8.8	C ₆ D ₆	283	1.9 x 10 ⁻³

Table 7.4. 2-Bromobenzotrifluoride was used as aryl halide for both experiments carried out with and without added dppf. Rates obtained from plotting the natural log of the integral of Ni⁰ versus time.

Entry	[RX] (mol L ⁻¹)	Additive	[Additive] (mmol L ⁻¹)	Solvent	T (K)	<i>k</i> _{obs} (s ⁻¹)
1a	0.44	None		C ₆ D ₆	303	2.3 x 10 ⁻⁴
1b	0.44	None		C ₆ D ₆	303	2.0 x 10 ⁻⁴
2a	0.44	dppf	6.6	C ₆ D ₆	303	1.7 x 10 ⁻⁴
2b	0.44	dppf	6.6	C ₆ D ₆	303	1.6 x 10 ⁻⁴

Table 7.5. Varying the initial concentration of Ni^0 , using a constant concentration of 2-bromoethylbenzene of 0.33 mol dm^{-3} (to rule out bimolecular reaction mechanisms). Rates obtained from plotting the natural log of the integral of Ni^0 versus time. $[\text{Ni}]$ refers to the concentration of $\text{Ni}(\text{COD})(\text{dppf})$ and $t=0$.

Entry	$[\text{Ni}]$ (mmol L^{-1})	$[\text{RX}]$ (mol L^{-1})	Additive	$[\text{Additive}]$ (mmol L^{-1})	Solvent	T (K)	k_{obs} (s^{-1})
1a	11.1	0.33	dppf	6.6	C_6D_6	283	2.3×10^{-3}
1b	11.1	0.33	dppf	6.6	C_6D_6	283	2.6×10^{-3}
2a	13.9	0.33	dppf	6.6	C_6D_6	283	2.3×10^{-3}
2b	13.9	0.33	dppf	6.6	C_6D_6	283	1.6×10^{-3}
3a	16.7	0.33	dppf	6.6	C_6D_6	283	1.5×10^{-3}
3b	16.7	0.33	dppf	6.6	C_6D_6	283	1.6×10^{-3}
4a	19.4	0.33	dppf	6.6	C_6D_6	283	1.6×10^{-3}
4b	19.4	0.33	dppf	6.6	C_6D_6	283	1.4×10^{-3}

7.2.3. Data Analysis

All experiments were performed in duplicate, unless otherwise stated. Each point on each graph represents an individual experiment, not an average of multiple replicates.

Without added dppf

Reactions were pseudo-zero order in $\text{Ni}(\text{COD})(\text{dppf})$ (as evident from a linear plot produced from $[\text{Ni}(\text{COD})(\text{dppf})]$ *versus* time), an inverse first order dependence on 1,5-cyclooctadiene (COD) and displayed saturation kinetics in 2-bromoethylbenzene.

Order in alkyl halide (without added dppf)

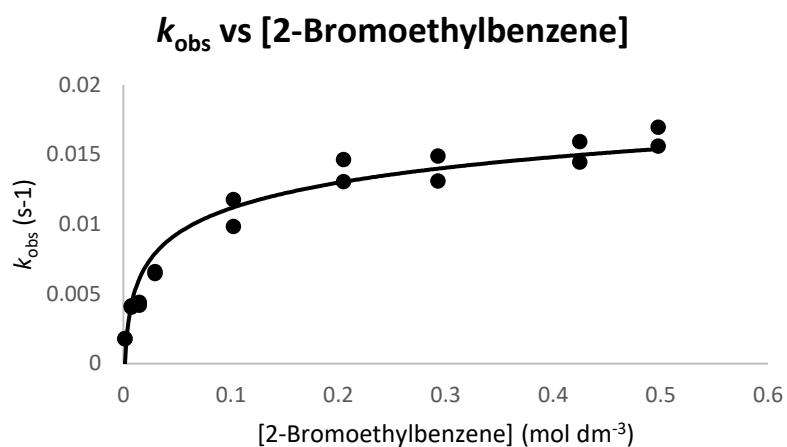


Figure 7.1. Saturation kinetics observed when the concentration of 2-bromoethylbenzene was varied.

Order in COD (without added dppf)

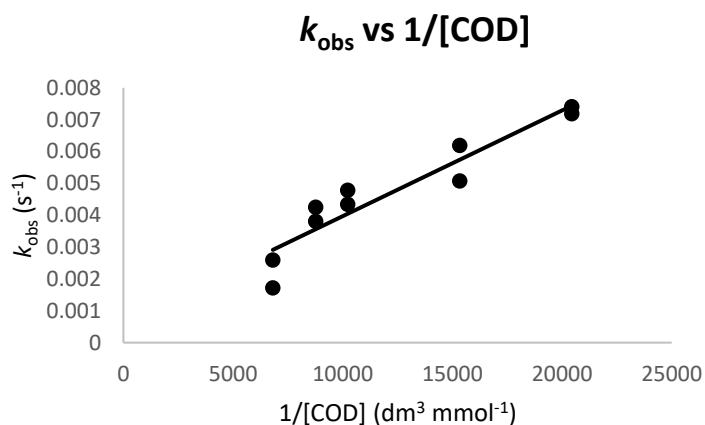


Figure 7.2. Linear plot of k_{obs} vs $1/[\text{COD}]$ to illustrate an inverse first-order dependence on ligand.

With added dppf

Order in alkyl halide and ligands

Order in $\text{Ni}(\text{COD})(\text{dppf})$ (with dppf as an additive) was determined from linear plots of the natural log of concentration versus time to be first-order. From varying amounts of substrate

used, adding various amounts of dppf and 1,5-cyclooctadiene independently, the orders of each of these could be determined.

Order in alkyl halide

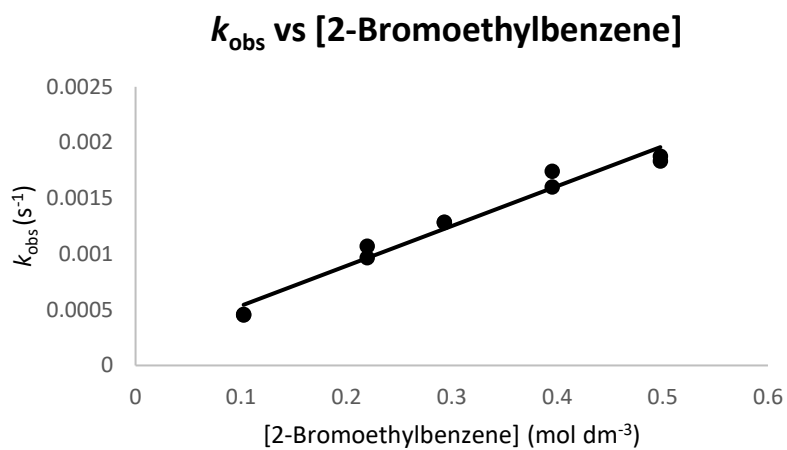


Figure 7.3. Linear plot of k_{obs} vs [2-bromoethylbenzene] to illustrate first-order dependence on substrate.

Order in dppf

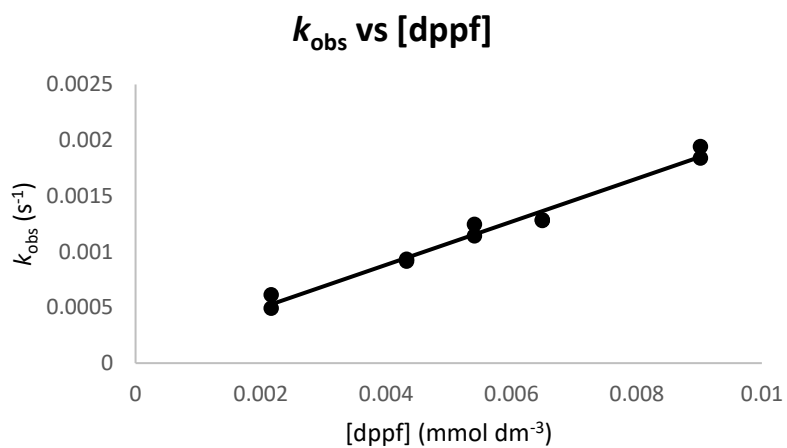


Figure 7.4. Linear plot of k_{obs} vs [dppf] to illustrate first-order dependence on dppf ligand.

Order in COD (with added dppf)

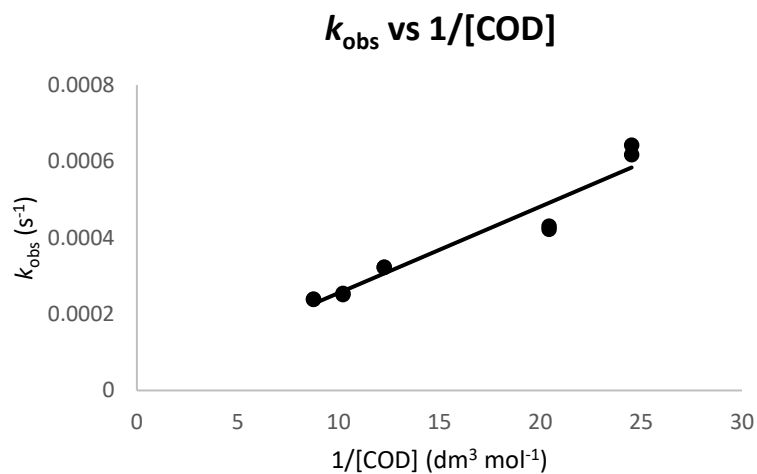


Figure 7.5. Linear plot of k_{obs} vs $1/[\text{COD}]$ to illustrate an inverse first-order dependence on COD ligand with added dppf.

Bimolecular Mechanisms

In order to rule out bimolecular systems, various concentrations of $[\text{Ni}(\text{COD})(\text{dppf})]$ were used whilst keeping the concentration of dppf, substrate and temperature the same. This allowed for the plots to be overlaid (with a time correction) which proved a unimolecular system is in operation.

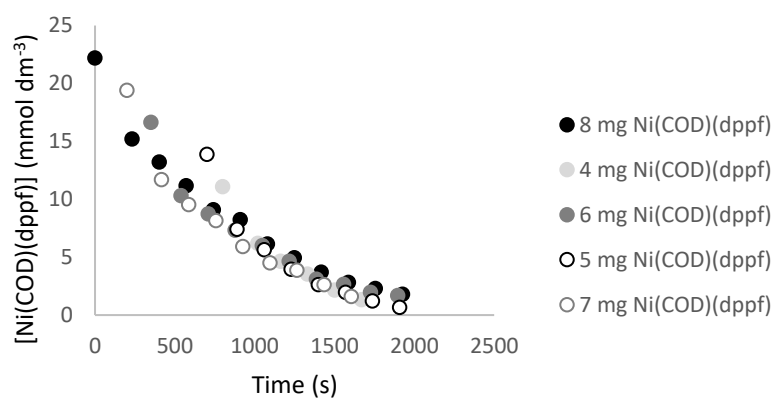


Figure 7.6. Several different $[\text{Ni}(\text{COD})(\text{dppf})]_0$ used and monitored over time. With time corrections, plots overlay to rule out bimolecular systems.

Eyring Analysis

Eyring analysis was carried out both for the formation of the active species Ni(dppf)_2 (Figure 7.8) and for the overall reaction (Figure 7.7). Therefore, the value of ΔH and ΔS for both formation of Ni(dppf)_2 and irreversible oxidative addition could be calculated independently (Table S6).

Eyring for overall reaction

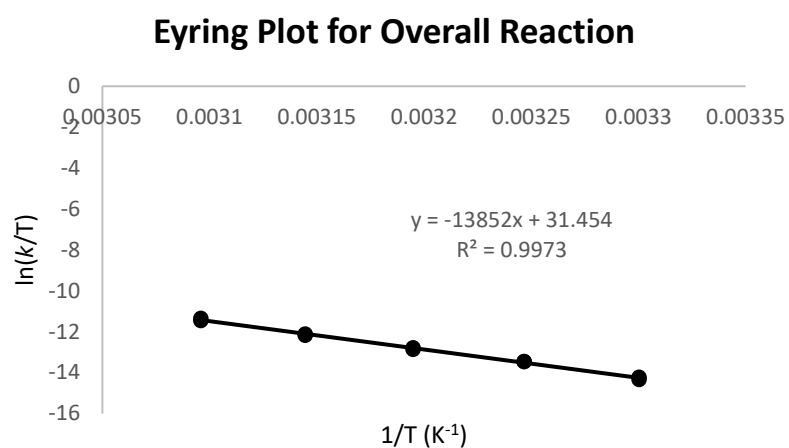


Figure 7.7. Eyring plot for the overall reaction including equilibrium to form the active species and irreversible oxidative addition.

Table 7.6. Calculation of ΔH and ΔS for overall reaction.

		$\Delta H \text{ (kcal mol}^{-1}\text{)}$	$\Delta S \text{ (cal mol}^{-1} \text{ K}^{-1}\text{)}$
Gradient	-13852	27.5	-
Intercept	31.454	-	15.3

Variable temperature plot for the equilibrium to form the active species

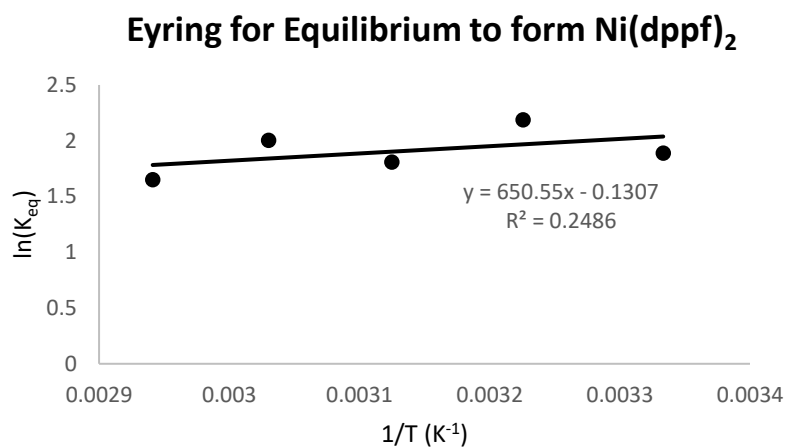


Figure 7.8. Eyring for the equilibrium to form the active species Ni(dppf)₂. Note: these were not carried out in duplicate due to data being collected by using the same sample at different temperatures.

Table 7.7. Calculation of ΔH and ΔS for the equilibrium to form the active species Ni(dppf)₂.

		$\Delta H \text{ (kcal mol}^{-1}\text{)}$	$\Delta S \text{ (cal mol}^{-1} \text{ K}^{-1}\text{)}$
Gradient	650.55	1.3	-
Intercept	-0.1307	-	-0.3

ΔH and ΔS for oxidative addition

Table 7.8. Calculation of ΔH and ΔS for just the oxidative addition step by subtracting the values in Table S5 from Table S4.

	Overall Reaction	Equilibrium to form Ni(dppf) ₂	Oxidative Addition
$\Delta H \text{ (Kcal mol}^{-1}\text{)}$	27.5	1.3	26.2
$\Delta S \text{ (Kcal mol}^{-1} \text{ K}^{-1}\text{)}$	15.3	-0.3	15.0

7.2.4. GC Calibrations

Conversions in both cross-couplings and product studies stated are in reference to an internal standard, either *n*-tetradecane or *n*-dodecane. All substrates and any products were

calibrated in reference to *n*-tetradecane or *n*-dodecane. All analysis was determined *via* a GC-FID and the specific method involved a temperature profile as follows: 40 °C per minute for 5 minutes, followed by 20 °C per minute for 5 minutes, up to 320 °C.

An example of how to calibrate for a material is shown below. This specific example is in regards to chloroethylbenzene:

- i. An accurately known amount of material (to be calibrated) was weighed into a medium sized vial (roughly 10 mg).
- ii. A different, accurately known mass of *n*-dodecane was put into each vial (approximately 10, 20, 50, 100, 250, 500 and 1000 mg).
- iii. These mixtures were diluted in chloroform and a sample of each one was analysed by GC-FID.
- iv. The areas of the peaks corresponding to both the substrate in question and *n*-dodecane were measured.
- v. The ratios of the mmol of compound/mmol *n*-dodecane vs peak area of substrate/peak area of *n*-dodecane were plotted (examples in Table S10, Figure S9).
- vi. The graph produced gave a straight line with an $R^2 > 0.99$, the gradient of this line was the response factor of the substrate being calibrated for.

This response factor is then taken into account through calculations when reactions have taken place – thus allowing the determination of the amount in the product mixtures.

Table 7.9. Data acquired for the calibration of substrates, this example was for chloroethylbenzene.

Sub (mg)	Sub (mmol)	Dodecane (mg)	Dodecane (mmol)	Peak area substrate	Peak area dodecane	mmol _{Sub} /mmol _{Dod}	Area _{Sub} /Area _{Dod}
18.8	0.134	12.5	0.073	564.596	457.591	1.826	1.234
21.7	0.154	26.1	0.153	683.906	1012.889	1.008	0.675
22.4	0.159	51.0	0.299	990.040	2772.268	0.532	0.357
20.9	0.149	114.7	0.671	707.634	4771.003	0.221	0.148

22.3	0.159	251.4	1.475	904.368	1.24×10^4	0.107	0.073
20.3	0.144	501.3	2.942	595.775	1.82×10^4	0.049	0.033
21.7	0.154	1014.1	5.951	665.318	3.84×10^4	0.026	0.017

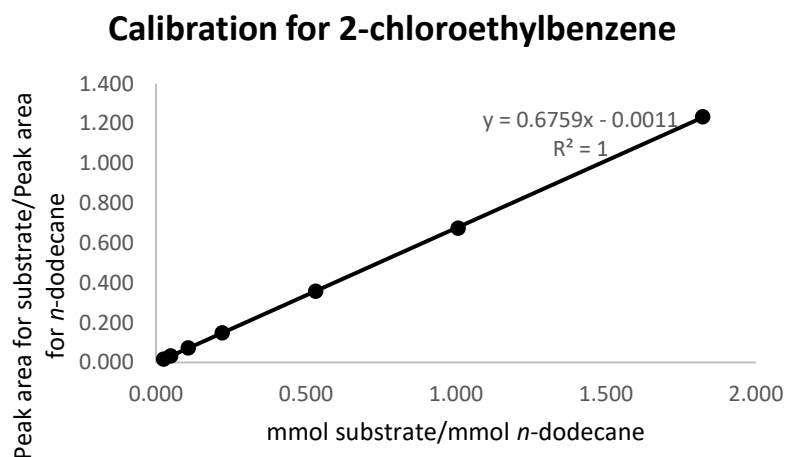


Figure 7.9. Calibration plot given for chloroethylbenzene to give a response factor of 0.6751. The response factors for substrates and products used for this work (and for which standards were used) are given in **Table S9**.

Table 7.10. Response factors given against standards for the substrates/products used in this work.

Substrate	Response factor against relative standards	
	<i>n</i> -Dodecane	<i>n</i> -Tetradecane
Iodoethylbenzene	0.5668	0.5209
Bromoethylbenzene	-	0.5757
Chloroethylbenzene	0.6751	0.4423
1,2-Diphenylethane	-	0.8814
1,1-Diphenylethane	-	1.0273
Ethylbenzene	0.5294	0.4636
Styrene	0.5712	0.5079
Biphenyl	0.9507	0.7207
4-Methyl biphenyl	-	0.8650

2-Chloromethyl-2-phenylpropane	0.7753	-
1-Chlorooctane	0.6529	-
2-Bromo-1-phenylpropane	-	0.5570

7.2.5. Cross-coupling Reactions

Procedure

In an argon-filled glovebox, the catalyst (0.0125 mmol, 5 mol%) and any solid additives were added to a microwave vial equipped with stirrer bar. The vial was sealed with a septum-fitted cap and removed from the glovebox. Anhydrous THF (1 mL) was added followed by phenylmagnesium chloride (2 M solution in THF, 0.28 mmol, 1.1 equiv.). The vial was then heated (whilst rapidly stirring) to 85 °C. When at the desired temperature, any liquid additives and the aryl halide (0.25 mmol) were added *via* microsyringe. The vials were left to stir at 85 °C for 24 h. The vials were then cooled to room temperature and pierced with a needle. The vials were opened and accurately known amounts of *n*-tetradecane were added. A sample was taken for GC-FID analysis. All reactions were performed in duplicate and average conversions are reported in results and discussion (manuscript).

Cross-coupling reactions of alkyl substrates

All cross-coupling reactions with alkyl substrates were performed in duplicate.

Table 7.11. Duplicate results of all cross-coupling reactions carried out. All substrates are 2-haloethylbenzene, X refers to the halide used.

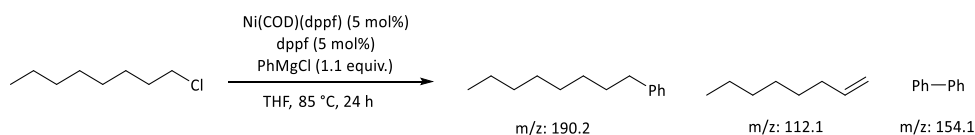
X	Catalyst	Additive	2 (%)	13 (%)	14 (%)	Biphenyl (%)	Styrene (%)	Ethylbenzene (%)
Cl	1	None	31	2	8	27	7	13
Cl	1	None	36	2	8	27	8	13
Br	1	None	18	12	19	23	16	11
Br	1	None	17	12	18	23	17	11
I	1	None	24	35	1	16	18	17
I	1	None	21	36	2	15	19	16

Cl	1	5 mol% dppf	0	6	43	8	4	11
Cl	1	5 mol% dppf	0	5	41	7	7	8
Br	1	5 mol% dppf	3	27	29	16	13	10
Br	1	5 mol% dppf	3	25	31	16	12	10
I	1	5 mol% dppf	0	63	5	4	9	6
I	1	5 mol% dppf	0	63	5	0	10	3
Cl	3-Cl	None	7	4	3	37	5	34
Cl	3-Cl	None	11	4	3	37	5	34
Br	3-Cl	None	3	19	6	41	12	26
Br	3-Cl	None	3	21	6	41	12	24
I	3-Cl	None	1	45	3	21	18	16
I	3-Cl	None	0	44	3	24	18	18
Cl	3-Cl	5 mol% dppf	12	3	19	25	3	20
Cl	3-Cl	5 mol% dppf	6	3	20	23	4	17
Br	3-Cl	5 mol% dppf	0	21	10	0	3	10
Br	3-Cl	5 mol% dppf	0	24	10	5	10	10
I	3-Cl	5 mol% dppf	0	63	3	6	5	6
I	3-Cl	5 mol% dppf	1	60	3	5	6	4
Cl	15	None	8	9	31	10	2	23
Cl	15	None	14	9	29	10	2	23
Br	15	None	6	34	20	15	21	6
Br	15	None	11	35	20	12	17	8
I	15	None	0	61	4	7	6	8
I	15	None	0	61	4	7	6	7
Cl	15	5 mol% dppf	22	5	28	10	1	13
Cl	15	5 mol% dppf	10	6	33	9	3	16
Br	15	5 mol% dppf	0	21	20	11	1	14
Br	15	5 mol% dppf	0	19	21	15	1	13

I	15	5 mol% dppf	0	61	4	7	6	7
I	15	5 mol% dppf	0	62	3	7	7	8
I	None	5 mol% dppf	0	0	0	25	0	106
I	None	5 mol% dppf	0	0	0	18	0	83

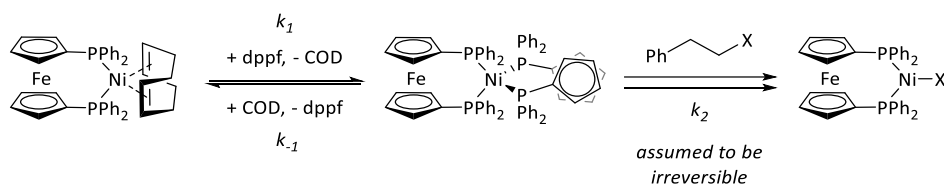
Cross-coupling of 1-chlorooctane

A cross-coupling reaction with 1-chlorooctane was carried out to ensure the phenyl ring on the substrates used in this study were not affecting the products (Scheme S1). The reaction mixture was analysed by GC-MS which confirmed that no other products formed during this reaction.



Scheme 7.1. Products confirmed (by GC-MS) from the coupling of 1-chlorooctane with PhMgCl.

7.2.6. Rate Expression



$$\frac{d}{dt} [\text{NiX(dppf)}] = k_2 [\text{Ni(dppf)}_2] \cdot [\text{RX}] \quad (7.1)$$

Two treatments to quantify $[\text{Ni(dppf)}_2]$:

- (i) Steady-state approximation, assumes $\frac{d}{dt} [\text{Ni(dppf)}_2] = 0$
- (ii) Equilibrium expression, assumes rapid establishment of an equilibrium

(1) Steady State Approximation:

Assume that $[\text{Ni(dppf)}_2]$ concentration does not change during the reaction:

$$\frac{d}{dt} [\text{Ni(dppf)}_2] = 0 \quad (7.2)$$

$$k_1[Ni(COD)(dppf)] \cdot [dppf] - k_{-1}[Ni(dppf)_2] \cdot [COD] - k_2[Ni(dppf)_2] \cdot [RX] = 0 \quad (7.3)$$

Rearrange to get (7.4) then (7.5) then (7.6):

$$k_{-1}[Ni(dppf)_2] \cdot [COD] + k_2[Ni(dppf)_2] \cdot [RX] = k_1[Ni(COD)(dppf)] \cdot [dppf] \quad (7.4)$$

$$(k_{-1}[COD] + k_2[RX]) \cdot [Ni(dppf)_2] = k_1[Ni(COD)(dppf)] \cdot [dppf] \quad (7.5)$$

$$[Ni(dppf)_2] = \frac{k_1[Ni(COD)(dppf)] \cdot [dppf]}{(k_{-1}[COD] + k_2[RX])} \quad (7.6)$$

Combining (7.1) and (7.6) gives (7.7):

$$\frac{d}{dt}[NiX(dppf)] = k_2[Ni(dppf)_2] \cdot [RX] = k_2[RX] \left(\frac{k_1[Ni(COD)(dppf)] \cdot [dppf]}{(k_{-1}[COD] + k_2[RX])} \right) \quad (7.7)$$

There are two limiting conditions:

(a) Under conditions where $k_{-1}[COD] \gg k_2[RX]$, (7.7) reduces to (7.8):

$$\begin{aligned} \frac{d}{dt}[NiX(dppf)] &= k_2[RX] \left(\frac{k_1[Ni(COD)(dppf)] \cdot [dppf]}{(k_{-1}[COD])} \right) = \frac{k_1 k_2 [Ni(COD)(dppf)] \cdot [dppf] \cdot [RX]}{k_{-1}[COD]} = \\ &= \frac{K_1 k_2 [Ni(COD)(dppf)] \cdot [dppf] \cdot [RX]}{[COD]} \end{aligned} \quad (7.8)$$

For first order reactions in $[Ni(COD)(dppf)]$ we observe (7.9):

$$\frac{d}{dt}[NiX(dppf)] = k_{obs}[Ni(COD)(dppf)] \quad (7.9)$$

Therefore, we can obtain (7.10):

$$k_{obs} = \frac{K_1 k_2 [dppf] \cdot [RX]}{[COD]} \quad (7.10)$$

So, first order in $[dppf]$, first order in $[RX]$, and inverse first order in $[COD]$. We know K_1 so can measure k_2 for the 'actual' reaction between $[Ni(dppf)_2]$ and alkyl halide.

(b) Under conditions where $k_{-1}[COD] \ll k_2[RX]$, (7.7) reduces to (7.11):

$$\frac{d}{dt} [NiX(dppf)] = k_2 [RX] \left(\frac{k_1 [Ni(COD)(dppf)] \cdot [dppf]}{(k_2 [RX])} \right) = k_1 [Ni(COD)(dppf)] \cdot [dppf] \quad (7.11)$$

For first order reactions in $[Ni(COD)(dppf)]$ we observe (7.9) above, so can obtain (7.12):

$$k_{obs} = k_1 [dppf] \quad (7.12)$$

First order in $[dppf]$, zero order in $[RX]$ and $[COD]$, so rate-limiting ligand exchange.

(2) Rapid Establishment of Equilibrium

Equation (7.13) describes the concentration of $[Ni(dppf)_2]$ from the initial equilibrium:

$$K_1 = \frac{[Ni(dppf)_2] \cdot [COD]}{[Ni(COD)(dppf)] \cdot [dppf]} \quad (7.13)$$

Rearrange to get equation (7.14):

$$[Ni(dppf)_2] = \frac{K_1 [Ni(COD)(dppf)] \cdot [dppf]}{[COD]} \quad (7.14)$$

Insert equation (7.14) into equation (7.1) to get equation (7.8) from above:

$$\begin{aligned} \frac{d}{dt} [NiX(dppf)] &= k_2 [Ni(dppf)_2] \cdot [RX] = (k_2 [RX]) \cdot \frac{K_1 [Ni(COD)(dppf)] \cdot [dppf]}{[COD]} = \\ &= \frac{K_1 k_2 [Ni(COD)(dppf)] \cdot [dppf] \cdot [RX]}{[COD]} \end{aligned} \quad (7.8)$$

(and so equation (7.10) follows)

7.2.7. Computational Details

General

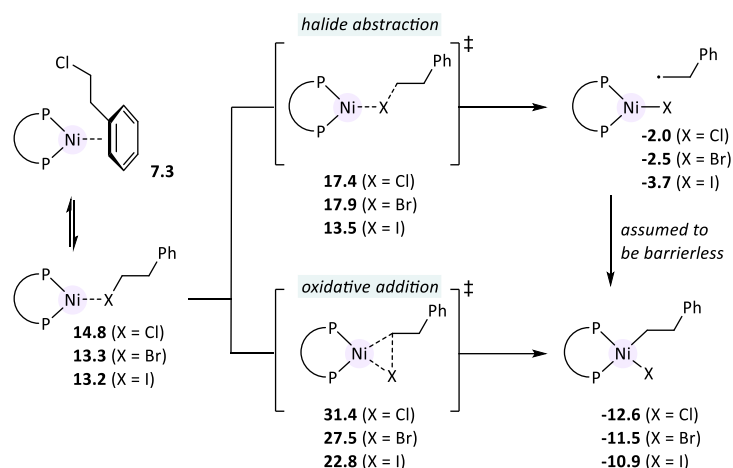
- All calculations were carried out using Gaussian16 Rev. A.03.²⁸²
- All energies are quoted in kcal mol⁻¹ with respect to $[Ni(COD)(dppf)]$.
- Free energy corrections were computed at 298 K and 1 atm.

- The B3LYP functional^{283–285} was used throughout, in combination with Grimme’s D3 dispersion corrections²⁸⁶ for both optimisation and single point calculations.
- No symmetry constraints were used.
- Solvation using the SMD model in benzene solvent was included for single point calculations only.
- For optimisation, the 6-31G(d) basis set^{287–289} was used for H, C, P, and Cl, the LANL2DZ(d,p) basis set²⁹⁰ was used for Br and I, and the LANL2TZ(f) basis set^{291–293} was used for Ni and Fe. For single point calculations, the 6-311+G(d,p) basis set²⁹⁴ was used for all atoms except I, for which the LANL2DZ(d,p) basis set was employed.
- The nature of all stationary points was confirmed using frequency calculations, with all minima having no imaginary frequencies and all transition states having one.
- For all transition states, IRC calculations were performed using either the IRC keyword in Gaussian, followed by optimisation of the resulting structures, or by adjusting and optimising the structures based on the animation of imaginary frequencies.
- The electronic energies of open shell singlet stationary points where $S^2 \neq 0$ were corrected for triplet contamination using Yamaguchi’s equation below,^{295–297} where E_{OSS} is the uncorrected energy of the open shell singlet, $E_{triplet}$ is the energy of the triplet state at the open shell singlet geometry, and $\langle S^2 \rangle_{OSS}$ is the S^2 value of the open shell singlet calculation.

$$E_{singlet} = \frac{2E_{OSS} - E_{triplet} \cdot \langle S^2 \rangle_{OSS}}{2 - \langle S^2 \rangle_{OSS}}$$

Reactions *via* [Ni(dppf)]

Oxidative addition (three-centre concerted) and halide abstraction were modelled for the reactions of [Ni(dppf)] with all three (2-haloethyl)benzenes.



Marcus-Hush Treatment

The four-point method was used to estimate the barriers for electron transfer from $[\text{Ni}(\text{dppf})_2]$, and $[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})]$ to $\text{PhCH}_2\text{CH}_2\text{X}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$). This assumes that the electron transfer event is fast, but that the subsequent reorganisations of the oxidised and reduced species present a barrier to the reaction. This can be estimated according to the following expression:

$$\Delta G^\ddagger = (\lambda_i / 4) \cdot (1 + \Delta G^\circ / \lambda_i)^2$$

$$\lambda_i = (1/2) \cdot (\lambda_i(\text{Ni}) + \lambda_i(\text{PhCH}_2\text{CH}_2\text{X})) \quad \text{where Ni is the nickel species concerned}$$

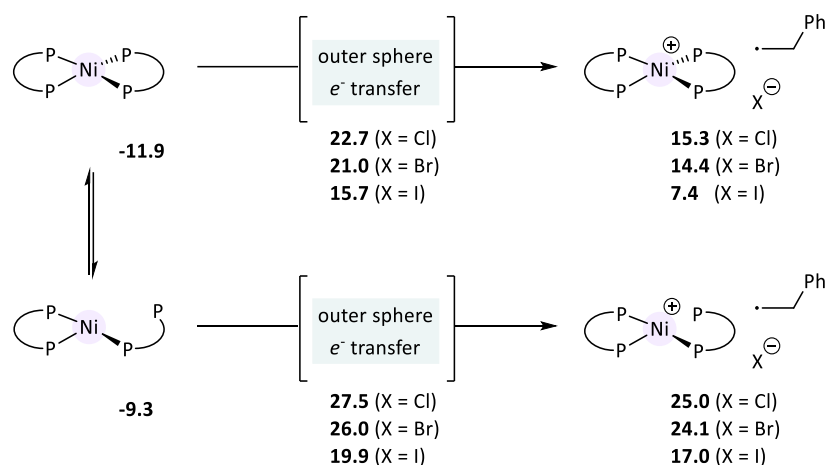
$$\lambda_i(\text{Ni}) = (E_{\text{neutral}}(\text{R}_{\text{cation}}) - E_{\text{neutral}}(\text{R}_{\text{neutral}})) + (E_{\text{cation}}(\text{R}_{\text{neutral}}) - E_{\text{cation}}(\text{R}_{\text{cation}}))$$

where $\text{R}_{\text{neutral}}$ is the optimised geometry of the neutral species, R_{cation} is the optimised geometry of the cationic nickel(I) species, E_{neutral} is the energy calculated using a single point calculation with charge 0 and multiplicity 1, and E_{cation} is the energy calculated using a single point calculation with charge +1 and multiplicity 2

$$\lambda_i(\text{PhCH}_2\text{CH}_2\text{X}) = (E_{\text{neutral}}(\text{R}_{\text{anion}}) - E_{\text{neutral}}(\text{R}_{\text{neutral}})) + (E_{\text{anion}}(\text{R}_{\text{neutral}}) - E_{\text{anion}}(\text{R}_{\text{anion}}))$$

where $\text{R}_{\text{neutral}}$ is the optimised geometry of the neutral species, R_{anion} is the optimised geometry of the radical anion, E_{neutral} is the energy calculated using a single point calculation with charge 0 and multiplicity 1, and E_{anion} is the

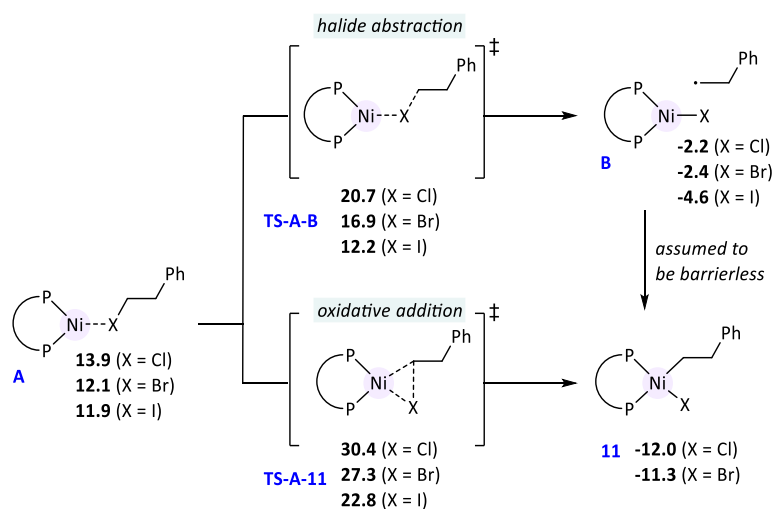
energy calculated using a single point calculation with charge -1 and multiplicity 2



Solvent Effect

Issues with optimisation in solvent mean that all structures are optimised in the gas phase with solvation added during single point calculations. Some structures could be optimised with the SMD solvation model (in benzene) and data are provided here for comparison. Optimisation in solvent has relatively little effect.

Reactions via [Ni(dppf)]



Marcus Hush Treatment

The structures of $[\text{Ni}(\text{dppf})_2]^+$ and $[\text{Ni}(\kappa^2\text{-dppf})(\kappa^1\text{-dppf})]^+$ could not be optimised in solvent, but those of $[\text{PhCH}_2\text{CH}_2\text{X}]^{\bullet-}$ could ($\text{X} = \text{Cl}, \text{Br}, \text{I}$), so these were used in the calculation to identify whether the solvation of the resulting halide anion (from spontaneous rearrangement of the alkyl halide radical anion) had a significant effect on the electron transfer barrier. The energies do not differ significantly and do not render outer sphere electron transfer competitive with halide abstraction.

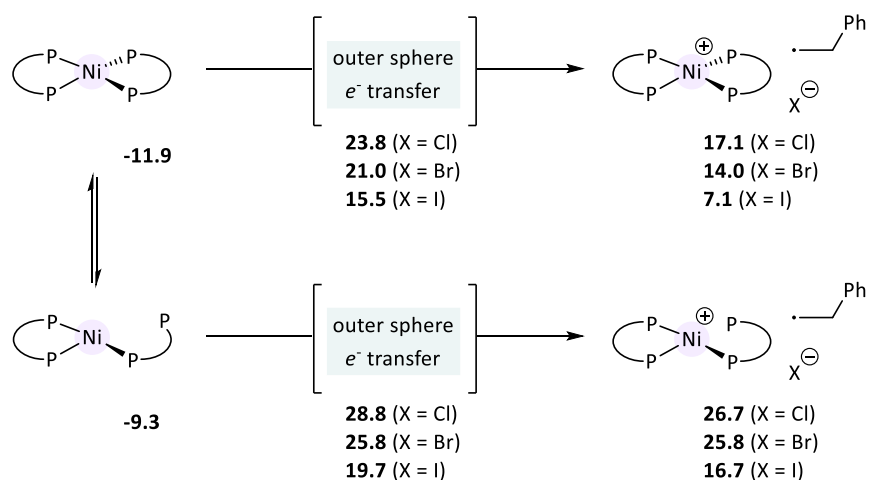
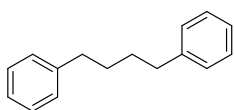


Table of Energies can be found at ACS, 2020, 10, 10717 - 10725.

7.3. Experimental Data for Chapter 3

7.3.1. Synthesis of Compounds



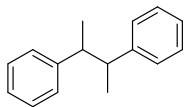
1,4-Diphenylbutane. 1,4-Diphenyl-1,3-butadiene (1 g, 4.8 mmol) was added to a RBF with Pd/C (0.1 g, 10wt%), which was then sealed with septum and evacuated and backfilled with nitrogen. Propan-2-ol (20 mL) was added and the flask was evacuated and backfilled again. A balloon of hydrogen was attached to the flask *via* a needle. The reaction was then stirred at room temperature for 24 h. The balloon was removed, the Pd/C was filtered off and the solvent was removed under reduced pressure to give 1,3-diphenylbutane as a white solid (0.7 g, 73%).

^1H NMR (400 MHz, CDCl_3): δ 1.71 (dt, 4H, $^3J_{\text{H-H}} = 7.0$ Hz, $\text{CH}_2\text{-aryl}$), 2.67 (t, 4H, $^3J_{\text{H-H}} = 7.1$ Hz, CH_2CH_2), 7.19 – 7.22 (m, 6H), 2.28 – 7.32 (m, 4H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 30.6, 35.3, 125.1, 127.8, 127.9, 142.2.

GC-MS ($\text{C}_{16}\text{H}_{18}$) m/z : 210.2.

NMR data consistent with the literature.²⁹⁸



2,3-Diphenylbutane. Benzil (2 g, 9.5 mmol) was dissolved in anhydrous THF (20 mL) under inert conditions. MeMgCl (12.6 mL, 3 M) was added dropwise and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched (HCl , 1 M, 100 mL) and extracted with DCM (3 x 20 mL). The organic layers combined, dried over MgSO_4 , filtered and concentrated to give 2,3-diphenylbutane-2,3-diol (used in the next step without purification).

Following a literature preparation.²⁹⁹ 2,3-Diphenylbutane-2,3-diol (1.5 g) was dissolved in hexamethylphosphoramide (20 mL) and stirred at room temperature for 2 h. The mixture was then refluxed for 90 mins. After cooling, Et_2O (25 mL) was added and washed with H_2O (100 mL). The aqueous layer was extracted with Et_2O (15 mL). Combined organic layers were then washed with H_2O (2 x 50 mL) and brine (25 mL), dried over MgSO_4 , filtered and concentrated to give a brown/red oil. Column chromatography (petroleum ether) was used to purify to give 2,3-diphenylbuta-1,3-diene as a white solid (used in the next step).

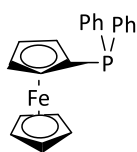
2,3-Diphenylbuta-1,3-diene (150 mg) was added to a RBF with Pd/C (15 mg, 10wt%), which was then sealed with septum and evacuated and backfilled with nitrogen. Propan-2-ol (20 mL) was added and the flask was evacuated and backfilled again. A balloon of hydrogen was attached to the flask *via* a needle. The reaction was then stirred at room temperature for 24 h. The balloon was removed, the Pd/C was filtered off and the solvent was removed under reduced pressure to give 2,3-diphenylbutane (95 mg, 5%) as a white solid.

^1H NMR (400 MHz, CDCl_3): δ 1.05 (dd, 6H, $^3J_{\text{H-H}} = 2.2, 6.7$ Hz), 1.31 (dd, 4H, $^3J_{\text{H-H}} = 1.9, 6.7$ Hz), 2.80 – 2.84 (m, 2H), 2.93 – 3.00 (m, 1.3H), 7.02 – 7.04 (m, 2.5H), 7.09 – 7.14 (m, 1.3H), 7.17 – 7.26 (m, 8.2H), 7.32 – 7.36 (m, 3.8H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 17.4, 20.5, 45.9, 46.8, 125.2, 125.5, 127.1, 127.2, 127.3, 127.8, 145.9.

GC-MS ($\text{C}_{16}\text{H}_{18}$) m/z : 210.2.

NMR data consistent with the literature.³⁰⁰



1,1'-Bis(diphenylphosphinyl)ferrocene. Prepared according to a literature procedure.³⁰¹ Ferrocene (1.9 g, 0.1 mmol) and aluminium chloride (1.3 g, 0.1 mmol) was dissolved in hexane (20 mL). Chlorodiphenyl phosphine was added and solution refluxed for 16 h. Hexane phase was decanted and solids extracted

with fresh hexane (50 mL). This was repeated with water (50 mL). Both extracts discarded. Solids extracted with hot PhMe (50 mL). PhMe organic phases dried over MgSO_4 , filtered and concentrated to dryness. The residue was extracted with hexane (100 mL) and this extracted concentrated to yield the product as a yellow powder (92 mg, 3%).

^1H NMR (400 MHz, CDCl_3): δ 4.12 (q, 4H, $^3J_{\text{H-H}} = 1.8$ Hz), 4.39 (t, 4H, $^3J_{\text{H-H}} = 1.8$ Hz), 7.33 – 7.41 (m, 20H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 68.6, 70.2 (d, $J_{\text{P-C}} = 3.9$ Hz), 72.4 (d, $J_{\text{P-C}} = 14.9$ Hz), 127.6 (d, $J_{\text{P-C}} = 14.9$ Hz), 127.9, 132.9, 133.1, 138.6 (d, $J_{\text{P-C}} = 9.6$ Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ -17.0.

7.3.2. Kinetic Experiments

All kinetic plots can be found online in the supplementary information at *Organometallics*, 2021, **40**, 1997 – 2007.¹⁵⁵

Table 7.12. Rate constants obtained from plotting the natural log of the concentration of Ni⁰ versus time (first-order dependence). All reactions carried out with Ni(COD)(dppf) (**1**) (22 mmol L⁻¹) 2-bromoethylbenzene (0.3 mol L⁻¹) as substrate and 13.2 mmol L⁻¹ of each additive in 0.5 mL Toluene-d₈.

Entry	Additive	T (K)	k_{obs} (s ⁻¹)
1a	P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	263	2.9 × 10 ⁻³
1b	P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	263	2.7 × 10 ⁻³
2a	P(<i>m</i> -C ₆ H ₄ Me) ₃	263	2.4 × 10 ⁻³
2b	P(<i>m</i> -C ₆ H ₄ Me) ₃	263	2.3 × 10 ⁻³
3a	P(<i>p</i> -C ₆ H ₄ F) ₃	263	2.3 × 10 ⁻³
3b	P(<i>p</i> -C ₆ H ₄ F) ₃	263	2.4 × 10 ⁻³
4a	P(<i>p</i> -C ₆ H ₄ Me) ₃	263	1.6 × 10 ⁻³
4b	P(<i>p</i> -C ₆ H ₄ Me) ₃	263	1.7 × 10 ⁻³
5a	PPh ₃	263	1.38 × 10 ⁻³
5b	PPh ₃	263	1.43 × 10 ⁻³
6a	P(<i>p</i> -C ₆ H ₄ OMe) ₃	263	1.2 × 10 ⁻³
6b	P(<i>p</i> -C ₆ H ₄ OMe) ₃	263	1.3 × 10 ⁻³
7a	P(<i>p</i> -C ₆ H ₄ OMe) ₃	273	4.3 × 10 ⁻³
7b	P(<i>p</i> -C ₆ H ₄ OMe) ₃	273	4.4 × 10 ⁻³
8a	P(<i>n</i> -Bu) ₃	273	8.3 × 10 ⁻⁴
8b	P(<i>n</i> -Bu) ₃	273	9.1 × 10 ⁻⁴
9a	(Diphenylphosphinyl)ferrocene	273	1.84 × 10 ⁻³
9b	(Diphenylphosphinyl)ferrocene	273	1.75 × 10 ⁻³
10a	dppf	273	4.9 × 10 ⁻⁴

10b	dppf	273	5.0×10^{-4}
11a	PMe ₃	293	3.2×10^{-3}
11b	PMe ₃	293	3.3×10^{-3}
12a	AsPh ₃	293	2.7×10^{-3}
12b	AsPh ₃	293	2.6×10^{-3}
13a	SbPh ₃	293	1.7×10^{-3}
13b	SbPh ₃	293	1.8×10^{-3}
14a	2,2'-Bipyridine	293	1.4×10^{-3}
14b	2,2'-Bipyridine	293	1.7×10^{-3}
15a	PCy ₃	293	9.6×10^{-4}
15b	PCy ₃	293	9.1×10^{-4}
16a	Pyridine	293	7.3×10^{-4}
16b	Pyridine	293	7.0×10^{-4}
17a	P(OPh) ₃	293	4.6×10^{-4}
17b	P(OPh) ₃	293	4.3×10^{-4}
18a	NEt ₃	293	4.7×10^{-4}
18b	NEt ₃	293	4.3×10^{-4}
19a	P(<i>o</i> -C ₆ H ₄ Me) ₃	273	5.1×10^{-5}
19b	P(<i>o</i> -C ₆ H ₄ Me) ₃	273	3.4×10^{-5}
20a	P(<i>o</i> -C ₆ H ₄ Me) ₃	293	4.7×10^{-3}
20b	P(<i>o</i> -C ₆ H ₄ Me) ₃	293	5.0×10^{-3}
21a	dppm	293	1.11×10^{-3}
21b	dppm	293	1.12×10^{-3}
22a	dppe	293	1.59×10^{-3}
22b	dppe	293	1.63×10^{-3}
23a	dppp	293	8.54×10^{-4}
23b	dppp	293	8.51×10^{-4}
24a	dppb	263	4.31×10^{-3}

24b	dppb	263	4.32×10^{-3}
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Table 7.13. The order in PPh_3 was investigated by varying amounts of PPh_3 added into each kinetic experiment. All reactions carried out with 2-bromoethylbenzene (0.3 mol L^{-1}) as substrate and ran in Toluene- d_8 .

Entry	$[\text{PPh}_3]$ (mmol L^{-1})	T (K)	k_{obs} (s^{-1})
1a	3.3	263	4.5×10^{-4}
1b	3.3	263	4.9×10^{-4}
2a	6.6	263	1.1×10^{-3}
2b	6.6	263	1.0×10^{-3}
3a	9.9	263	1.5×10^{-3}
3b	9.9	263	1.6×10^{-3}
4a	16.5	263	2.1×10^{-3}
4b	16.5	263	2.1×10^{-3}

7.3.3. Data Analysis

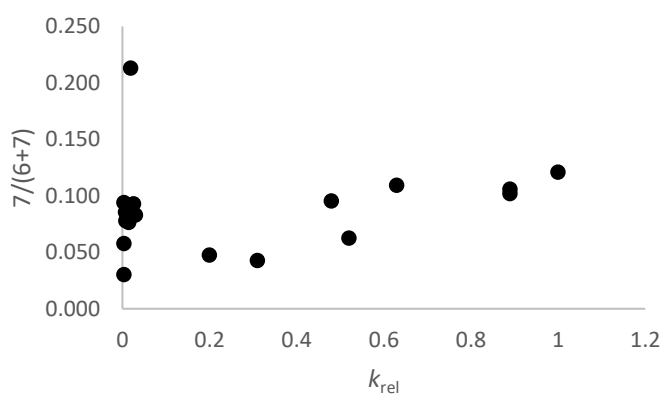


Figure 7.7.10. Ratio of products vs k_{rel} for iodoethylbenzene.

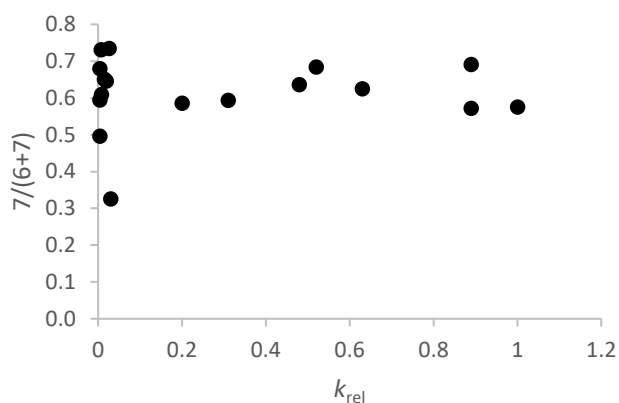


Figure 7.11. Ratio of products vs k_{rel} for bromoethylbenzene.

7.3.4. GC Calibrations

Table 7.14. Response factors given against standards for the substrates/products used in this work.

Substrate	Response factor against <i>n</i> -tetradecane
2,3-Diphenylbutane	1.1518
1,4-Diphenylbutane	0.8355

7.3.5. Cross-Coupling Reactions

Table 7.15. Duplicate results of all cross-coupling reactions carried out with 2-chloroethylbenzene (**4-Cl**). Ni(COD)(dppf) (**1**) (5 mol%) was used as the catalyst for all reactions, with 5 mol% of the additive present.

Entry	Additive	4-Cl (%)	6 (%)	7 (%)	8(%)	Styrene (%)	PhEt (%)	PhPh (%)
1a	PPh ₃	14	1	25	7	2	1	53
1b	PPh ₃	13	1	24	7	5	3	50
2a	FcPPh ₂	26	2	19	6	7	2	42
2b	FcPPh ₂	28	2	20	5	8	2	38
3a	P(<i>o</i> -C ₆ H ₄ Me) ₃	5	2	10	3	5	2	65
3b	P(<i>o</i> -C ₆ H ₄ Me) ₃	9	2	9	4	4	2	60

4a	$P(m\text{-C}_6\text{H}_4\text{Me})_3$	0	4	30	1	4	3	48
4b	$P(m\text{-C}_6\text{H}_4\text{Me})_3$	0	4	29	1	6	3	44
5a	$P(p\text{-C}_6\text{H}_4\text{Me})_3$	4	2	27	1	5	3	43
5b	$P(p\text{-C}_6\text{H}_4\text{Me})_3$	0	4	25	1	4	3	49
6a	$P(p\text{-C}_6\text{H}_4\text{OMe})_3$	11	3	39	12	8	4	81
6b	$P(p\text{-C}_6\text{H}_4\text{OMe})_3$	7	2	27	8	7	4	50
7a	$P(p\text{-C}_6\text{H}_4\text{CF}_3)_3$	42	1	12	6	8	3	58
7b	$P(p\text{-C}_6\text{H}_4\text{CF}_3)_3$	43	1	11	5	5	2	60
8a	$P(p\text{-C}_6\text{H}_4\text{F})_3$	16	1	21	9	5	3	54
8b	$P(p\text{-C}_6\text{H}_4\text{F})_3$	19	1	19	9	5	2	57
9a	PMe_3	12	2	11	7	1	0	57
9b	PMe_3	13	2	11	7	1	2	57
10a	PBu_3	3	2	8	13	6	3	68
10b	PBu_3	0	2	10	13	4	3	75
11a	PCy_3	7	2	15	10	1	3	62
11b	PCy_3	15	2	15	7	3	3	52
12a	P(OPh)_3	5	2	4	10	4	4	55
12b	P(OPh)_3	9	3	5	7	9	3	52
13a	AsPh_3	5	2	4	11	4	4	65
13b	AsPh_3	9	3	5	12	9	3	70
14a	SbPh_3	28	15	5	6	3	2	72
14b	SbPh_3	26	14	5	6	4	3	64
15a	2,2'-bipyridine	7	1	5	8	7	0	74
15b	2,2'-bipyridine	7	3	6	9	6	2	70
16a	NEt_3	13	2	8	11	3	3	63
16b	NEt_3	7	2	10	11	8	3	68
17a	dppm	46	1	7	0	0	0	60
17b	dppm	20	0	3	0	0	0	52

18a	dppe	33	1	5	0	0	0	60
18b	dppe	50	1	14	0	0	0	52
19a	dppp	33	1	36	0	10	4	64
19b	dppp	50	1	36	0	0	4	55
20a	dppb	82	3	5	0	7	0	36
20b	dppb	89	3	6	0	6	2	35

Table 7.16. Duplicate results of all cross-coupling reactions carried out with 2-bromoethylbenzene (**4-Br**). Ni(COD)(dppf) (**1**) (5 mol%) was used as the catalyst for all reactions, with 5 mol% of the additive present.

Entry	Additive	4-Br (%)	6 (%)	7 (%)	8 (%)	Styrene (%)	Ethylbenzene (%)	Biphenyl (%)
1a	PPh ₃	0	14	33	5	2	2	52
1b	PPh ₃	0	15	31	4	4	3	43
2a	FcPPh ₂	9	17	24	3	9	2	31
2b	FcPPh ₂	11	17	24	3	10	2	32
3a	P(<i>o</i> -C ₆ H ₄ Me) ₃	0	12	19	8	3	15	24
3b	P(<i>o</i> -C ₆ H ₄ Me) ₃	0	11	16	8	3	17	26
4a	P(<i>m</i> -C ₆ H ₄ Me) ₃	0	24	35	3	7	8	10
4b	P(<i>m</i> -C ₆ H ₄ Me) ₃	0	28	36	2	7	5	7
5a	P(<i>p</i> -C ₆ H ₄ Me) ₃	0	21	36	3	7	9	10
5b	P(<i>p</i> -C ₆ H ₄ Me) ₃	0	20	34	3	4	10	9
6a	P(<i>p</i> -C ₆ H ₄ OMe) ₃	0	18	34	3	6	3	38
6b	P(<i>p</i> -C ₆ H ₄ OMe) ₃	0	20	34	3	2	2	44
7a	P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	2	19	25	4	5	13	17
7b	P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	5	17	25	4	5	8	14
8a	P(<i>p</i> -C ₆ H ₄ F) ₃	0	14	29	6	2	2	52
8b	P(<i>p</i> -C ₆ H ₄ F) ₃	0	13	29	6	6	3	45
9a	PMe ₃	0	42	21	2	10	3	33

9b	PMe ₃	0	44	20	1	6	2	35
10a	PBu ₃	0	12	17	7	7	0	52
10b	PBu ₃	0	16	25	10	5	0	68
11a	PCy ₃	0	13	21	6	0	3	50
11b	PCy ₃	2	12	17	4	6	2	29
12a	P(OPh) ₃	0	28	27	3	10	3	38
12b	P(OPh) ₃	0	28	29	3	9	2	45
13a	AsPh ₃	0	6	13	9	3	3	70
13b	AsPh ₃	0	4	15	8	8	3	48
14a	SbPh ₃	0	14	25	4	10	3	54
14b	SbPh ₃	0	14	26	4	10	3	53
15a	2,2'-bipyridine	0	6	11	5	11	4	50
15b	2,2'-bipyridine	0	8	14	6	9	3	67
16a	NEt ₃	0	10	20	8	10	3	51
16b	NEt ₃	0	8	17	5	8	3	33
17a	dppm	0	21	5	0	0	0	47
17b	dppm	0	23	16	0	2	2	49
18a	dppe	0	18	12	0	4	0	52
18b	dppe	0	15	6	0	3	0	57
19a	dppp	0	24	15	0	4	3	46
19b	dppp	0	21	13	0	7	3	41
20a	dppb	0	35	31	0	10	3	34
20b	dppb	0	34	31	0	9	2	31

Table 7.17. Duplicate results of all cross-coupling reactions carried out with 2-iodoethylbenzene (**4-I**). Ni(COD)(dppf) (**1**) (5 mol%) was used as the catalyst for all reactions, with 5 mol% of the additive present.

Entry	Additive	4-I (%)	6 (%)	7 (%)	8 (%)	Styrene (%)	Ethylbenzene (%)	Biphenyl (%)
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1a	PPh ₃	0	59	5	1	10	8	15
1b	PPh ₃	0	48	2	1	9	15	21
2a	FcPPh ₂	8	40	2	1	10	2	31
2b	FcPPh ₂	9	40	2	1	8	2	32
3a	P(<i>o</i> -C ₆ H ₄ Me) ₃	0	46	3	1	6	14	19
3b	P(<i>o</i> -C ₆ H ₄ Me) ₃	0	49	3	1	8	14	17
4a	P(<i>m</i> -C ₆ H ₄ Me) ₃	0	56	7	1	8	4	11
4b	P(<i>m</i> -C ₆ H ₄ Me) ₃	0	59	6	1	8	5	9
5a	P(<i>p</i> -C ₆ H ₄ Me) ₃	0	55	6	1	5	7	12
5b	P(<i>p</i> -C ₆ H ₄ Me) ₃	0	54	7	1	7	7	12
6a	P(<i>p</i> -C ₆ H ₄ OMe) ₃	0	58	6	1	7	4	8
6b	P(<i>p</i> -C ₆ H ₄ OMe) ₃	0	59	6	1	6	6	12
7a	P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	0	50	7	1	8	3	14
7b	P(<i>p</i> -C ₆ H ₄ CF ₃) ₃	0	53	7	1	7	4	10
8a	P(<i>p</i> -C ₆ H ₄ F) ₃	0	56	7	1	8	5	11
8b	P(<i>p</i> -C ₆ H ₄ F) ₃	0	60	6	1	6	5	12
9a	PMe ₃	0	54	5	1	10	3	44
9b	PMe ₃	0	51	5	1	8	3	43
10a	PBu ₃	0	50	2	0	5	12	14
10b	PBu ₃	0	50	2	0	4	17	16
11a	PCy ₃	0	59	4	1	8	16	21
11b	PCy ₃	0	59	6	1	8	10	18
12a	P(OPh) ₃	0	53	6	2	12	4	39
12b	P(OPh) ₃	0	49	5	2	9	3	40
13a	AsPh ₃	0	39	4	1	12	4	49
13b	AsPh ₃	0	38	4	1	10	4	51
14a	SbPh ₃	0	22	6	3	10	3	51
14b	SbPh ₃	0	21	6	3	12	4	50

15a	2,2'-bipyridine	0	45	4	1	10	3	49
15b	2,2'-bipyridine	0	44	4	1	10	4	45
16a	NEt ₃	12	31	1	1	11	3	32
16b	NEt ₃	8	33	1	2	11	3	35
17a	dppm	0	44	3	0	9	3	44
17b	dppm	0	32	1	0	9	0	50
18a	dppe	0	34	1	0	2	2	52
18b	dppe	0	40	2	0	2	2	50
19a	dppp	0	39	1	0	4	0	50
19b	dppp	0	46	2	0	11	4	46
20a	dppb	0	51	6	0	8	3	44
20b	dppb	0	49	8	0	12	3	40

7.3.6. Computational Details

Methodology

Software. All DFT calculations were carried out using Gaussian16 Rev. A.03.²⁸² All DLPNO-CCSD(T) calculations^{302–304} were carried out using Orca 4.2.1.^{305,306}

Optimisation. All geometry optimisations were carried out using the B3LYP functional^{283–285,307} with the Grimme D3 empirical dispersion correction.²⁸⁶ The LANL2TZ(f) pseudopotential/ECP was used for nickel and iron, while LANL2DZ(d,p) was used for bromine, arsenic, and antimony.^{290,292,293} The 6-31G(d) basis set was used for all other atoms. Optimisations were carried out without symmetry constraints in the gas phase. Frequency calculations were used to verify the nature of stationary points (zero imaginary frequencies for each of the minima; one imaginary frequency for each of the transition states). Each transition state was checked using IRC calculations or by optimisations along the reaction coordinate.

Single Points. Unless otherwise stated, the energies of each of the structure were calculated using single point calculations with the M06 functional,³⁰⁸ the LANL2DZ(d,p)

pseudopotential/ECP on antimony, and the 6-311+G(d,p) basis set on all other atoms. Solvation was modelled using the SMD model (in benzene).³⁰⁹

Corrections. The free energy of each species was corrected for solution-phase behaviour by adding 1.89 kcal/mol.¹⁴⁶ The electronic energies of each open shell singlet species was corrected for triplet contamination using Yamaguchi's approach:²⁹⁵

$$E_{corr.OSS} = \frac{2E_{OSS} - (E_{triplet} \cdot \langle S^2 \rangle_{OSS})}{2 - \langle S^2 \rangle_{OSS}}$$

Free Energies. All energies quoted in the manuscript are free energies in kcal/mol with respect to [Ni(COD)(dppf)].

%V_{bur} Calculations for L in [Ni(dppf)(L)]

All buried volume calculations were carried out using SambVca v2.1, which can be accessed for free *via* the internet at <https://www.molnac.unisa.it/OMtools/sambvca2.1/index.html>. Further details about this tool can be found in the relevant publications.^{208–210}

Table 7.18. %V_{bur} for L in [Ni(dppf)L].

Ligand	%V _{bur}	Ligand	%V _{bur}
PMe ₃	24.0	PPh ₃	31.2
PCy ₃	31.9	(<i>p</i> -MeOC ₆ H ₄) ₃ P	31.3
AsPh ₃	22.7	(<i>p</i> -MeC ₆ H ₄) ₃ P	31.3
SbPh ₃	27.7	(<i>p</i> -FC ₆ H ₄) ₃ P	31.4
(<i>p</i> -F ₃ CC ₆ H ₄) ₃ P	31.3		

Benchmarking Studies

Benchmarking was carried out using the published geometries for [Ni(COD)(dppf)], COD, and [Ni(dppf)₂] obtained at the B3LYP-D3/6-31G(d)+LANL2DZ(d,p)+LANL2TZ(f) level of theory in the gas phase. A new geometry was obtained for dppf which is typically *ca.* 1- 2 kcal/mol lower in energy depending on the level of theory used.

Single point calculations were carried out using different functionals, basis sets, grids, and dispersion corrections. Benzene solvation (SMD model) was applied in each case. Free energy

changes were obtained by applying the correction to free energy obtained during the geometry optimisation for each structure (which included a frequency calculation).

Species	[Ni(COD)(dppf)]	dppf	COD	[Ni(dppf) ₂]
G _{corr} (Ha)	0.631292	0.452033	0.149935	0.946725

Table 7.19. DLPNO-CCSD(T) using the cc-pVTZ basis set, and TIGHTSCF and RIJCOSX options. $\Delta G = -3.8$ kcal/mol.

Species	[Ni(COD)(dppf)]	dppf	COD	[Ni(dppf) ₂]
E (Ha)	-5074.026353	-3254.895329	-311.444404	-8017.493088

Table 7.20. Electronic energies in Ha. Free energy change in kcal/mol.

Functional	Basis Set	Disp. Corr.	Grid	[Ni(COD)(dppf)]	dppf	[Ni(dppf) ₂]	COD	ΔG
B3LYP	6-311+G(d,p)	D3	UltraFine	-5079.936888	-3259.399194	-8027.22525	-312.1423956	-11.9
B3LYP	6-311+G(d,p)	D3	SuperFine	-5079.936883	-3259.399194	-8027.225207	-312.1423932	-11.9
B3LYP	6-311+G(d,p)	D3BJ	UltraFine	-5080.065996	-3259.499706	-8027.446896	-312.1604942	-17.9
B3LYP	6-311+G(2d,2p)	D3	UltraFine	-5080.005417	-3259.453800	-8027.336275	-312.1550359	-12.2
B3LYP	6-311+G(2d,2p)	XDM ^a	UltraFine	-5080.097799	-3259.529563	-8027.480728	-312.1668943	- 5.2
CAM-B3LYP	6-311+G(d,p)	-	UltraFine	-5078.888514	-3258.552238	-8025.497539	-311.9309316	17.5
CAM-B3LYP	6-311+G(d,p)	D3	UltraFine	-5078.999192	-3258.617940	-8025.699386	-311.9417672	- 7.2
CAM-B3LYP	6-311+G(d,p)	D3BJ	UltraFine	-5079.043832	-3258.655317	-8025.7848	-311.9466062	-12.1
BP86	6-311+G(d,p)	D3	UltraFine	-5080.436661	-3259.642782	-8027.992979	-312.1269391	-17.8
BP86	6-311+G(d,p)	D3BJ	UltraFine	-5080.543627	-3259.726679	-8028.18413	-312.1398999	-25.4
M06	6-311+G(d,p)	- ^b	UltraFine	-5078.288467	-3258.130334	-8024.572644	-311.8618736	- 1.9
M06	6-311+G(d,p)	D3	UltraFine	-5078.319811	-3258.149504	-8024.636856	-311.8640859	-12.7
M06-L	6-311+G(d,p)	- ^b	UltraFine	-5079.44428	-3259.057408	-8026.453381	-312.0715822	- 7.1
M11	6-311+G(d,p)	- ^b	UltraFine	-5078.343213	-3258.275085	-8024.728845	-311.9027729	- 0.9
M11-L	6-311+G(d,p)	- ^b	UltraFine	-5079.673051	-3259.151228	-8026.775909	-312.052852	4.7
MN15	6-311+G(d,p)	- ^b	UltraFine	-5078.092054	-3257.676285	-8024.082175	-311.7037077	- 3.9
ω B97X-D	6-311+G(d,p)	(D2) ^c	UltraFine	-5079.246492	-3258.838687	-8026.089777	-312.021771	- 9.2

^a Single point calculation carried out without dispersion correction, and XDM correction added subsequently using postg.

^b M06(-L), M11(-L), and MN15 include dispersion treatments in the functional.

^c ω B97X-D includes the D2 empirical correction.

Table of Energies can be found at *Organometallics*, 2021, **40**, 1997 – 2007.¹⁵⁵

7.4. Experimental Data for Chapter 4

7.4.1. Synthesis of Compounds

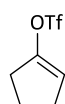
Vinyl Triflates

General Procedure A

Prepared following a literature preparation.²²¹ To a solution of ketone (1 equiv.), 2,6-di-tert-butyl-4-methylpyridine (DTBMP, 1.1 equiv) in DCM at 0 °C, Tf₂O (1.2 equiv.) was added dropwise. The reaction was left to warm to room temperature at stirred overnight. Solvent was evaporated and petroleum ether was used to extract from the solid residue and concentrated under reduced pressure. The crude product was purified by Kugelrohr.

General Procedure B

Preparing following a literature preparation.²²¹ To a solution of ketone (1 equiv.) in THF, LiHMDS (1.2 equiv.) was added dropwise at -78 °C. After stirring for 1 hour at -78 °C, PhNTf₂ (1.2 equiv.) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched with H₂O and extracted with EtOAc. The combined organic layers were washed with saturated NH₄Cl and brine, dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography.



Cyclopent-1-en-1-yl trifluoromethanesulfonate. Synthesised from cyclopentanone (2 mL, 22.6 mmol) following general procedure A. Isolated as a colourless oil (1.1 g, 23%).

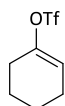
¹H NMR (400 MHz, CDCl₃): δ 1.91 – 1.97 (m, 2H), 2.30 – 2.34 (m, 2H), 2.46 – 2.50 (m, 2H), 5.23 – 5.54 (m, 1H).

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 20.9, 27.9, 30.8, 118.1 (q, *J*_{C-F} = 319.8 Hz), 149.6.

¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -73.6.

GC-MS (C₆H₇F₃O₃S) *m/z*: 216.1.

NMR data consistent with the literature.²²¹



Cyclohex-1-en-1-yl trifluoromethanesulfonate. Synthesised from cyclohexanone (1 mL, 10 mmol) following general procedure A. Isolated as a colourless oil (1.3 g, 56%).

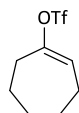
¹H NMR (400 MHz, CDCl₃): δ 1.59 – 1.66 (m, 2H), 1.78 – 1.84 (m, 2H), 2.18 – 2.23 (m, 2H), 2.32 – 2.37 (m, 2H), 5.77 – 5.79 (m, 1H).

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 20.5, 22.2, 23.4, 27.1, 117.9 (q, *J*_{C-F} = 319.7 Hz), 148.8.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -74.1.

GC-MS ($\text{C}_7\text{H}_9\text{F}_3\text{O}_3\text{S}$) m/z : 230.1.

NMR data consistent with the literature.²²¹



Cyclohept-1-en-1-yl trifluoromethanesulfonate. Synthesised from cycloheptanone (2.6 mL, 22.6 mmol) following general procedure A. Isolated as a colourless oil (2.3 g, 42%).

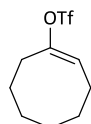
^1H NMR (400 MHz, CDCl_3): δ 1.63 – 1.78 (m, 6H), 2.16 – 2.21 (m, 2H), 2.53 – 2.55 (m, 2H), 5.90 (t, $^3J_{\text{H-H}} = 6.9$ Hz, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 24.2, 24.3, 25.8, 29.4, 32.7, 118.0 (q, $J_{\text{C-F}} = 320.7$ Hz), 122.6, 152.6.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -74.0.

GC-MS ($\text{C}_8\text{H}_{11}\text{F}_3\text{O}_3\text{S}$) m/z : 244.2.

NMR data consistent with the literature.²²¹



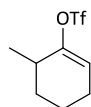
Cyclooct-1-en-1-yl trifluoromethanesulfonate. Synthesised from cyclooctanone (3 g, 23.8 mmol) following general procedure A. Isolated as a colourless oil (4.3 g, 70%).

^1H NMR (400 MHz, CDCl_3): δ 1.55 – 1.67 (m, 6H), 1.72 – 1.78 (m, 2H), 2.17 – 2.22 (m, 2H), 2.48 – 2.51 (m, 2H), 5.72 (t, $^3J_{\text{H-H}} = 6.8$ Hz, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 24.4, 25.0, 25.3, 26.6, 28.6, 29.0, 118.0 (q, $J_{\text{C-F}} = 320.6$ Hz), 120.1, 150.4.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -74.2.

NMR data consistent with the literature.²²¹



6-Methylcyclohex-1-en-1-yl trifluoromethanesulfonate. Synthesised from 2-methylcyclohexanone (1 mL, 8.2 mmol) following general procedure B. Isolated as a colourless oil (1.1 g, 51%).

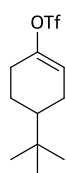
^1H NMR (400 MHz, CDCl_3): δ 1.17 (d, $^3J_{\text{H-H}} = 7.1$ Hz), 1.45 – 1.53 (m, 1H), 1.54 – 1.64 (m, 1H), 1.65 – 1.74 (m, 1H), 1.92 – 1.99 (m, 1H), 2.17 – 2.22 (m, 2H), 2.53 – 2.60 (m, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 17.3, 18.7, 23.9, 31.0, 31.9, 117.6, 118.0 (q, $J_{\text{C-F}} = 320.9$ Hz), 152.8.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -74.3.

GC-MS ($\text{C}_8\text{H}_{11}\text{F}_3\text{O}_3\text{S}$) m/z : 244.2.

NMR data consistent with the literature.²²¹



4-(*tert*-Butyl)cyclohex-1-en-1-yl trifluoromethanesulfonate. Synthesised from 4-*tert*-butylcyclohexanone (2 g, 13.0 mmol) following general procedure B. Isolated as a colourless oil (1.5 g, 40%).

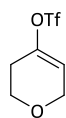
^1H NMR (400 MHz, CDCl_3): δ 0.92 (s, 9H), 1.30 – 1.44 (m, 2H), 1.93 – 2.02 (m, 2H), 2.19 – 2.27 (m, 1H), 2.31 – 2.46 (m, 2H), 5.75 – 5.78 (m, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 23.6, 24.8, 26.7, 28.1, 31.6, 42.4, 117.9, 118.1 (q, $J_{\text{C-F}} = 319.7$ Hz), 148.8.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -74.1.

GC-MS ($\text{C}_{11}\text{H}_{17}\text{F}_3\text{O}_3\text{S}$) m/z : 286.2.

NMR data consistent with the literature.²²¹



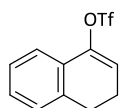
3,6-Dihydro-2H-pyran-4-yl trifluoromethanesulfonate. Synthesised from 4-oxotetrahydropyran (1 mL, 10.8 mmol) following general procedure A. Isolated as a colourless oil (0.6 g, 24%).

^1H NMR (400 MHz, CDCl_3): δ 2.47 – 2.51 (m, 2H), 3.91 (t, $^3J_{\text{H-H}} = 5.6$ Hz, 2H), 4.28 (q, $^3J_{\text{H-H}} = 2.8$ Hz, 2H), 5.83 – 5.85 (m, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 27.8, 63.4, 63.7, 116.4, 118.0 (q, $J_{\text{C-F}} = 319.3$ Hz), 145.3.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -73.8.

NMR data consistent with the literature.²²¹



3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate. Synthesised from 1-tetralone (1 mL, 7.5 mmol) following general procedure A. Isolated as a colourless oil (1.6 g, 77%).

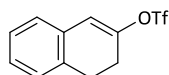
^1H NMR (400 MHz, CDCl_3): δ 2.40 – 2.44 (m, 2H), 2.78 (t, $^3J_{\text{H-H}} = 8.2$ Hz, 2H), 5.93 (t, $^3J_{\text{H-H}} = 4.9$ Hz, 1H), 7.07 – 7.28 (m, 4H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 22.3, 26.9, 117.8, 118.6 (q, $J_{\text{C-F}} = 320.9$ Hz), 121.2, 126.9, 127.8, 129.2, 136.3, 146.4.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -73.7.

GC-MS ($\text{C}_{11}\text{H}_9\text{F}_3\text{O}_3\text{S}$) m/z : 278.1.

NMR data consistent with the literature.³¹⁰



3,4-Dihydronaphthalen-2-yl trifluoromethanesulfonate. Synthesised from 2-tetralone (1 mL, 7.5 mmol) following general procedure A. Isolated as a colourless oil (1.1 g, 50%).

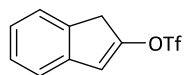
^1H NMR (400 MHz, CDCl_3): δ 2.72 (td, $^3J_{\text{H-H}} = 8.6$ Hz, $^4J_{\text{H-H}} = 1.2$ Hz, 2H), 3.09 (t, $^3J_{\text{H-H}} = 8.2$ Hz), 6.51 (s, 1H), 7.09 – 7.27 (m, 4H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 26.1, 28.1, 118.1, 118.2 (q, $J_{\text{C-F}} = 324.8$ Hz), 126.8, 127.0, 127.9, 130.6, 132.4, 149.7.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -73.5.

GC-MS ($\text{C}_{11}\text{H}_9\text{F}_3\text{O}_3\text{S}$) m/z : 278.1.

NMR data consistent with the literature.³¹¹



1H-Inden-2-yl trifluoromethanesulfonate. Synthesised from 2-indanone (1 g, 7.6 mmol) following general procedure A. Isolated as a colourless oil (1.1 g, 55%).

^1H NMR (400 MHz, CDCl_3): δ 3.69 (s, 2H), 6.72 – 6.73 (m, 1H), 7.27 – 7.36 (m, 2H), 7.39 – 7.42 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 37.2, 118.2 2 (q, $J_{\text{C-F}} = 321.3$ Hz), 119.0, 112.7, 123.3, 125.7, 126.8, 136.9, 139.7, 152.7.

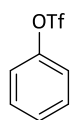
$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -72.8.

NMR data consistent with the literature.²²¹

Aryl Triflates

General Procedure

Prepared following a literature preparation.²¹⁹ To a biphasic mixture of PhMe and 30% (w/v) aqueous K_3PO_4 and phenol (1 equiv.), at 0 °C, Tf_2O (1.2 equiv.) was added dropwise. Mixture was left to stir at room temperature for 15 mins. The organic layer was concentrated and crude product purified by column chromatography.



Phenyl trifluoromethanesulfonate. Synthesised from phenol (2 g, 21.3 mmol).
Isolated as a colourless oil (2.2 g, 46%).

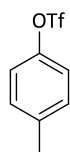
^1H NMR (400 MHz, CDCl_3): δ 7.28 – 7.32 (m, 2H), 7.39 – 7.51 (m, 3H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 118.4 (q, $J_{\text{C-F}} = 320.6$ Hz), 120.8, 127.9, 129.8, 149.2.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -72.9.

GC-MS ($\text{C}_7\text{H}_5\text{F}_3\text{O}_3\text{S}$) m/z : 226.1.

NMR data consistent with the literature.³¹²



p-Tolyl trifluoromethanesulfonate. Synthesised from *p*-cresol (1 mL, 9.6 mmol).
Isolated as a colourless oil (1.4 g, 61%).

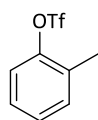
^1H NMR (400 MHz, CDCl_3): δ 2.40 (s, 3H), 7.16 – 7.12 (m, 2H), 7.24 – 7.28 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 20.4, 118.3 (q, $J_{\text{C-F}} = 320.3$ Hz), 120.5, 130.2, 138.1, 147.1.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -72.9.

GC-MS ($\text{C}_8\text{H}_7\text{F}_3\text{O}_3\text{S}$) m/z : 240.1.

NMR data consistent with the literature.³¹²



***o*-Tolyl trifluoromethanesulfonate.** Synthesised from *o*-cresol (1 g, 9.2 mmol).

Isolated as a colourless oil (1.1 g, 50%).

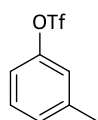
^1H NMR (400 MHz, CDCl_3): δ 2.41 (s, 3H), 7.26 – 7.34 (m, 4H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 15.8, 118.1 (q, $J_{\text{C-F}} = 314.1$ Hz), 120.8, 127.1, 127.7, 130.4, 131.7, 148.1.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -73.9.

GC-MS ($\text{C}_8\text{H}_7\text{F}_3\text{O}_3\text{S}$) m/z : 240.1.

NMR data consistent with the literature.³¹³



***m*-Tolyl trifluoromethanesulfonate.** Synthesised from *m*-cresol (1 g, 9.6 mmol).

Isolated as a colourless oil (1.4 g, 61%).

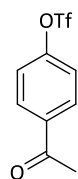
^1H NMR (400 MHz, CDCl_3): δ 2.43 (s, 3H), 7.09 – 7.11 (m, 2 H), 7.22 (d, $^3J_{\text{H-H}} = 7.6$ Hz, 1H), 7.35 (t, $^3J_{\text{H-H}} = 7.6$ Hz, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 20.8, 117.7, 118.3 (q, $J_{\text{C-F}} = 321.2$ Hz), 121.3, 128.6, 129.4, 140.4, 149.1.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -73.0.

GC-MS ($\text{C}_8\text{H}_7\text{F}_3\text{O}_3\text{S}$) m/z : 240.1.

NMR data consistent with the literature.³¹⁴



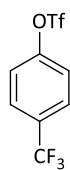
4-Acetylphenyl trifluoromethanesulfonate. Synthesised from 1-(4-hydroxyphenyl)ethan-1-one (1 g, 7.3 mmol). Isolated as a colourless oil (1.5 g, 77%).

^1H NMR (400 MHz, CDCl_3): δ 2.64 (s, 3H), 7.38 – 7.42 (m, 2H), 8.06 – 8.09 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 26.1, 118.2 (q, $J_{\text{C-F}} = 322.7$ Hz), 121.1, 130.1, 136.5, 152.0, 195.6.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -72.8.

NMR data consistent with the literature.³¹²



4-(Trifluoromethyl)phenyl trifluoromethanesulfonate. Synthesised from 4-(trifluoromethyl)phenol (1 mL, 8.2 mmol). Isolated as a colourless oil (3.0 g, 62%).

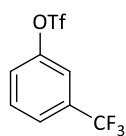
^1H NMR (400 MHz, CDCl_3): δ 7.45 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 2H), 7.79 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 118.1 (q, $J_{\text{C-F}} = 318.3$ Hz), 121.5, 123.5 (q, $J_{\text{C-F}} = 110.2$ Hz), 127.3 (q, $J_{\text{C-F}} = 3.7$ Hz), 130.4 (q, $J_{\text{C-F}} = 33.4$ Hz), 150.9.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -62.7, -72.7.

GC-MS ($\text{C}_8\text{H}_4\text{F}_6\text{O}_3\text{S}$) m/z : 294.0.

NMR data consistent with the literature.³¹⁵



3-(Trifluoromethyl)phenyl trifluoromethanesulfonate. Synthesised from 3-(trifluoromethyl)phenol (1 mL, 8.2 mmol). Isolated as a colourless oil (1.0 g, 41%).

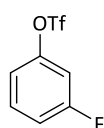
^1H NMR (400 MHz, CDCl_3): δ 7.53 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H), 7.57 (s, 1H), 7.65 (t, $^3J_{\text{H-H}} = 8.0$ Hz, 1H), 7.71 (d, $^3J_{\text{H-H}} = 7.6$ Hz, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 118.2 (q, $J_{\text{C-F}} = 320.6$ Hz), 118.3 (q, $J_{\text{C-F}} = 3.7$ Hz), 124.2 (q, $J_{\text{C-F}} = 72.5$ Hz), 124.4, 124.9 (q, $J_{\text{C-F}} = 3.7$ Hz), 130.6, 132.7 (q, $J_{\text{C-F}} = 33.8$ Hz), 148.9.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -62.9, -72.7.

GC-MS ($\text{C}_8\text{H}_4\text{F}_6\text{O}_3\text{S}$) m/z : 294.0.

NMR data consistent with the literature.³¹⁵



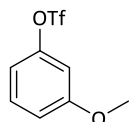
3-Fluorophenyl trifluoromethanesulfonate. Synthesised from 3-fluorophenol (1 mL, 11.0 mmol). Isolated as a colourless oil (1.4 g, 52%).

^1H NMR (400 MHz, CDCl_3): δ 7.44 – 7.49 (m, 1H), 7.06 – 7.09 (m, 2H), 7.12 – 7.19 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 109.3 (d, $J_{\text{C-F}} = 25.4$ Hz), 115.3 (d, $J_{\text{C-F}} = 21.9$ Hz), 116.7 (d, $J_{\text{C-F}} = 3.9$ Hz), 118.2 (q, $J_{\text{C-F}} = 321.6$ Hz), 130.6 (d, $J_{\text{C-F}} = 9.3$ Hz), 149.2 (d, $J_{\text{C-F}} = 10.4$ Hz), 162.2 (d, $J_{\text{C-F}} = 252.1$ Hz).

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -72.8, -108.2.

GC-MS ($\text{C}_7\text{H}_4\text{F}_4\text{O}_3\text{S}$) m/z : 244.1.



3-Methoxyphenyl trifluoromethanesulfonate. Synthesised from 3-methoxyphenol (1 mL, 9.1 mmol). Isolated as a colourless oil (1.1 g, 47%).

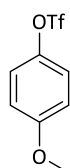
^1H NMR (400 MHz, CDCl_3): δ 3.85 (s, 3H), 6.83 (t, $^4J_{\text{H-H}} = 3.2$ Hz, 1H), 6.88 – 6.96 (m, 2H), 7.37 (t, $^3J_{\text{H-H}} = 8.1$ Hz, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 55.2, 107.0, 112.7, 113.6, 118.2 (q, $J_{\text{C-F}} = 323.1$ Hz), 130.0, 149.8, 160.4.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -72.9.

GC-MS ($\text{C}_8\text{H}_7\text{F}_3\text{O}_4\text{S}$) m/z : 256.1.

NMR data consistent with the literature.³¹²



4-Methoxyphenyl trifluoromethanesulfonate. Synthesised from 3-methoxyphenol (1 mL, 9.1 mmol). Isolated as a colourless oil (1.6 g, 77%).

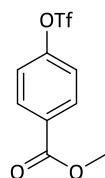
^1H NMR (400 MHz, CDCl_3): δ 3.84 (s, 3H), 6.92 – 6.97 (m, 2H), 7.20 – 7.24 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 55.2, 114.5, 118.3 (q, $J_{\text{C-F}} = 319.5$ Hz), 122.8, 142.5, 158.7.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -72.8.

GC-MS ($\text{C}_8\text{H}_7\text{F}_3\text{O}_4\text{S}$) m/z : 256.1.

NMR data consistent with the literature.³¹⁶



Methyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate. Synthesised from methyl 4-hydroxybenzoate (1 g, 6.6 mmol). Isolated as a colourless oil (1.4 g, 71%).

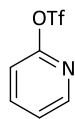
^1H NMR (400 MHz, CDCl_3): δ 3.96 (s, 3H), 7.36 – 7.39 (m, 2H), 8.15 – 8.18 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 52.1, 118.2 (q, $J_{\text{C-F}} = 318.6$ Hz), 120.9, 1312.5, 151.9, 164.9.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -72.8.

GC-MS ($\text{C}_9\text{H}_7\text{F}_3\text{O}_5\text{S}$) m/z : 284.1.

NMR data consistent with the literature.³¹⁶



Pyridin-2-yl trifluoromethanesulfonate. Synthesised from 2-hydroxypyridine (1 g, 10.5 mmol). Isolated as a colourless oil (1.2 g, 50%).

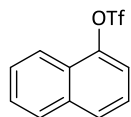
¹H NMR (400 MHz, CDCl₃): δ 7.21 (d, J = 8.2, 1H), 7.41 (dd, J = 7.4, 4.8, 1H), 7.93 (td, J = 7.8, 2.1, 1H), 8.43 (dd, J = 4.7, 1.6, 1H).

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 114.8, 118.1 (q, J_{C-F} = 321.3 Hz), 123.7, 140.5, 148.3, 155.5.

¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -73.2.

GC-MS (C₆H₅F₃NO₃S) m/z: 227.0

NMR data consistent with the literature.³¹⁷



Naphthalen-1-yl trifluoromethanesulfonate. Synthesised from naphthalen-1-ol (1 mL, 7.6 mmol). Isolated as a colourless oil (1.3 g, 68%).

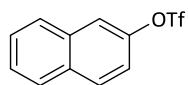
¹H NMR (400 MHz, CDCl₃): δ 7.48 – 7.52 (m, 2H), 7.61 – 7.71 (m, 2H), 7.87 – 7.96 (m, 2H), 8.14 (d, ³J_{H-H} = 8.8 Hz, 1H).

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 117.9, 118.3 (q, J_{C-F} = 320.2 Hz), 120.3, 124.6, 125.9, 126.9, 127.4, 127.6, 128.1, 134.4, 145.2.

¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -73.4.

GC-MS (C₁₁H₇F₃O₃S) m/z: 276.1.

NMR data consistent with the literature.³¹⁶



Naphthalen-2-yl trifluoromethanesulfonate. Synthesised from naphthalen-2-ol (1 mL, 7.6 mmol). Isolated as a white solid (1.4 g, 73%).

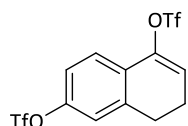
¹H NMR (400 MHz, CDCl₃): δ 7.41 (d, ³J_{H-H} = 6.6 Hz, ⁴J_{H-H} = 2.4 Hz, 1H), 7.57 – 7.64 (m, 2H), 7.79 (d, ⁴J_{H-H} = 2.4 Hz), 7.88 – 7.96 (m, 3H).

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 118.4 (q, J_{C-F} = 316.7 Hz), 118.1, 119.1, 126.7, 127.1, 127.5, 127.6, 130.1, 131.9, 132.9, 146.6.

¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -72.8.

GC-MS ($C_{11}H_7F_3O_3S$) m/z : 276.1.

NMR data consistent with the literature.³¹⁸



3,4-Dihydronaphthalene-1,6-diyl bis(trifluoromethanesulfonate).

Synthesised from 6-hydroxytetralone (2 g, 12.3 mmol). The aryl triflate was installed first according to the general procedure before following general procedure A for formation of vinyl triflate. Isolated as a white solid (3.2 g, 61%).

1H NMR (400 MHz, $CDCl_3$): δ 2.59 (td, $^3J_{H-H} = 8.2$ Hz, $^4J_{H-H} = 4.7$ Hz, 2H), 2.94 (t, $^3J_{H-H} = 8.2$ Hz, 2H), 6.14 (t, $^3J_{H-H} = 4.7$ Hz, 1H), 7.14 (s, 1H), 7.20 (dd, $^3J_{H-H} = 8.5$ Hz, $^4J_{H-H} = 2.5$ Hz, 1H), 7.44 (d, $^3J_{H-H} = 8.5$ Hz, 1H).

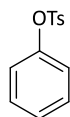
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.4, 26.3, 118.1 (q, $J_{C-F} = 321.7$ Hz), 118.2 (q, $J_{C-F} = 321.7$ Hz), 118.9, 119.3, 120.4, 122.6, 128.4, 138.5, 144.4, 148.9.

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ -72.8 (3F), -73.5 (3F).

GC-MS ($C_{12}H_8F_6O_6S_2$) m/z : 426.1.

NMR data consistent with the literature.³¹⁹

Other Electrophiles



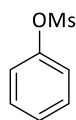
Phenyl tosylate. Prepared following a literature preparation.⁷⁴ A RBF was charged with phenol (2 g, 22.8 mmol), $TsCl$ (4 g, 20.9 mmol), NEt_3 (2.9 mL, 20.9 mmol) and DCM (40 mL) and stirred at 45 °C for 6 hours. The reaction mixture was cooled to room temperature and washed with NaOH (50 mL, sat. solution), HCl (50 mL, 1 M) and H_2O . Organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The solid was recrystallised from EtOH to give the product as a white crystalline solid (4.2 g, 81%).

1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 6.99 – 7.02 (m, 2H), 7.24 – 7.33 (m, 5H), 7.72 (d, $^3J_{H-H} = 8.8$ Hz, 2H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 21.2, 121.9, 126.6, 128.1, 129.1, 129.2, 131.9, 144.8, 149.2.

GC-MS ($C_{17}H_{13}F_3O_3S$) m/z : 248.1.

NMR data consistent with the literature.³²⁰



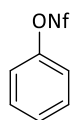
Phenyl mesylate. Prepared following a literature preparation.²⁴⁵ Phenol (2 g, 22.8 mmol) was dissolved in DCM (40 mL) and cooled in ice bath. NEt_3 (3.2 mL, 22.8 mmol) was added and then MsCl (1.8 mL, 22.8 mmol) was added dropwise. The mixture was stirred at room temperature for 90 mins. It was then quenched with HCl (10 mL, 1 M) and the organic layer washed with NaHCO_3 (40 mL, sat. solution). Organic layer washed with water (3 x 30 mL) and dried over MgSO_4 , filtered and concentrated under reduced pressure. The solid was recrystallised from EtOH to give the product as a white crystalline solid (2.2 g, 56%).

^1H NMR (400 MHz, CDCl_3): δ 3.16 (s, 3H), 7.28 – 7.37 (m, 2H), 7.43 – 7.47 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 36.7, 121.7, 126.8, 129.6, 148.9.

GC-MS ($\text{C}_7\text{H}_8\text{O}_3\text{S}$) m/z : 172.1.

NMR data consistent with the literature.³²¹



Phenyl nonaflate. Prepared following a literature preparation.²⁴⁶ Phenol (2 g, 22.8 mmol) and K_2CO_3 (4.4 g, 31.9 mmol) were dissolved in MeCN (40 mL) and stirred vigorously. Perfluorobutanesulfonyl fluoride (4.6 mL, 25.6 mmol) was added in one portion and the reaction was stirred at room temperature overnight. The mixture was filtered and concentrated under reduced pressure, the crude product was purified by column chromatography to give the product as a colourless oil (5.7 g, 97%).

^1H NMR (400 MHz, CDCl_3): δ 7.31 – 7.34 (m, 2H), 7.39 – 7.43 (m, 2H), 7.46 – 7.50 (m, 2H).

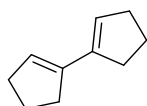
$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 105.1 – 108.5 (m), 109.4 (t, $J_{\text{C-F}} = 31.0$ Hz), 110.5 – 112.6 (m), 113.9 – 115.5 (m), 116.9 – 118.4 (m), 120.9, 127.9, 129.8, 149.4.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): -80.7 - -80.8 (m, 3F), -109.0 - -109.1 (m, 2F), -120.9 - -121.0 (m, 2F), -125.8 - -125.9 (m, 2F).

GC-MS ($\text{C}_{10}\text{H}_5\text{F}_9\text{O}_3\text{S}$) m/z : 376.1.

NMR data consistent with the literature.³²²

Products from Cross-Coupling Reactions



[1,1'-Bi(cyclopentane)]-1,1'-diene. Prepared following a literature preparation.³²³ To a stirred solution of 1,1'-bicyclopentyl-1,1'-diol (1 g, 5.9 mmol) in pyridine (10 mL), with internal thermometer, phosphorus oxychloride (1.2 mL, 12.9 mmol) was added. The solution was heated to 70 °C, using an ice bath, the solution was kept at 90 °C after a self-exotherm. It was stirred at 90 °C for 2 hours. The solution was then cooled to ambient temperature and poured into stirred pentane (20 mL). The pentane was decanted and solid residue quenched with HCl (1 M, 50 mL) and extracted with pentane (2 x 20 mL). The combined organic extracts were washed with HCl, (1 M, 50 mL), dried over MgSO₄ and filtered through a silica plug. Concentration of solution gave the product as a yellow oil (0.3 g, 38%).

¹H NMR (400 MHz, CDCl₃): δ 1.94 ((quint., ³J_{H-H} = 7.7 Hz, 2H), 2.43 – 2.53 (m, 8H), 5.61 (s, 2H).

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 22.9, 32.4, 32.5, 126.1, 139.9.

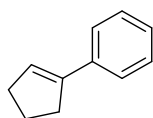
GC-MS

(C₁₀H₁₄) m/z: 134.2.

NMR data consistent with the literature.³²⁴

General Procedure

Prepared following a literature preparation.³²⁵ To form a PhMgBr, under an N₂ atmosphere, bromobenzene (1.3 equiv.) was added dropwise to magnesium (1.4 equiv.) and a crystal of I₂ in dry Et₂O (20 mL). A solution of cyclic ketone (1 equiv.) in Et₂O (10 mL) was added dropwise and the mixture stirred for 2 hours. The solution was poured into an ice cold solution of HCl (50 mL, 1M). The mixture was extracted with Et₂O (3 x 20 mL). The organic phase was washed with brine (3 x 20 mL) and dried over MgSO₄, filtering and concentrating yielded the crude addition product. The crude product was dissolved in PhMe (30 mL) and *p*-TsOH (30 mg) was added. The mixture was refluxed overnight and then concentrated. The crude product was purified by column chromatography.



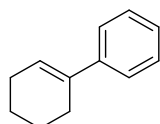
Cyclopent-1-en-1-ylbenzene. Isolated as a yellow oil (2.6 g, 51%).

^1H NMR (400 MHz, CDCl_3): δ 2.07 (qunit., $^3J_{\text{H-H}} = 8.0$ Hz, 2H), 2.55 – 2.60 (m, 2H), 2.73 – 2.79 (m, 2H), 6.22 (s, 1H), 7.23 – 7.29 (m, 1H), 7.33 – 7.39 (m, 2H), 7.47 – 7.51 (m, 2H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 22.9, 32.7, 32.9, 125.1, 125.6, 126.3, 127.8.

GC-MS ($\text{C}_{11}\text{H}_{12}$) m/z : 144.1.

NMR data consistent with the literature.³²⁶



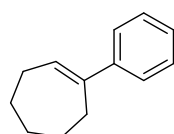
Cyclohex-1-en-1-ylbenzene. Isolated as a yellow oil (2.3 g, 51%).

^1H NMR (400 MHz, CDCl_3): δ 1.66 – 1.74 (m, 2H), 1.78 – 1.84 (m, 2H), 2.21 – 2.27 (m, 2H), 2.42 – 2.47 (m, 2H), 6.13 – 6.16 (m, 1H), 7.2 – 7.49 (m, 5H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 21.7, 22.6, 25.4, 26.9, 124.3, 124.5, 126.0, 127.7, 136.1, 142.2.

GC-MS ($\text{C}_{12}\text{H}_{14}$) m/z : 158.2.

NMR data consistent with the literature.³²⁷



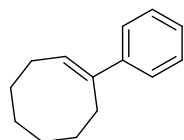
Cyclohept-1-en-1-ylbenzene. Isolated as a yellow oil (3.3 g, 68%).

^1H NMR (400 MHz, CDCl_3): δ 1.56 – 1.62 (m, 2H), 1.65 – 1.71 (m, 2H), 1.84 – 1.90 (m, 2H), 2.30 – 2.34 (m, 2H), 2.64 – 2.66 (m, 2H), 6.13 (t, $^3J_{\text{H-H}} = 6.5$ Hz, 1H), 7.21 – 7.36 (m, 5H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 26.3, 26.4, 28.4, 32.3, 125.2, 125.7, 127.6, 129.9, 144.5, 144.5.

GC-MS ($\text{C}_{13}\text{H}_{16}$) m/z : 172.2.

NMR data consistent with the literature.³²⁷



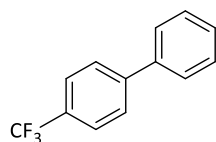
Cyclooct-1-en-1-ylbenzene. Isolated as a yellow oil (3.0 g, 57%).

^1H NMR (400 MHz, CDCl_3): δ 1.55 – 1.69 (m, 8H), 2.30 – 2.39 (m, 2H), 2.65 – 2.69 (m, 2H), 6.05 (t, $^3J_{\text{H-H}} = 8.2$ Hz, 1H), 7.22 – 7.49 (m, 5H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 25.7, 26.4, 26.9, 27.9, 28.9, 29.5, 125.3, 125.9, 127.5, 127.7, 139.8, 142.7.

GC-MS ($\text{C}_{14}\text{H}_{18}$) m/z : 186.2.

NMR data consistent with the literature.³²⁷



4-(Trifluoromethyl)-1,1'-biphenyl. To a 25 mL microwave vial, $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$ (171 mg, 0.21 mmol), phenylboronic acid (293 mg, 2.4 mmol) and K_3PO_4 (1.3 g, 6.3 mmol) were added. The vial was capped and backfilled three times with nitrogen. A degassed solution of THF/ H_2O (4/1, 8 mL) was added plus 4-bromobenzotrifluoride (0.3 mL, 2.1 mmol) and the reaction stirred at 85 °C for 6 hours. The mixture was cooled and filtered through a pad of celite. The crude product was purified *via* column chromatography to give the product as a white solid (0.3 g, 65%).

^1H NMR (400 MHz, CDCl_3): δ 7.41 – 7.52 (m, 3H), 7.62 – 7.64 (m, 2H), 7.72 (s, 4H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ 125.2 (q, $J_{\text{C-F}} = 4.0$ Hz), 126.7, 126.8, 126.9, 127.7, 128.3, 128.4, 139.3, 144.3.

$^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3): δ -62.4.

GC-MS ($\text{C}_{13}\text{H}_9\text{F}_3$) m/z : 222.2.

NMR data consistent with the literature.³²⁸

7.4.2. Kinetic Experiments

Kinetic data was obtained in the same manner as that used for our previous papers by following the decay of the starting Ni^0 complex.^{74,75}

In an argon-filled glovebox, a septum-fitted NMR tube was charged with a solution of $[\text{Ni}(\text{COD})(\text{dppf})]$ (**1**) (8 mg, 0.011 mmol, except in Table S5) in dry benzene- d_6 or toluene- d_8 (0.5 mL). Once dissolved, any liquid additives (or stock solutions of additives) were then added. This sample was used to tune, match, lock and shim the spectrometer, and to set the receiver gain. A spectrum was acquired to check the integrity of the sample. The aryl halide (5-25 equiv.) was added to start the reaction and $^{31}\text{P}\{^1\text{H}\}$ NMR spectra (16 scans/spectrum;

interpulse delay = 2 s) were acquired at intervals until >87% conversion ($3t_{1/2}$) was achieved. All experiments were performed in duplicate.

In all reactions, which were pseudo-first order in **1**, rate constants were obtained by plotting the natural log of the integral for **1** versus time.

Table 7.21. Rate constants obtained for vinyl triflates from plotting the natural log of the concentration of Ni⁰ versus time (first-order dependence). All reactions carried out with Ni(COD)(dppf) (**1**) (22 mmol L⁻¹), 20 equivalents of vinyl triflate (0.44 mol L⁻¹) in 0.5 mL benzene-d₆ or toluene-d₈.

Entry	Substrate	Solvent	T (K)	k _{obs} (s ⁻¹)
1a	Cyclopent-1-en-1-yl trifluoromethanesulfonate	C ₆ D ₆	323	1.59 x 10 ⁻³
1b				1.64 x 10 ⁻³
2a	Cyclohex-1-en-1-yl trifluoromethanesulfonate	Tol- <i>d</i> ₈	343	1.49 x 10 ⁻³
2b				1.66 x 10 ⁻³
3a		C ₆ D ₆	323	1.19 x 10 ⁻⁴
3b				1.63 x 10 ⁻⁴
3a	Cyclohept-1-en-1-yl trifluoromethanesulfonate	C ₆ D ₆	323	2.20 x 10 ⁻³
3b				2.09 x 10 ⁻³
4a			293	1.80 x 10 ⁻⁴
5a				1.97 x 10 ⁻⁴
5b			283	8.99 x 10 ⁻⁵
6a				8.89 x 10 ⁻⁵
7a	Cyclooct-1-en-1-yl trifluoromethanesulfonate	C ₆ D ₆	323	1.33 x 10 ⁻³
7b				1.19 x 10 ⁻³
8a	6-Methylcyclohex-1-en-1-yl trifluoromethanesulfonate	C ₆ D ₆	323	2.10 x 10 ⁻³
8b				2.22 x 10 ⁻³
9a	4-(<i>t</i> -Butyl)cyclohex-1-en-1-yl trifluoromethanesulfonate	Tol- <i>d</i> ₈	343	2.06 x 10 ⁻³
9b				1.88 x 10 ⁻³

10a	3,6-Dihydro-2H-pyran-4-yl trifluoromethanesulfonate	Tol- <i>d</i> ₈	343	1.18 x 10 ⁻³
10b				9.28 x 10 ⁻⁴
11a	3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate	C ₆ D ₆	323	7.84 x 10 ⁻³
11b				7.37 x 10 ⁻³
12a	3,4-Dihydronaphthalen-2-yl trifluoromethanesulfonate	C ₆ D ₆	323	1.87 x 10 ⁻³
12b				1.21 x 10 ⁻³
13a	1H-Inden-2-yl trifluoromethanesulfonate	C ₆ D ₆	323	4.15 x 10 ⁻³
13b				4.00 x 10 ⁻³

Table 7.22. Rate constants obtained for aryl triflates from plotting the natural log of the concentration of Ni⁰ versus time (first-order dependence). All reactions carried out with Ni(COD)(dppf) (**1**) (22 mmol L⁻¹), 20 equivalents of aryl triflate (0.44 mol L⁻¹) in 0.5 mL benzene-*d*₆ or toluene-*d*₈.

Entry	Substrate	Solvent	T (K)	k _{obs} (s ⁻¹)
1a	Phenyl trifluoromethanesulfonate	C ₆ D ₆	323	3.87 x 10 ⁻⁴
1b				4.05 x 10 ⁻⁴
2a	3-Methoxyphenyl trifluoromethanesulfonate	C ₆ D ₆	323	7.01 x 10 ⁻⁴
2b				5.96 x 10 ⁻⁴
3a	<i>p</i> -Tolyl trifluoromethanesulfonate	Tol- <i>d</i> ₈	343	5.44 x 10 ⁻⁴
3b				5.27 x 10 ⁻⁴
4a	<i>o</i> -Tolyl trifluoromethanesulfonate	Tol- <i>d</i> ₈	343	1.05 x 10 ⁻³
4b				1.17 x 10 ⁻³
5a	<i>m</i> -Tolyl trifluoromethanesulfonate	Tol- <i>d</i> ₈	343	1.33 x 10 ⁻³
5b				1.08 x 10 ⁻³
6a	4-Acetylphenyl trifluoromethanesulfonate	C ₆ D ₆	293	3.49 x 10 ⁻³
6b				3.79 x 10 ⁻³
7a	4-(Trifluoromethyl)phenyl trifluoromethanesulfonate	Tol- <i>d</i> ₈	343	6.57 x 10 ⁻⁴

7b				6.55×10^{-4}
8a	3-(Trifluoromethyl)phenyl trifluoromethanesulfonate	C_6D_6	293	9.33×10^{-4}
8b				7.71×10^{-4}
9a	3-Fluorophenyl trifluoromethanesulfonate	C_6D_6	323	2.93×10^{-3}
9b				3.84×10^{-3}
10a	4-Methoxyphenyl trifluoromethanesulfonate	Tol- d_8	343	7.82×10^{-4}
10b				8.70×10^{-4}
11a	Methyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate	Tol- d_8	343	1.84×10^{-3}
11b				1.95×10^{-3}
12a	Naphthalen-1-yl trifluoromethanesulfonate	C_6D_6	293	3.43×10^{-3}
12b				3.24×10^{-3}
13a	Naphthalen-2-yl trifluoromethanesulfonate	C_6D_6	283	3.48×10^{-3}
13b				3.26×10^{-3}
14a	Pyridin-2-yl trifluoromethanesulfonate	C_6D_6	293	9.52×10^{-4}
14b				9.48×10^{-4}
15a	Phenyl tosylate	C_6D_6	333	9.38×10^{-4}
15b				9.39×10^{-4}
16a	Phenyl mesylate	C_6D_6	333	9.88×10^{-4}
16b				9.11×10^{-4}
17a	Phenyl nonaflate	C_6D_6	333	1.43×10^{-3}
17b				1.47×10^{-3}

Table 7.23. Order in substrate was investigated by varying the concentration of various vinyl and aryl substrates in reactions. Rate constants obtained from plotting the natural log of the concentration of Ni^0 versus time (first-order dependence). All reactions carried out with $Ni(COD)(dppf)$ (**1**) (22 mmol L^{-1}), 5 – 20 equivalents of triflate ($0.11 - 0.55 \text{ mol L}^{-1}$) in 0.5 mL benzene- d_6 or toluene- d_8 .

Entry	Substrate	[RX] (mol L^{-1})	Solvent	T (K)	k_{obs} (s^{-1})
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1a	Cyclopent-1-en-1-yl trifluoromethanesulfonate	0.11	C ₆ D ₆	323	2.70 x 10 ⁻⁴
1b					2.35 x 10 ⁻⁴
2a		0.22			5.81 x 10 ⁻⁴
2b					5.96 x 10 ⁻⁴
3a		0.33			8.52 x 10 ⁻⁴
3b					8.56 x 10 ⁻⁴
4a	4-(^t Butyl)cyclohex-1-en-1-yl trifluoromethanesulfonate	0.11	Tol- <i>d</i> ₈	343	5.77 x 10 ⁻⁴
4b					6.47 x 10 ⁻⁴
5a		0.22			1.01 x 10 ⁻³
5b					1.00 x 10 ⁻³
6a		0.33			1.52 x 10 ⁻³
6b					1.17 x 10 ⁻³
7a	Cyclohept-1-en-1-yl trifluoromethanesulfonate	0.11	C ₆ D ₆	323	2.94 x 10 ⁻⁴
7b					3.37 x 10 ⁻⁴
8a		0.22			9.55 x 10 ⁻⁴
8b					9.31 x 10 ⁻⁴
9a		0.33			1.57 x 10 ⁻³
9b					1.54 x 10 ⁻³
10a	Cyclooct-1-en-1-yl trifluoromethanesulfonate	0.11	C ₆ D ₆	323	3.40 x 10 ⁻⁴
10b					3.33 x 10 ⁻⁴
11a		0.22			5.54 x 10 ⁻⁴
11b					5.35 x 10 ⁻⁴
12a		0.33			1.03 x 10 ⁻³
12b					1.06 x 10 ⁻³
13a	Phenyl trifluoromethanesulfonate	0.22	C ₆ D ₆	333	7.06 x 10 ⁻⁴
13b					7.28 x 10 ⁻⁴
14a		0.33			9.04 x 10 ⁻⁴
14b					8.62 x 10 ⁻⁴

15a		0.44			1.35 x 10 ⁻³
15b					1.15 x 10 ⁻³
16a		0.55			1.45 x 10 ⁻³
16b					1.39 x 10 ⁻³

Table 7.24. Order in COD was investigated by varying the concentration of COD added to kinetic experiments. Rate constants obtained from plotting the natural log of the concentration of Ni^0 versus time (first-order dependence). All reactions carried out with $\text{Ni}(\text{COD})(\text{dppf})$ (**1**) (22 mmol L^{-1}), 20 equivalents of triflate (0.44 mol L^{-1}) in 0.5 mL benzene- d_6 or toluene- d_8 .

Entry	Substrate	[COD] (mmol L ⁻¹)	Solvent	T (K)	k _{obs} (s ⁻¹)
1a	Cyclopent-1-en-1-yl trifluoromethanesulfonate	22	C ₆ D ₆	323	6.88 x 10 ⁻⁴
1b					6.44 x 10 ⁻⁴
2a		33			6.12 x 10 ⁻⁴
2b					6.29 x 10 ⁻⁴
3a		44			3.39 x 10 ⁻⁴
3b					3.19 x 10 ⁻⁴
4a		66			2.32 x 10 ⁻⁴
4b					2.53 x 10 ⁻⁴
5a	Cyclohept-1-en-1-yl trifluoromethanesulfonate	22	C ₆ D ₆	323	1.66 x 10 ⁻³
5b					1.78 x 10 ⁻³
6a		44			1.18 x 10 ⁻³
6b					1.25 x 10 ⁻³
7a		66			9.48 x 10 ⁻⁴
7b					1.01 x 10 ⁻³
8a		88			8.32 x 10 ⁻⁴
8b					7.89 x 10 ⁻⁴
9a		11			8.97 x 10 ⁻⁴

9b	Cyclooct-1-en-1-yl trifluoromethanesulfonate		C ₆ D ₆	323	9.69 x 10 ⁻⁴
10a		22			6.61 x 10 ⁻⁴
10b					7.40 x 10 ⁻⁴
11a		33			5.13 x 10 ⁻⁴
11b					5.60 x 10 ⁻⁴
12a		44			4.61 x 10 ⁻⁴
12b					5.37 x 10 ⁻⁴
13a	Phenyl trifluoromethanesulfonate	22	C ₆ D ₆	333	5.01 x 10 ⁻⁴
13b					5.01 x 10 ⁻⁴
14a		33			3.04 x 10 ⁻⁴
14b					3.35 x 10 ⁻⁴
15a		44			2.81 x 10 ⁻⁴
15b					2.90 x 10 ⁻⁴
16a		66			2.14 x 10 ⁻⁴
16b					1.90 x 10 ⁻⁴

Table 7.25. To obtain activation parameters from the Eyring-Polanyi equation, kinetic experiments were conducted at different temperatures for various triflates. Rate constants obtained from plotting the natural log of the concentration of Ni⁰ versus time (first-order dependence). All reactions carried out with Ni(COD)(dppf) (1) (22 mmol L⁻¹), 20 equivalents of triflate (0.44 mol L⁻¹) in 0.5 mL benzene-d₆ or toluene-d₈.

Entry	Substrate	Solvent	T (K)	k _{obs} (s ⁻¹)
1a	Cyclohept-1-en-1-yl trifluoromethanesulfonate	C ₆ D ₆	300	3.97 x 10 ⁻⁴
1b				3.91 x 10 ⁻⁴
2a			313	1.18 x 10 ⁻³
2b				1.26 x 10 ⁻³
3a			328	5.12 x 10 ⁻⁴
3b				5.41 x 10 ⁻⁴

4a	Cyclohex-1-en-1-yl trifluoromethanesulfonate	C ₆ D ₆	333	6.28 x 10 ⁻⁴
5a				7.48 x 10 ⁻⁴
5b			338	1.60 x 10 ⁻³
6a				1.48 x 10 ⁻³
7a	Cyclopent-1-en-1-yl trifluoromethanesulfonate	C ₆ D ₆	328	2.55 x 10 ⁻³
7b				2.22 x 10 ⁻³
8a			318	9.15 x 10 ⁻⁴
8b				
9a			313	6.72 x 10 ⁻⁴
9b				6.49 x 10 ⁻⁴
10a	Cyclooct-1-en-1-yl trifluoromethanesulfonate	C ₆ D ₆	333	2.97 x 10 ⁻³
10b				3.58 x 10 ⁻³
11a			328	1.94 x 10 ⁻³
11b				2.00 x 10 ⁻³
12a			318	9.79 x 10 ⁻⁴
12b				9.83 x 10 ⁻⁴
13a			313	5.67 x 10 ⁻⁴
13b				5.76 x 10 ⁻⁴
14a	Phenyl trifluoromethanesulfonate	C ₆ D ₆	318	2.62 x 10 ⁻⁴
14b				2.46 x 10 ⁻⁴
15a			328	6.81 x 10 ⁻⁴
15b				7.16 x 10 ⁻⁴

7.4.3. Data Analysis

All experiments were performed in duplicate, unless otherwise stated. Each point on each graph represents an individual experiment, not an average of multiple replicates duplicates.

Order in Substrates

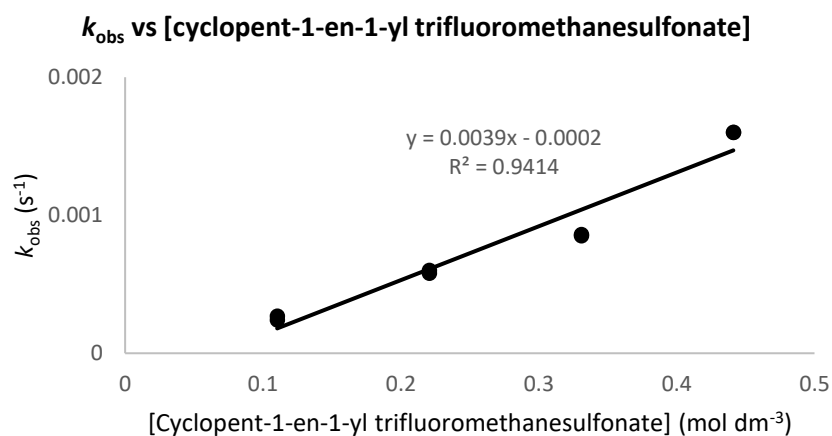


Figure 7.12. Order in substrate for cyclopent-1-en-1-yl trifluoromethanesulfonate.

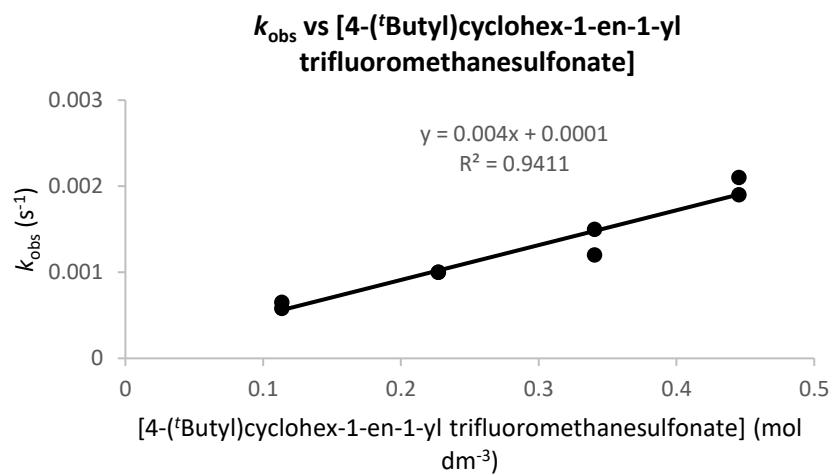


Figure 7.13. Order in substrate for 4-(^tButyl)cyclohex-1-en-1-yl trifluoromethanesulfonate.

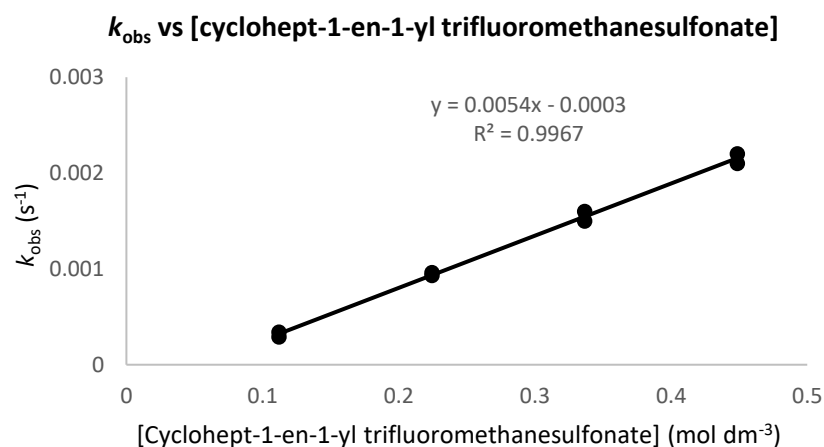


Figure 7.14. Order in substrate for cyclohept-1-en-1-yl trifluoromethanesulfonate.

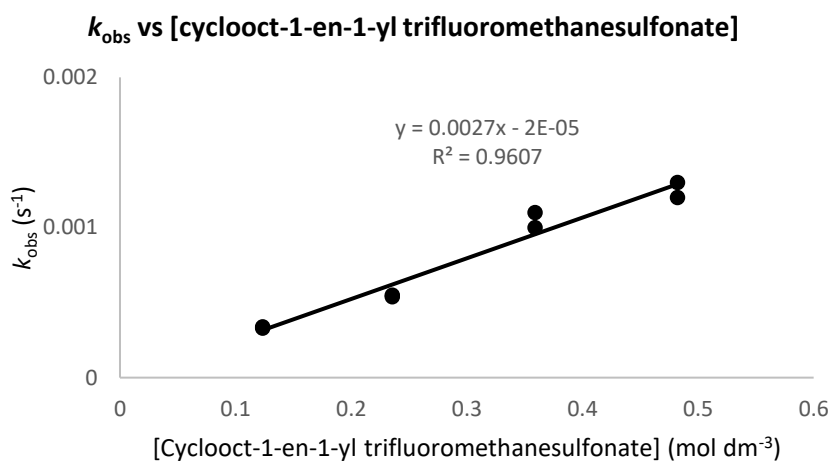


Figure 7.15. Order in substrate for cyclooct-1-en-1-yl trifluoromethanesulfonate.

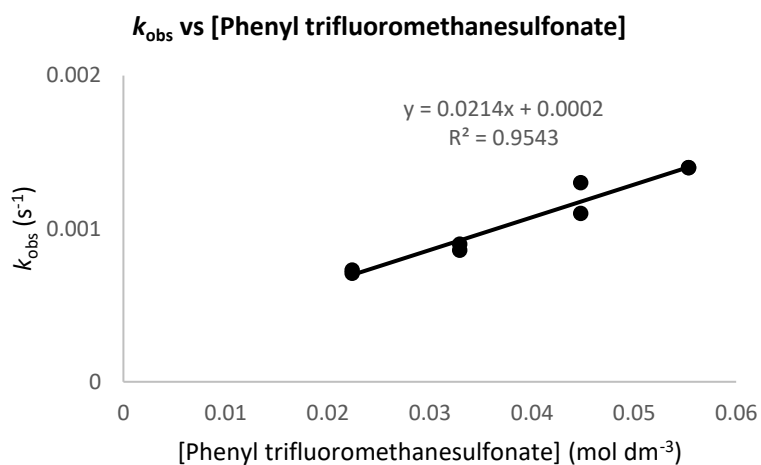


Figure 7.16. Order in substrate for phenyl trifluoromethanesulfonate.

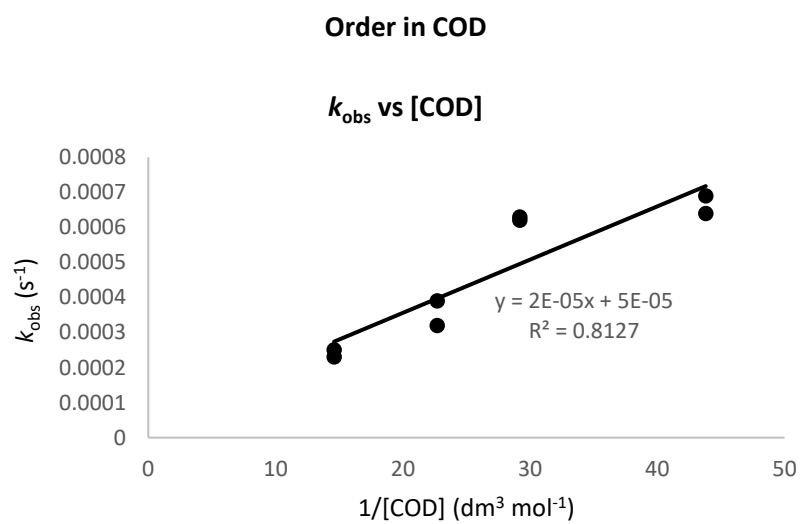


Figure 7.17. Order in COD for cyclopent-1-en-1-yl trifluoromethanesulfonate.

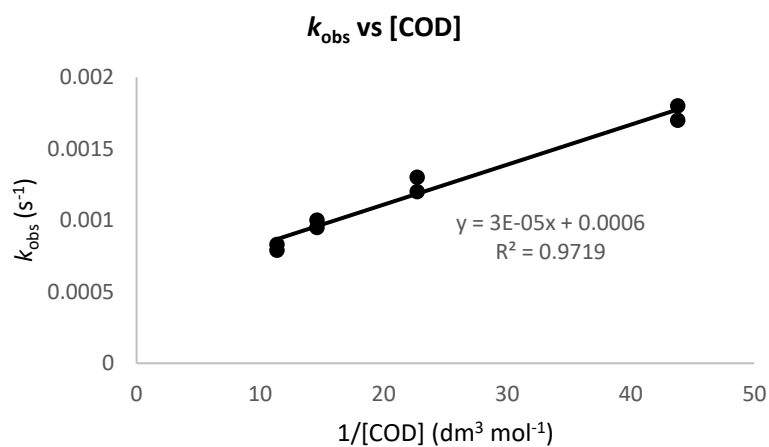


Figure 7.18. Order in COD for cyclohept-1-en-1-yl trifluoromethanesulfonate.

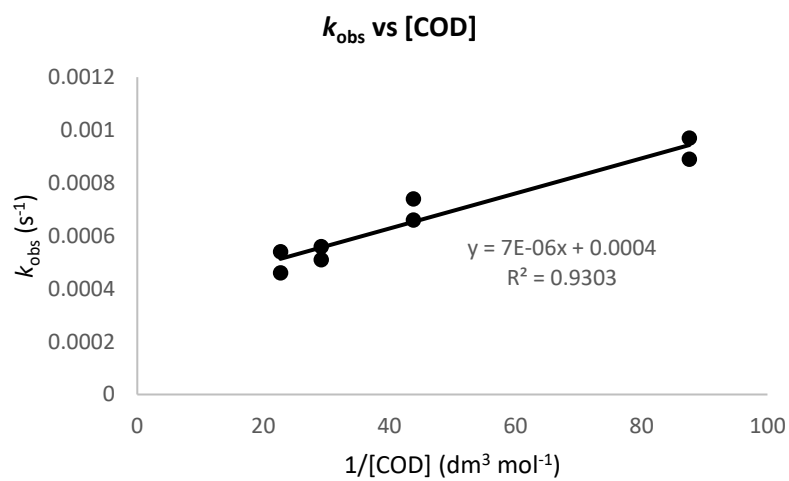


Figure 7.19. Order in COD for cyclooct-1-en-1-yl trifluoromethanesulfonate.

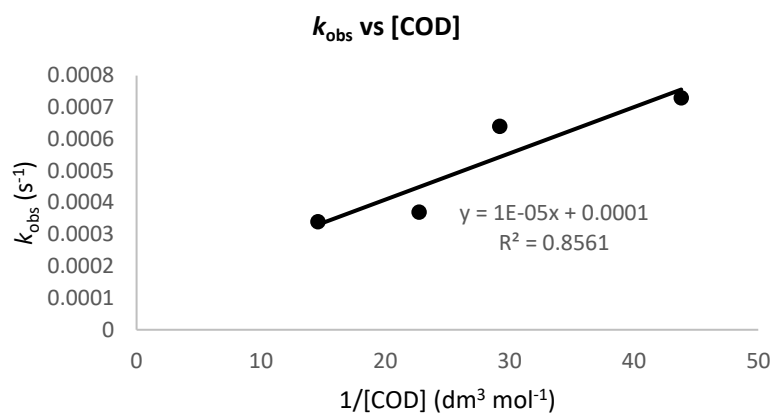


Figure 7.20. Order in COD for phenyl trifluoromethanesulfonate.

Eyring-Polanyi Plots

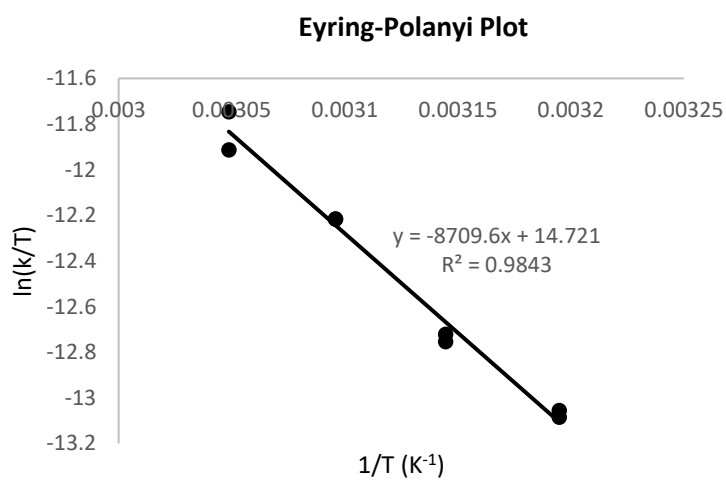


Figure 7.21. Eyring-Polanyi plot for cyclopent-1-en-1-yl trifluoromethanesulfonate

Table 7.26. ΔH and ΔS for cyclopent-1-en-1-yl trifluoromethanesulfonate.

		ΔH (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)
Gradient	-8709.6	17.3	-
Intercept	14.721	-	-18.0

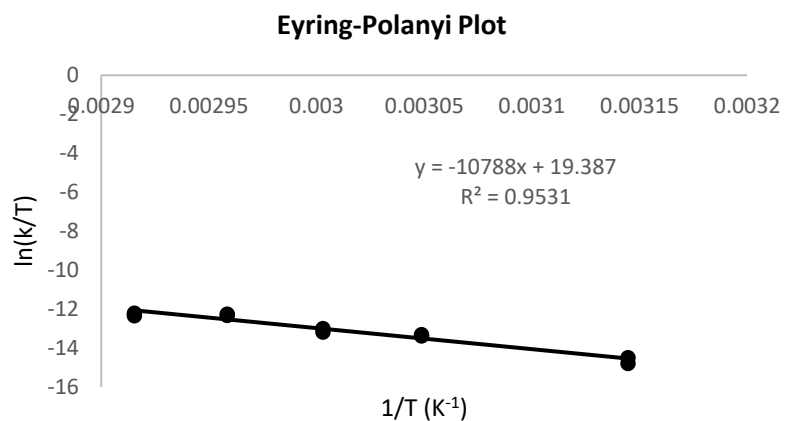


Figure 7.22. Eyring-Polanyi plot for cyclohex-1-en-1-yl trifluoromethanesulfonate.

Table 7.27. ΔH and ΔS for cyclohex-1-en-1-yl trifluoromethanesulfonate.

		ΔH (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)
Gradient	-10788	21.4	-
Intercept	19.397	-	-8.7

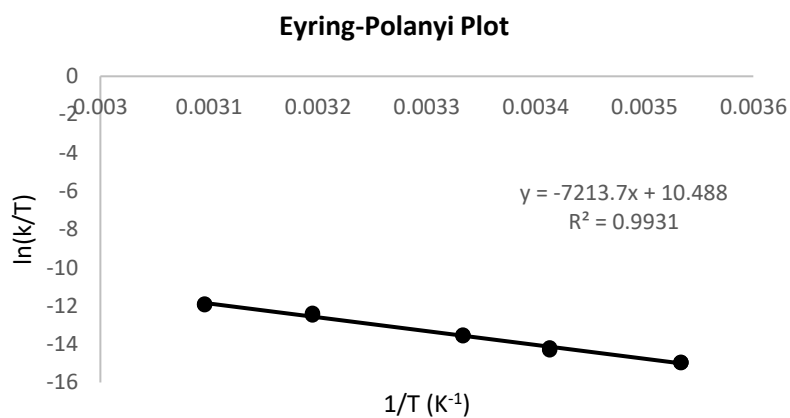


Figure 7.23. Eyring-Polanyi plot for cyclohept-1-en-1-yl trifluoromethanesulfonate.

Table 7.28. ΔH and ΔS for cyclohept-1-en-1-yl trifluoromethanesulfonate.

		ΔH (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)
Gradient	-7213.7	14.3	-

Intercept	10.488	-	-26.4
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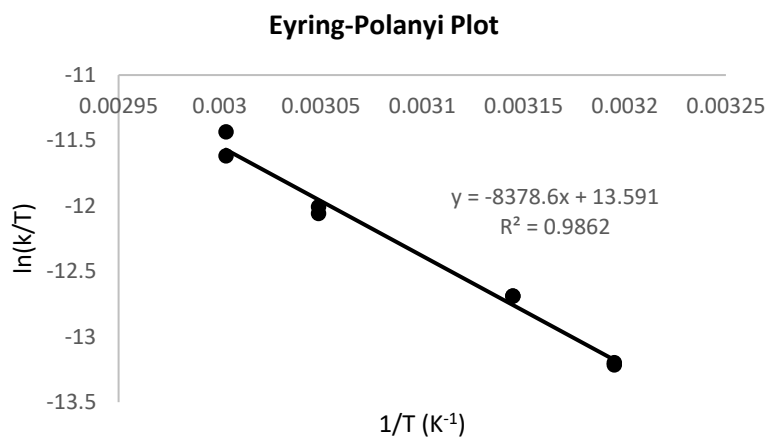


Figure 7.24. Eyring-Polanyi plot for cyclooct-1-en-1-yl trifluoromethanesulfonate

Table 7.29. ΔH and ΔS for cyclooct-1-en-1-yl trifluoromethanesulfonate.

		ΔH (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)
Gradient	-8378.6	16.6	-
Intercept	13.591	-	-20.2

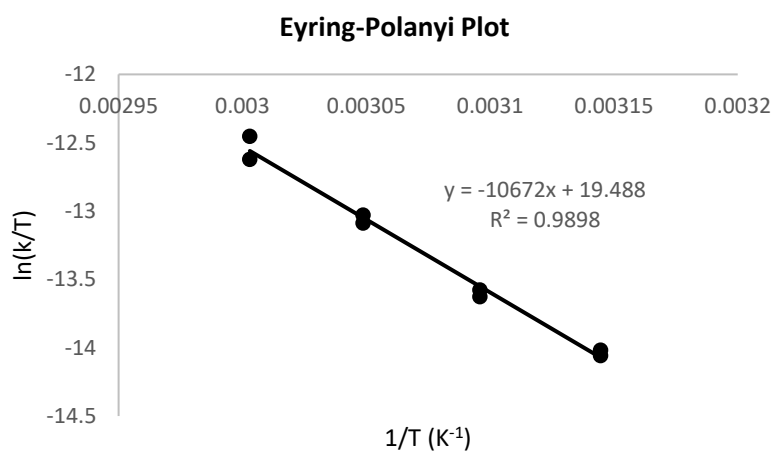


Figure 7.25. Eyring-Polanyi plot for phenyl trifluoromethanesulfonate.

Table 7.30. ΔH and ΔS for phenyl trifluoromethanesulfonate.

		ΔH (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)
Gradient	-10627	21.2	-
Intercept	19.488	-	-8.5

7.4.4. GC Calibrations

Table 7.31. Response factors given against n-dodecane for the substrates/products used in this work.

Substrate	Response factor against	
	Dodecane	Tetradecane
Cyclopent-1-en-1-yl triflate	0.3713	-
Cyclohex-1-en-1-yl triflate	0.4842	-
Cyclohept-1-en-1-yl triflate	0.5350	-
Cyclooct-1-en-1-yl triflate	0.5291	-
4-(Trifluoromethyl)phenyl triflate	0.5617	-
Pyridin-2-yl triflate		0.2778
3,4-Dihydronaphthalene-1,6-diyl bis(triflate)		
[1,1'-Bi(cyclopentane)]-1,1'-diene	0.7760	-
Cyclopent-1-en-1-ylbenzene	0.9814	-
Cyclohex-1-en-1-ylbenzene	0.7916	-
Cyclohept-1-en-1-ylbenzene	0.8930	-
Cyclooct-1-en-1-ylbenzene	0.9487	-
4-(Trifluoromethyl)-1,1'-biphenyl	0.8786	-
2-Phenylpyridine		0.7066

7.4.5. Cross-Couplings

Cross-coupling Reaction Procedure

In an argon-filled glovebox, Ni(COD)(dppf) (0.0125 mmol, 5 mol%) and any solid additives were added to a microwave vial equipped with stirrer bar. The vial was sealed with a septum-fitted cap and removed from the glovebox. Anhydrous THF (1 mL) was added, followed by Grignard reagent (0.28 mmol, 1.1 equiv.). The vial was then heated (whilst rapidly stirring) to 85 °C. When at the desired temperature, triflate (0.25 mmol) was added *via* microsyringe. The vials were left to stir at 85 °C for 24 h. The vials were then cooled to room temperature and pierced with a needle. The vials were opened and accurately known amounts of *n*-tetradecane were added. A sample was taken for GC-FID analysis. All reactions were performed in duplicate and average conversions are reported in the manuscript text.

Cross-coupling reactions

Table 7.32. Results from cross-coupling reactions of vinyl and aryl triflates following the above procedure. All reactions carried out in duplicate.

Entry	Triflate	Remaining Triflate (%)	Cross-coupled product (%)
1a	Cyclopent-1-en-1-yl	5	48
1b		5	51
2a	Cyclohex-1-en-1-yl	0	84
2b		0	86
3a	Cyclohept-1-en-1-yl	0	91
3b		0	82
4a	Cyclooct-1-en-1-yl	0	96
4b		0	96
5a	4-(Trifluoromethyl)phenyl	8	80
5b		11	78

Table 7.33. Results from cross-coupling reactions where cyclopent-1-en-1-yl triflate was used as the substrate.

Entry	Additive	Remaining Triflate (%)	Cross-coupled product (%)
1a	Tetrabutylammonium iodide	0	44
1b		0	59
2a	LiCl	0	60
2b		0	62

7.4.6. Computational Details

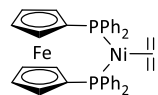
Computational details are the same as used in the previous study,¹⁵⁵ the details of which are in section 7.3.

As there are no Br, I, As or Sb atoms involved in this study, LANL2Dz(dp) has not been required.

All DFT calculations were carried out using Gaussian16 Rev. C.03.²⁸²

7.5. Experimental Data for Chapter 5

7.5.1. Synthesis of Compounds

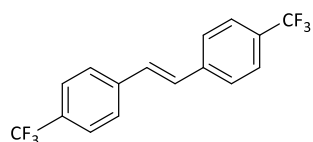


[Ni(dppf)ethene]. Prepared according to a literature procedure.²⁷³ A 100 mL Schlenk flask (in the glovebox) was charged with Ni(COD)₂ (300 mg, 1.1 mmol) and dppf (604 mg, 1.1 mmol) and dissolved in PhMe (15 mL). The mixture was stirred at room temperature overnight. The flask was removed from the glovebox, cannula filtered and solid washed with hexane (3 x 20 mL). The orange solid was dried under vacuum for 1 h and dissolved in Et₂O (10 mL). The contents of the flask was frozen in liquid nitrogen and put under vacuum. Once frozen, the flask was warmed to room temperature and filled with ethene. This freeze-pump-thaw process was repeated twice and the solution was left to stir at room temperature for 2 h. The reaction mixture was cannula filtered at -78 °C (dry ice/acetone bath) and solids washed with Et₂O (10 mL). The solid was dried under vacuum for 1 h to yield the product as a yellow powder (290 mg, 41%).

¹H NMR (400 MHz, CDCl₃): δ 2.76 (s, 4H), 3.91 (s, 4H), 4.30 (s, 4H), 7.03 – 7.04 (m, 12 H), 7.77 – 7.81 (m, 8H).

³¹P{¹H} NMR (162 MHz): δ 23.6.

NMR data consistent with the literature.²⁷³



(E)-1,2-bis(4-(trifluoromethyl)phenyl)ethene. Prepared according to a literature procedures.^{279,329} 4-(Trifluoromethyl)benzyl bromide (5.7 g, 24.0 mmol) was added to a solution of PPh₃ (6.3 g, 24.0 mmol) in PhMe (50 mL). The solution was refluxed for 1 h and cooled. The Wittig salt was collected by filtration and washed with hexane (50 mL), it was used in the next step without purification.

The Wittig salt (5.4 g, 13.0 mmol) and LiOH (0.42 g, 17.7 mmol) was dissolved in propan-2-ol (200 mL) and stirred at room temperature for 20 mins. 4-(Trifluoromethyl)benzaldehyde (1.6 mL, 11.8 mmol) was added and the solution was refluxed overnight. Once cooled, EtOAc (250 mL) was added and organic layer washed with brine (100 mL). Organic portion dried over

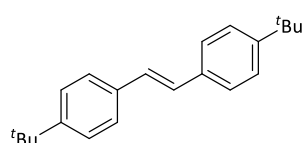
MgSO₄, filtered and concentrated. The resulting solid was recrystallised from MeOH to yield (E)-1,2-bis(4-(trifluoromethyl)phenyl)ethene (0.92 g, 51%) as a white crystalline solid.

¹H NMR (400 MHz, CDCl₃): δ 7.22 (s, 4H), 7.65 (s, 8H).

¹³C{¹H} NMR (101 MHz, CDCl₃): δ 123.7 (q, *J*_{C-F} = 276.4 Hz), 125.3 (q, *J*_{C-F} = 4.1 Hz), 126.5, 129.1, 129.4 (q, *J*_{C-F} = 33.2 Hz), 139.6.

¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ -62.6.

NMR data consistent with the literature.³³⁰

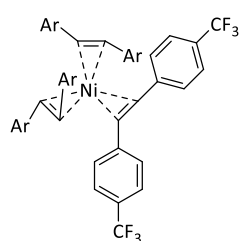


(E)-1,2-bis(4-(tert-butyl)phenyl)ethene. Prepared according to a literature procedures.^{279,329} Same method as for preparation of (E)-1,2-bis(4-(trifluoromethyl)phenyl)ethene using 4-(tert-butyl)benzyl bromide (4.2 mL, 22.9 mmol), PPh₃ (6 g, 22.9 mmol) to form the Wittig salt. For the second step; 4-(tert-butyl)benzaldehyde (3.7 mL, 22.0 mmol), Wittig salt (12 g, 24.5 mmol) and LiOH (0.79 g, 33.0 mmol) gave (E)-1,2-bis(4-(tert-butyl)phenyl)ethene (2.4 g, 37%) as a white crystalline solid.

¹H NMR (400 MHz, CDCl₃): δ 1.36 (s, 18H), 7.09 (s, 2H), 7.39 – 7.42 (m, 4H), 7.46 – 7.48 (m, 4H).

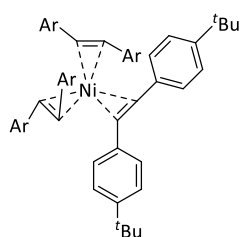
¹³C{¹H} NMR (101 MHz, CDCl₃): δ 30.9, 34.2, 125.1, 125.6, 127.2, 134.3, 150.1.

NMR data consistent with the literature.³³¹



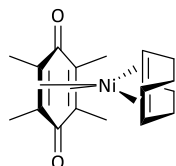
[Ni(CF₃stb)₃]. Prepared according to a literature procedure.¹² Ni(acac)₂ (603 mg, 2.3 mmol) was charged to a 100 mL Schlenk flask in the glovebox. Outside of the glovebox, Et₂O (20 mL) was added and the mixture was cooled to -20 °C, AlMe₃ (2.5 mL, 2 M, 4.9 mmol) was added dropwise over 5 minutes. The reaction was stirred at -20 °C for 15 minutes and warmed to -5 °C and stirred for 3 hours. The suspension was cooled to -35 °C and cannula filtered, the solids were washed with Et₂O (2 x 5 mL) and dried under high vacuum to give the product as a red solid (1.6 g, 71%).

NMR data consistent with the literature.²⁵⁷



[Ni(^{4-tBu}stb)₃]. Prepared according to a literature procedure.²⁵⁷ The same preparation as [Ni(CF₃stb)₃] was used with 1,2-bis(4-(tert-butyl)phenyl)ethene, the product was isolated as a red solid (1.6 g, 75%).

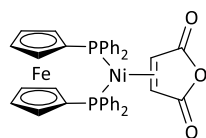
NMR data consistent with the literature.²⁵⁷



[Ni(COD)DQ]. Prepared according to a literature procedure.²⁶⁰ Ni(COD)₂ (1 g, 3.6 mmol) and duroquinone 597 mg (3.6 mmol) were charged to a Schlenk flask in the glovebox. The flask was removed from the glovebox and degassed DCM (15 mL) was added. The reaction was stirred at 45 °C

overnight, after cooling to room temperature, the mixture was filtered through a pad of celite and washed with DCM (50 mL). The filtrate was concentrated under reduced pressure to give a red residue. DCM (0.5 mL) and pentane (16 mL) was added to the residue and precipitate formed, this was filtered. The solid was washed with DCM/pentane (1/50, 2 x 10 mL). The solid was dried under high vacuum to give the product as a red solid (0.9 g, 76%).

¹H NMR (400 MHz, CDCl₃): δ 1.51 – 1.57 (m, 4H), 1.76 – 1.86 (m, 5H), 1.95 (s, 12H), 3.43 – 3.47 (m, 4H).



[Ni(dppf)MA]. Ni(COD)₂ (100 mg, 0.36 mmol) and dppf (202 mg, 0.36 mmol) were added to a Schlenk flask in the glovebox and dissolved in PhMe (10 mL). The reaction was stirred at room temperature for 4 hours

and maleic anhydride (36 mg, 0.36 mmol) was added. The reaction was stirred for a further 2 hours at room temperature and the solvent removed under reduced pressure. The remaining solid was washed with hexane (3 x 20 mL) and dried under vacuum to yield the product as an orange solid (178 mg, 70%).

¹H NMR (400 MHz, CDCl₃): δ 3.47 (s, 2H), 3.80 (d, ³J_{H-H} = 24.8 Hz, 4H), 4.14 (d, ³J_{H-H} = 9.7 Hz, 4H), 7.05 – 7.12 (m, 12H), 7.72 – 7.76 (m, 4H), 7.84 – 7.88 (m, 4H).

³¹P{¹H} NMR (162 MHz): δ 20.2.

7.6. Crystal Structure Data

7.6.1. Data for Chapter 4

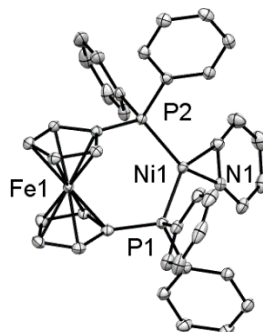


Table 7.34. Data for [Ni(dppf)(C₅NH₄)] [OTf].

Empirical formula	C ₄₀ H ₃₂ F ₃ FeNNiO ₃ P ₂ S
Formula weight	840.22
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 12.7001(2) Å b = 12.7903(2) Å c = 14.1264(2) Å
Volume	1793.83(6) Å ³
Z	2
Density (calculated)	1.556 Mg/m ³
Absorption coefficient	5.763 mm ⁻¹
F(000)	860
Crystal size	0.25 x 0.20 x 0.15 mm ³
Theta range for data collection	3.585 to 71.401°
Index ranges	-14<=h<=15, -15<=k<=15, -17<=l<=14
Reflections collected	31389
Independent reflections	6934 [R(int) = 0.0250]
Completeness to theta = 70.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.46946
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6934 / 0 / 470
Goodness-of-fit on F ²	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0289, wR2 = 0.0741
R indices (all data)	R1 = 0.0296, wR2 = 0.0744
Extinction coefficient	n/a
Largest diff. peak and hole	0.585 and -0.476 e.Å ⁻³

7.6.2. Data for Chapter 5

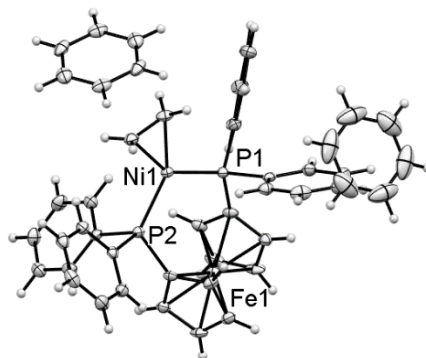


Table 7.35. Data for [Ni(dppf)(ethene)].

Empirical formula	C ₄₂ H ₃₂ D ₆ FeNiP ₂
Formula weight	725.26
Temperature	123(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 10.5179(5) Å b = 13.7824(9) Å c = 13.8611(11) Å
Volume	1713.5(2) Å ³
Z	2
Density (calculated)	1.406 Mg/m ³
Absorption coefficient	1.096 mm ⁻¹
F(000)	748
Crystal size	0.4 x 0.1 x 0.06 mm ³
Theta range for data collection	3.405 to 28.603°.
Index ranges	-13<=h<=13, -18<=k<=18, -18<=l<=18
Reflections collected	11839
Independent reflections	11839 [R(int) = 0.0640]
Completeness to theta = 26.000°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.98458
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	11839 / 0 / 450
Goodness-of-fit on F ²	0.920
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.0670
R indices (all data)	R1 = 0.0604, wR2 = 0.0700
Extinction coefficient	n/a
Largest diff. peak and hole	0.546 and -0.382 e.Å ⁻³

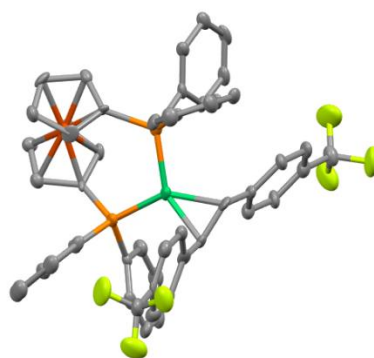


Table 7.36. Data for [Ni(dppf)(f'stb)].

Empirical formula	C ₅₈ H ₅₄ F ₆ FeNiO ₂ P ₂
Formula weight	1073.51
Temperature	123(2) K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 11.2106(11) Å b = 13.1009(17) Å c = 17.6636(15) Å
Volume	2399.9(5) Å ³
Z	2
Density (calculated)	1.486 Mg/m ³
Absorption coefficient	4.114 mm ⁻¹
F(000)	1112
Crystal size	0.4 x 0.15 x 0.04 mm ³
Theta range for data collection	3.644 to 69.179°.
Index ranges	-9<=h<=13, -15<=k<=14, -19<=l<=21
Reflections collected	14666
Independent reflections	8704 [R(int) = 0.1362]
Completeness to theta = 65.000°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.35869
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	8704 / 108 / 631
Goodness-of-fit on F ²	1.018
Final R indices [I>2sigma(I)]	R1 = 0.1179, wR2 = 0.2754
R indices (all data)	R1 = 0.1862, wR2 = 0.3458
Extinction coefficient	n/a
Largest diff. peak and hole	1.258 and -1.168 e.Å ⁻³

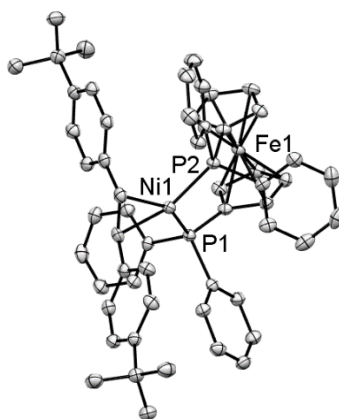


Table 7.37. Data for [Ni(dppf)(^tBuStb)].

Empirical formula	C ₅₆ H ₅₆ FeNiP ₂
Formula weight	905.50
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 2 ₁ /n
Unit cell dimensions	a = 12.8602(2) Å b = 26.4408(4) Å c = 13.9169(2) Å
Volume	4585.94(12) Å ³
Z	4
Density (calculated)	1.312 Mg/m ³
Absorption coefficient	3.977 mm ⁻¹
F(000)	1904
Crystal size	0.35 x 0.33 x 0.14 mm ³
Theta range for data collection	3.343 to 71.485°
Index ranges	-15 ≤ h ≤ 15, -31 ≤ k ≤ 32, -16 ≤ l ≤ 10
Reflections collected	26184
Independent reflections	8797 [R(int) = 0.0413]
Completeness to theta = 70.000°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.42047
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	8797 / 0 / 555
Goodness-of-fit on F ²	1.053
Final R indices [I > 2σ(I)]	R1 = 0.0462, wR2 = 0.1214
R indices (all data)	R1 = 0.0535, wR2 = 0.1252
Extinction coefficient	n/a
Largest diff. peak and hole	0.640 and -0.660 e.Å ⁻³

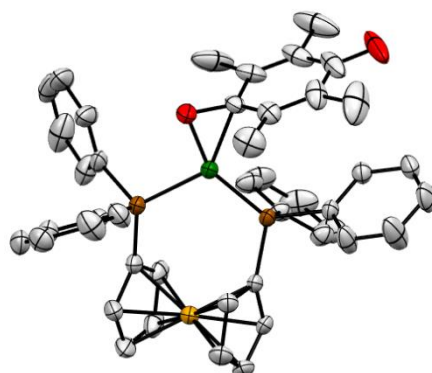


Table 7.38. Data for [Ni(dppf)DQ].

Empirical formula	C _{49.36} H _{46.64} FeNiO _{2.64} P ₂
Formula weight	858.57
Temperature	123(2) K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 9.7316(4) Å b = 11.0862(5) Å c = 20.9357(8) Å
Volume	2082.46(16) Å ³
Z	2
Density (calculated)	1.369 Mg/m ³
Absorption coefficient	4.398 mm ⁻¹
F(000)	896
Crystal size	0.41 x 0.15 x 0.06 mm ³
Theta range for data collection	4.266 to 73.165°.
Index ranges	-8<=h<=11, -11<=k<=13, -25<=l<=25
Reflections collected	13970
Independent reflections	8079 [R(int) = 0.0369]
Completeness to theta = 70.000°	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.26500
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	8079 / 47 / 527
Goodness-of-fit on F ²	1.019
Final R indices [I>2sigma(I)]	R1 = 0.0547, wR2 = 0.1412
R indices (all data)	R1 = 0.0704, wR2 = 0.1531
Extinction coefficient	n/a
Largest diff. peak and hole	0.823 and -0.362 e.Å ⁻³

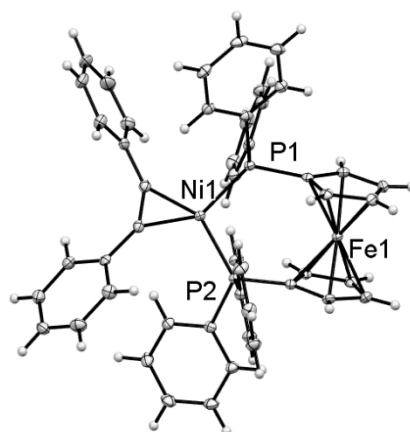


Table 7.39. Data for [Ni(dppf)DPA].

Empirical formula	C ₅₂ H ₄₆ FeNiOP ₂
Formula weight	863.39
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 11.3787(2) Å b = 12.7267(3) Å c = 16.2305(4) Å
Volume	2029.95(9) Å ³
Z	2
Density (calculated)	1.413 Mg/m ³
Absorption coefficient	4.486 mm ⁻¹
F(000)	900
Crystal size	0.28 x 0.08 x 0.05 mm ³
Theta range for data collection	2.920 to 71.398°
Index ranges	-12<=h<=13, -15<=k<=15, -19<=l<=19
Reflections collected	20782
Independent reflections	7824 [R(int) = 0.0289]
Completeness to theta = 70.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.00375
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	7824 / 0 / 518
Goodness-of-fit on F ²	1.080
Final R indices [I>2sigma(I)]	R1 = 0.0325, wR2 = 0.0885
R indices (all data)	R1 = 0.0342, wR2 = 0.0892
Extinction coefficient	n/a
Largest diff. peak and hole	0.636 and -0.502 e.Å ⁻³

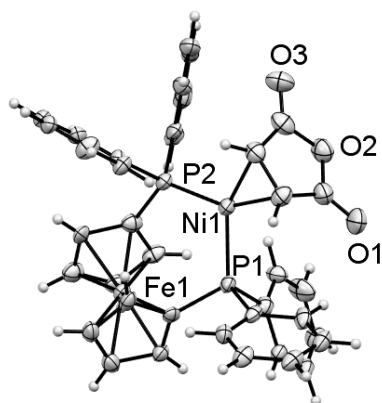


Table 7.40. Data for [Ni(dppf)MA].

Empirical formula	C ₃₈ H ₃₀ FeNiO ₃ P ₂
Formula weight	711.12
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	I a
Unit cell dimensions	a = 17.4431(3) Å b = 8.3280(2) Å c = 21.5555(3) Å
Volume	3102.23(10) Å ³
Z	4
Density (calculated)	1.523 Mg/m ³
Absorption coefficient	5.785 mm ⁻¹
F(000)	1464
Crystal size	0.18 x 0.08 x 0.04 mm ³
Theta range for data collection	4.140 to 71.026°.
Index ranges	-21<=h<=21, -10<=k<=10, -25<=l<=26
Reflections collected	14681
Independent reflections	4831 [R(int) = 0.0967]
Completeness to theta = 70.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.34920
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4831 / 2 / 407
Goodness-of-fit on F ²	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0560, wR2 = 0.1506
R indices (all data)	R1 = 0.0570, wR2 = 0.1517
Absolute structure parameter	0.001(7)
Extinction coefficient	n/a

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