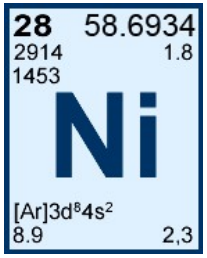
Shenvi Lab Group Meeting
01/18/16

Nickel - A Brief History and Modern Application

Robert Demoret

Nickel was discovered by the Swedish chemist Axel Fredrik Cronstedt in the mineral niccolite (NiAS) in 1751 who mistook the ore as a copper mineral.

The name is from the German word **Nickel** which means "Old Nick", a name for the devil. This name also personifies the fact that copper-nickel ores resisted refinement into copper.



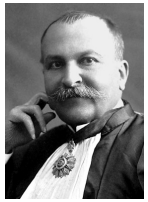
In the 1890s, Ludwig Mond discovered a process to extract and purify nickel oxides to pure nickel in what is now known as the Mond process.

This process utilizes nickels propensity to reversibly bind carbon monoxide to give nickel carbonyl which decomposes to Ni(s) upon heating.

$$NiO(s) + H_2(g) \xrightarrow[200\ ^\circ C]{} Ni(s) + H_2O(g)$$

$$Ni(s) + 4\ CO(g) \xrightarrow[50 - 60\ ^\circ C]{} Ni(CO)_4(g)$$

$$Ni(CO)_4(g) \xrightarrow[250\ ^\circ C]{} Ni(s) + 4\ CO$$



The first nickel catalyzed reaction was performed by Paul Sabatier in 1897 in which ethylene was hydrogenated to ethane at 40 °C. A mixture of equal volumes of hydrogen and ethylene were cleanly converted to ethane when passed over freshly reduced nickel without the formation of any byproducts. Most importantly, he noted that the nickel was completely unchanged and could be used repeatedly.

In 1912 Sebatier was awarded a Nobel Prize in chemistry for his work improving the hydrogenation of organic species in the presence of metals.

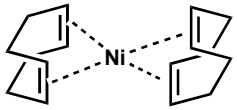
Ziegler, Wilke, and coworkers accidentally discovered the dimerization of ethylene while investigating the production of polyethylene and ethylene oligimers during what is know now as the Ziegler Process.

It was noted that only 1-butene was recovered from the "oligimerization" of ethylene, however they also noted that there were nickel and acetylene contaminants.

It was then discovered that nickel catalyzes the dimerization of ethylene gas through the mechanism shown to the right. This transformation was coined **The Nickel Effect**

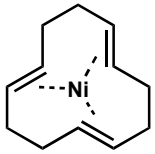
In order to utilize the nickel effect for the continuous dimerization of ethylene to 1-butene, a stable nickel catalyst needed to be developed.

The study of the nickel effect led to the simultaneous discovery of the stable nickel complexes $Ni(COD)_2$ and Ni(CDT).



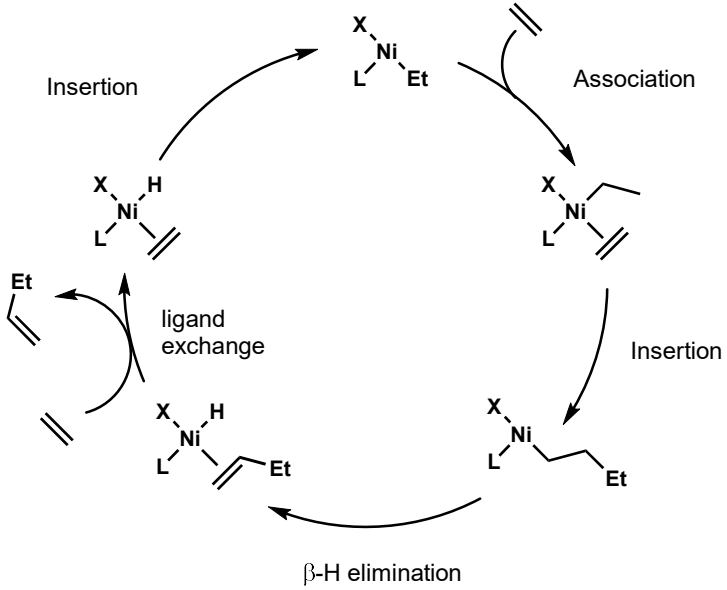
$Ni(cod)_2$

18e complex



Ni(CDT)

16e complex



"100 years of organonickel chemistry seems to be just a beginning."
-Günther Wilke

General Outline and References taken from:
T. F. Jamison *Nature* **2014**, 509, 299–309

(1) *J. Chem. Soc., Trans.*, **1890**, 57, 749-753; (2) *Angew. Chem. Int. Ed. Engl.*, **1988**, 27, 185-206; (3) Tamaru, Y. (ed.) Modern Organonickel Chemistry (Wiley-VCH, 2005)

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Properties of Nickel

Robert Demoret

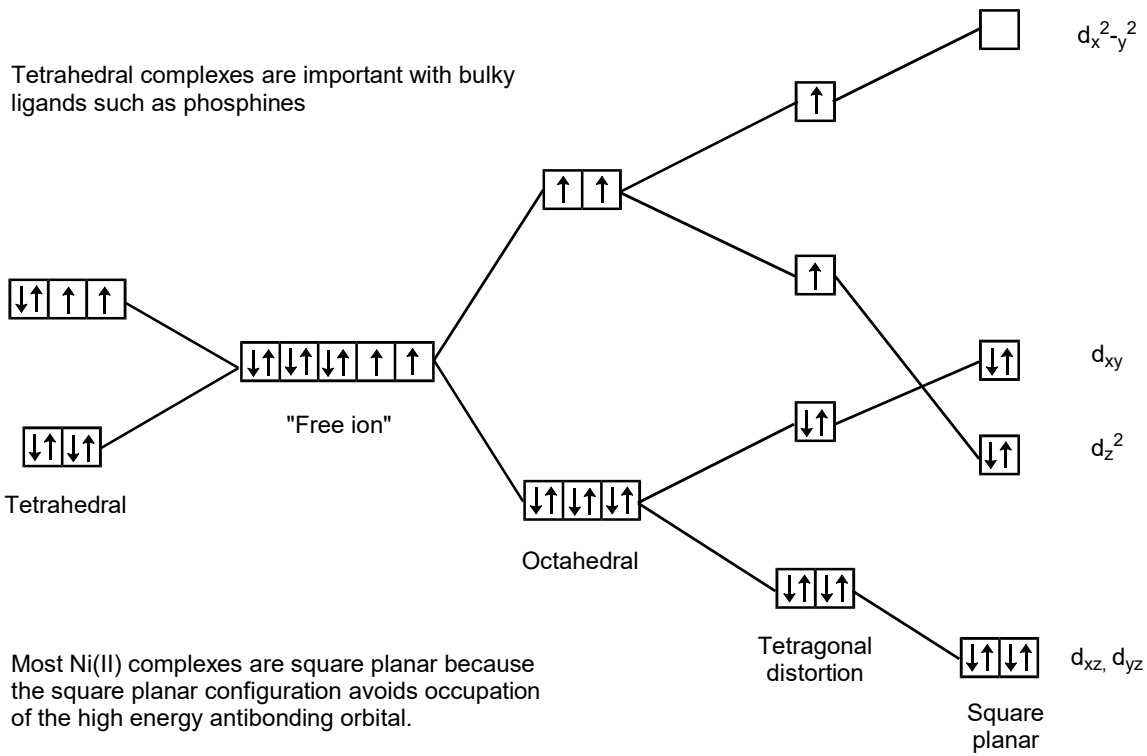
Nickel is a late electropositive d^{10} transition metal which allows oxidative addition to occur quite readily, however this corresponds to a more difficult reductive elimination.

This feature has led to the development of cross-coupling reactions that can utilize nickel in place of palladium or platinum.

Due to the facile oxidative addition, nickel can be used to couple electrophiles that were unsuitable for palladium catalyzed cross-couplings such as phenol derivatives.

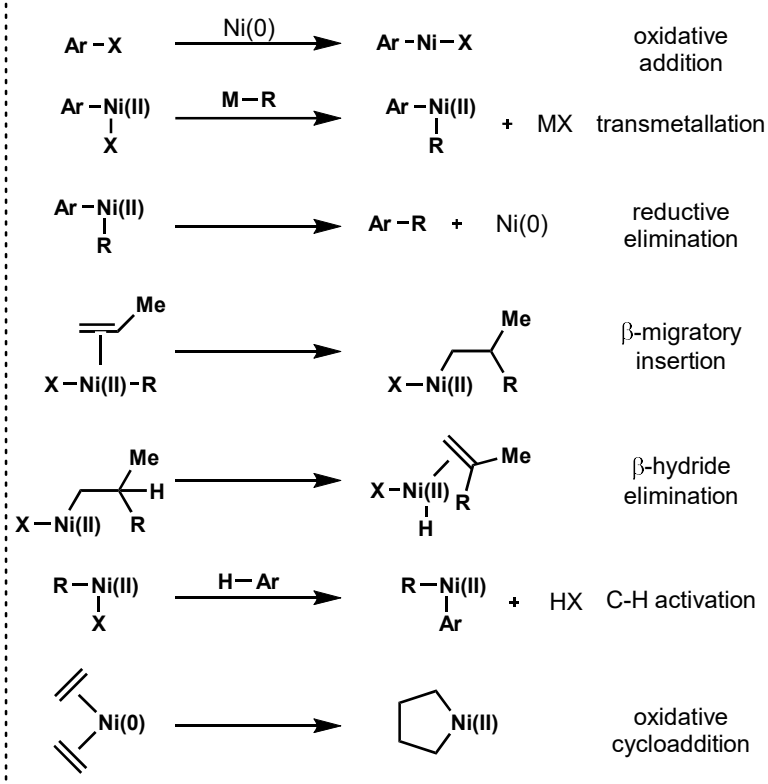
Nickel	Palladium
-1, **0**, **+1**, **+2**,**+3**,+4	**0**, +1, **+2**,+3,**+4**
Smaller atomic radius	Larger atomic radius
Less electronegative	More electronegative
Harder	Softer
Facile oxidative addition	Facile reductive elimination
Facile β-migratory insertion	Facile β-hydride elimination
Radical pathways are more accessible	
$0.488/mol	$1,817.84/mol

Tetrahedral complexes are important with bulky ligands such as phosphines



Most Ni(II) complexes are square planar because the square planar configuration avoids occupation of the high energy antibonding orbital.

Common nickel catalyzed transformations

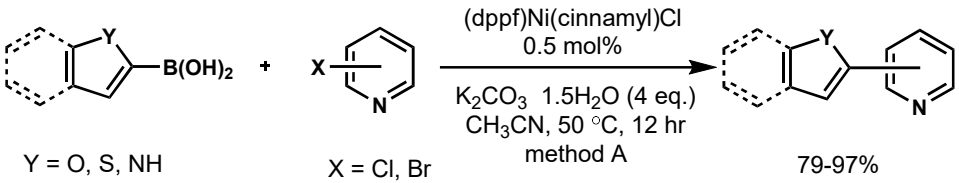


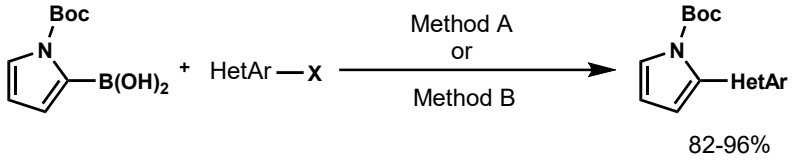
J. Am. Chem. Soc., ***1979***, 101, 6319–6332; *J. Am. Chem. Soc.*, **2009**, 131, 16573–16579; Greenwood, Chemistry of the elements; p. 1347

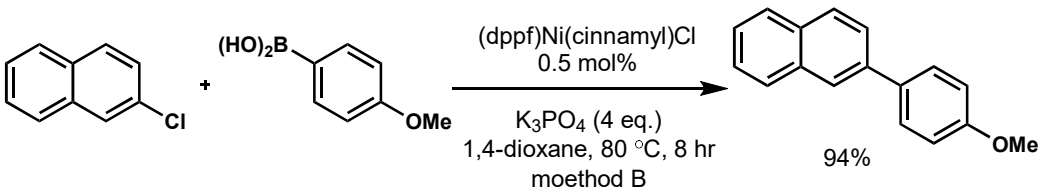
Cross-Coupling of Aryl Halides

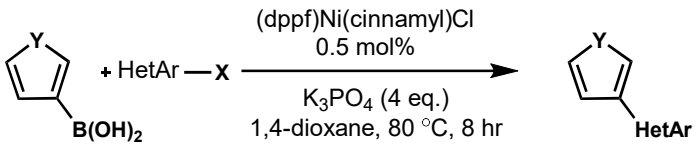
Robert Demoret

The typical Suzuki coupling uses 2-4 mol% palladium loading while the average nickel catalyzed coupling requires anywhere from 3-10 mol%. Nickel catalysis also had very poor substrate scope for the synthesis of hetero-biaryl compounds until a new method by Hartwig and Ge was reported in 2012. This method requires very low catalyst loading (0.5 mol%) and can be applied to the synthesis of biaryl systems. Notably, the nickel precatalyst (dppf)Ni(cinnamyl)Cl is an airstable catalyst.



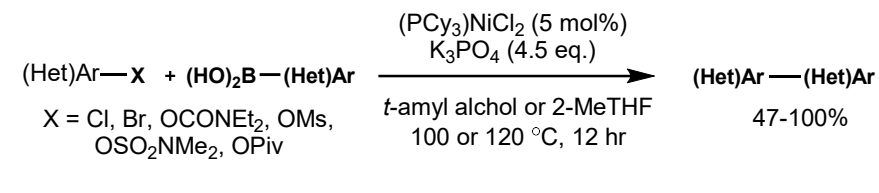


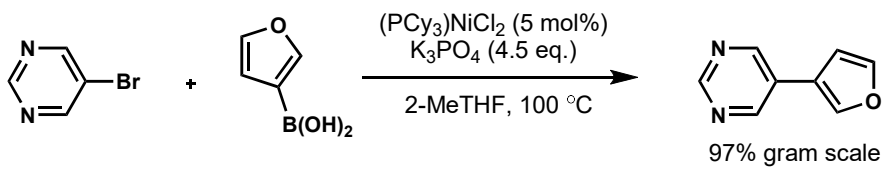




A related method was soon after disclosed by Garg et al. in 2013 where the the efficiency of the method was further improved upon, including the employment of green solvents such as 2-MeTHF and *t*-amyl alcohol.

Over 30 different solvents were surveyed and more than half gave quantitative yields for the formation of a biaryl system using the same catalytic system.





Angew. Chem. Int. Ed. **2012**, 51, 12837 –12841; *Org. Lett.*, **2013**, 15, 3950–3953

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Cross-Coupling of Phenol Derivatives

Robert Demoret

While it is now possible to prepare a wide array of aryl, polyaryl, vinyl, allyl, and alkyl halides these species are much less available from natural sources.

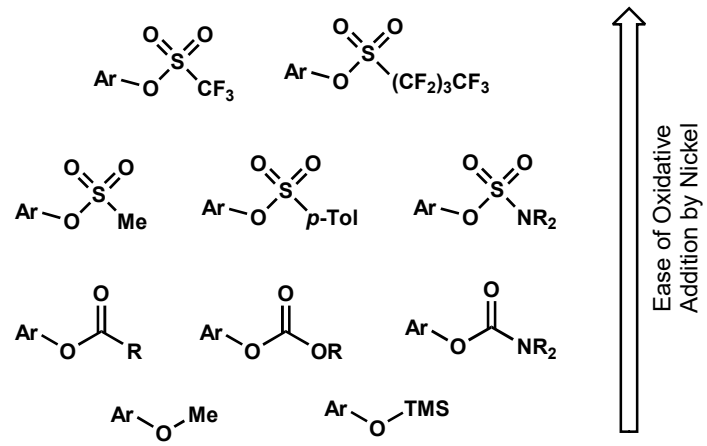
Over 50,000 phenol and polyol derivatives are commercially available while enol derived electrophiles can also be prepared from abundant carbonyl starting materials.

Oxidative addition is not nearly as straightforward across a C-O bond as it is for a C-X bond due to the high bond strength of the C-O bond.

This high activation energy rivals the energy pathways for deleterious side reactions which diminishes the selectivity for the cross-coupling.

Previosly, In order to overcome this issue the C-O bond has to be activated through conversion to more reactive sulfonates.

A major drawback to this method is the lability of the sulfonate and it has to be noted that as the lability of the sulfonate is decreased, the ease of oxidative addition also decreases.



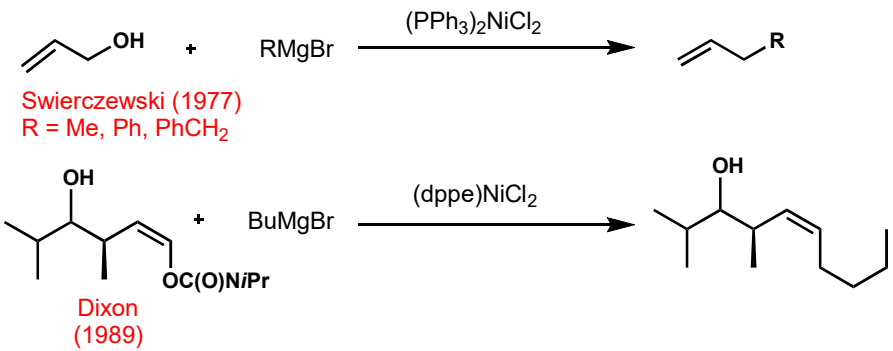
With this in mind, nickel has been known to activate and oxidatively add across C-O bonds since 1977 and it readily undergoes oxidative addition.

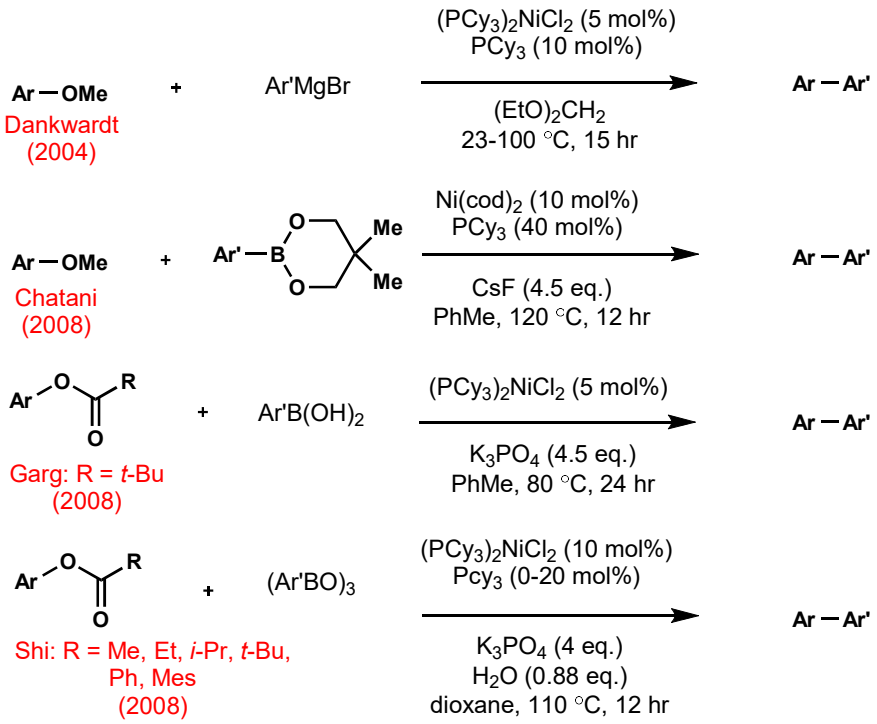
Original methods coupled a vinyl or aryl carbamate and an organomagnesium reagent.

Major advancements came from the work of Dankwardt with the Kumada type coupling of aryl ethers with arylmagnesium reagents.

Chatani further advanced the field with the Suzuki type coupling between aryl ethers and boronic esters. By moving away from organomagnesium reagents the authors considerably improved the substrate scope of these couplings.

Shi and Garg simultaneously reported the coupling of aryl pivalates or esters with aryl boronic acids.





J. Organomet. Chem., **1977**, 127, 371–384; *Synlett* **1989**, 52–54 (1989); *J. Org. Chem.* **1992** 57, 4066–4068; *J. Am. Chem. Soc.* **2008,** 130,14468–14470;*J. Am. Chem. Soc.* **2008**, *130, 14422–14423*

Benzylic Cross-Coupling

Robert Demoret

Benzylic C-O bonds are also activated by low valent nickel to undergo coupling reactions with organometallic reagents.

Historically racemization of the sterocenter of the sp^3 electrophile occured during nickel catalyzed cross-couplings.

Jarvo reported the first stereoinvertive alkyl-alkyl cross-coupling without the aid of a chiral catalyst or a directing group.

Jarvo then reported a stereoretentive or stereoinvertize Suzuki coupling of benzylic esters with aryl boronic esters depending on which class of ligand is used for the transformation.

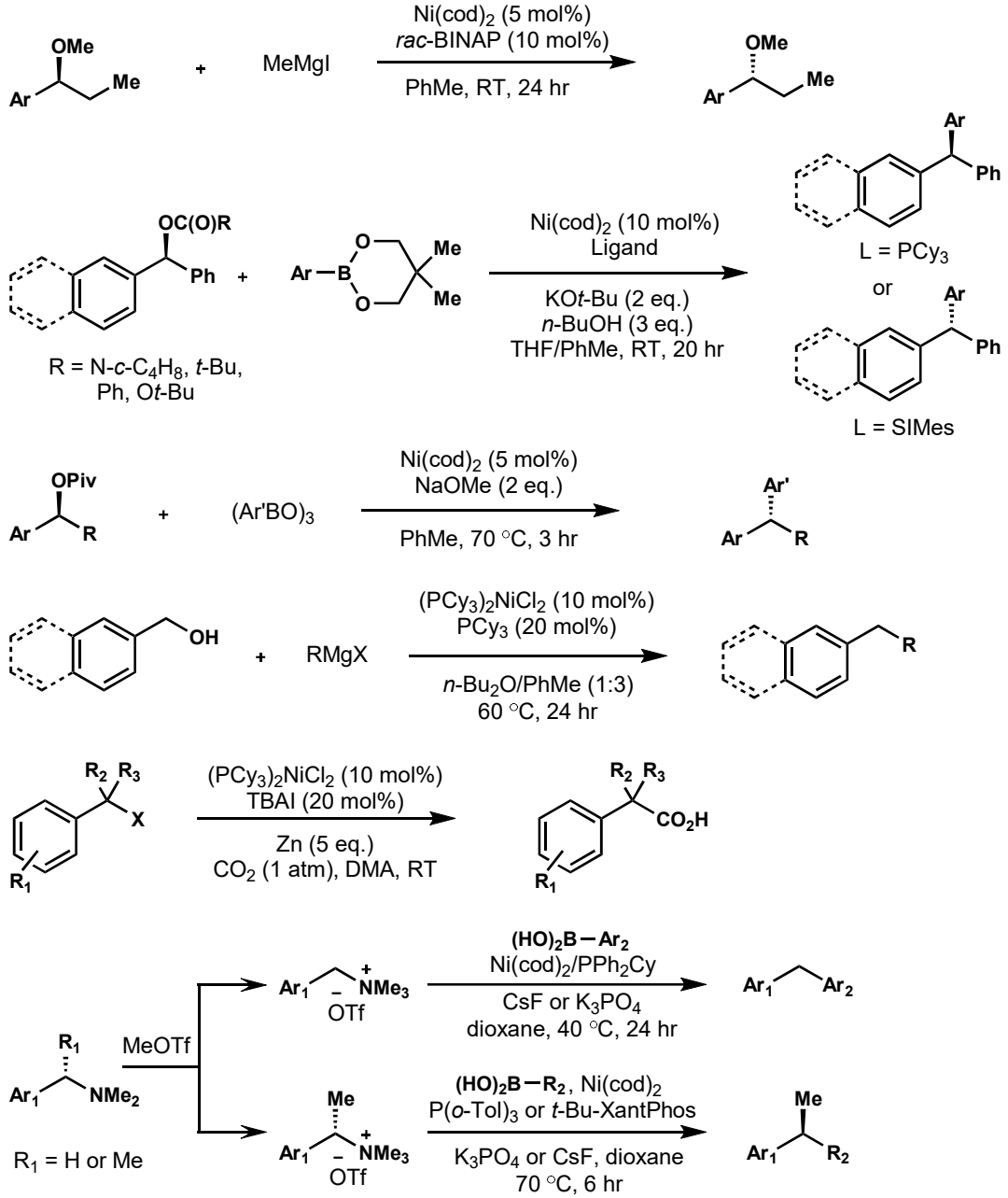
Simultaneously, Watson reported a very similar stereoinvertive transformation in the absence of any ligand.

Mechanism: The mechanism has not currently been elucidated, however the most common theory is that oxidative addition into nickel is stereo-retentive in the presence of a phosphine ligand. It is also well known for other metals that transmetallation and reductive elimination are stereo-retentive as well, which explains the stereochemical outcome of the reaction in the presence of a phosphine ligand.

Shi has reported the coupling of benzylic alcohols with Grignard reagents through an activated magnesium alkoxide.

Martin et. al. has used this chemistry to transform benzylic halides to the corresponding phneylacetic acid with CO_2 as the carbon source.

Watson and co-workers have also expanded the scope of the benzylic electrophile to include benzylic ammonium salts by activating the corresponding benzylic amine with MeOTf.



J. Am. Chem. Soc. **2011**,133, 389–391; *J. Am. Chem. Soc.* **2013**, 135, 3303–3306; *J. Am. Chem. Soc.* **2013**, 135, 3307–3310; *J. Am. Chem. Soc.* **2012**, 134, 14638–14641; *J. Am. Chem. Soc.* **2013**, 135, 1221–1224; *J. Am. Chem. Soc.* **2013**, 135, 280–285

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C(sp^3)-C(sp^3) Cross-Couplings

Robert Demoret

Suzuki reported the first Csp_3-Csp_3 coupling of primary alkyl iodides with alkyl boranes with Pd and Ni in 1992 however there was a significant amount of reduction and elimination products.

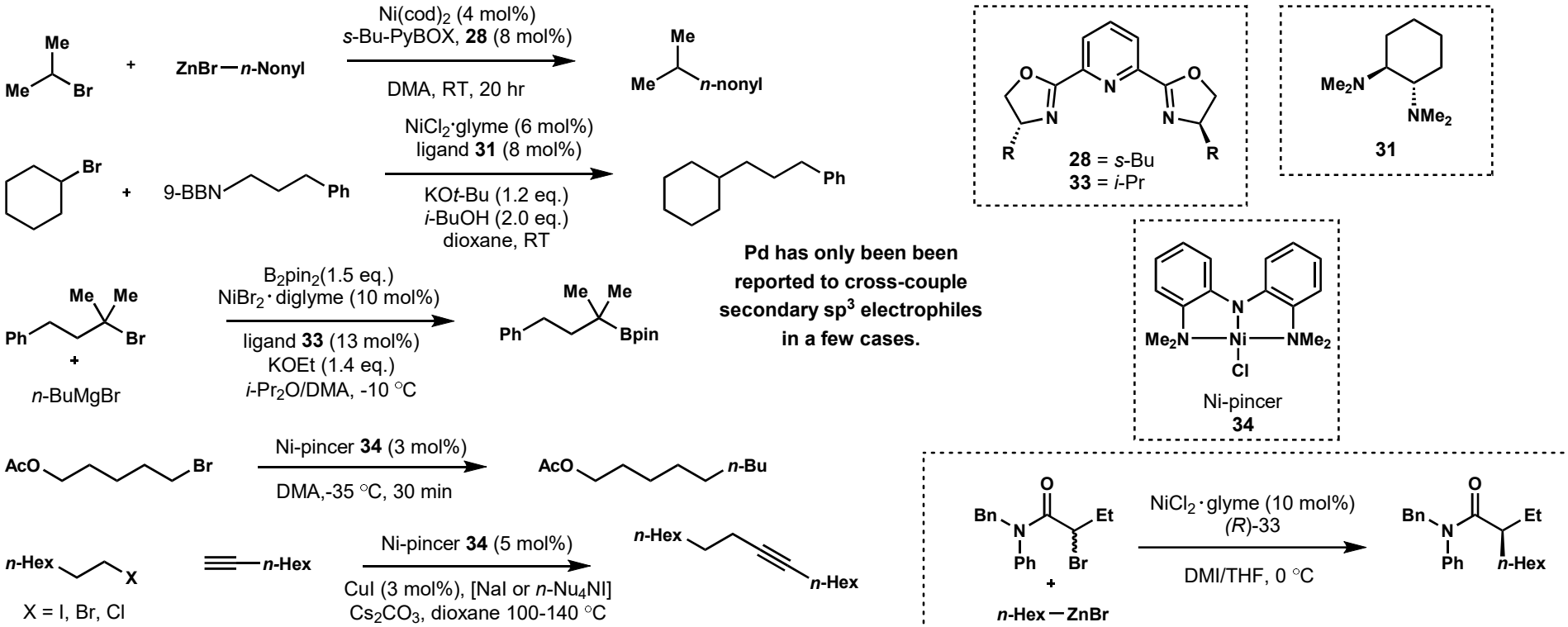
Knochel Improved upon the nickel catalyzed coupling method by treating primary iodides with organozinc reagents in the presence of 4-(trifluoromethyl)-styrene which acts as a promoter and facilitates the reductive elimination of the dialkyl Ni(II) species.

The bigest contribution to the field of Csp_3-Csp_3 coupling was by Fu and co-workers in 2003 in which the coupling of secondary alkyl bromides with β-hydrogens and organozinc reagents was reported. This opened the door to the formation of asymmetric syntheses of tertiary or quaternary centers.

The key to the success of these couplings lies in the ligands which slow the rate of β-hydride elimination since the tridentate ligands do not leave a vacant coordination site.

Another report by Hu introduces the Ni-pincer complex which is active for Kumada and Sonogashira couplings with primary alkyl iodides.

The first asymetric secondary Csp_3-Csp_3 cross-coupling was perfromed by Fu et. al. in 2005 with the aid of a directing group and an (R)-PyBOX ligand.

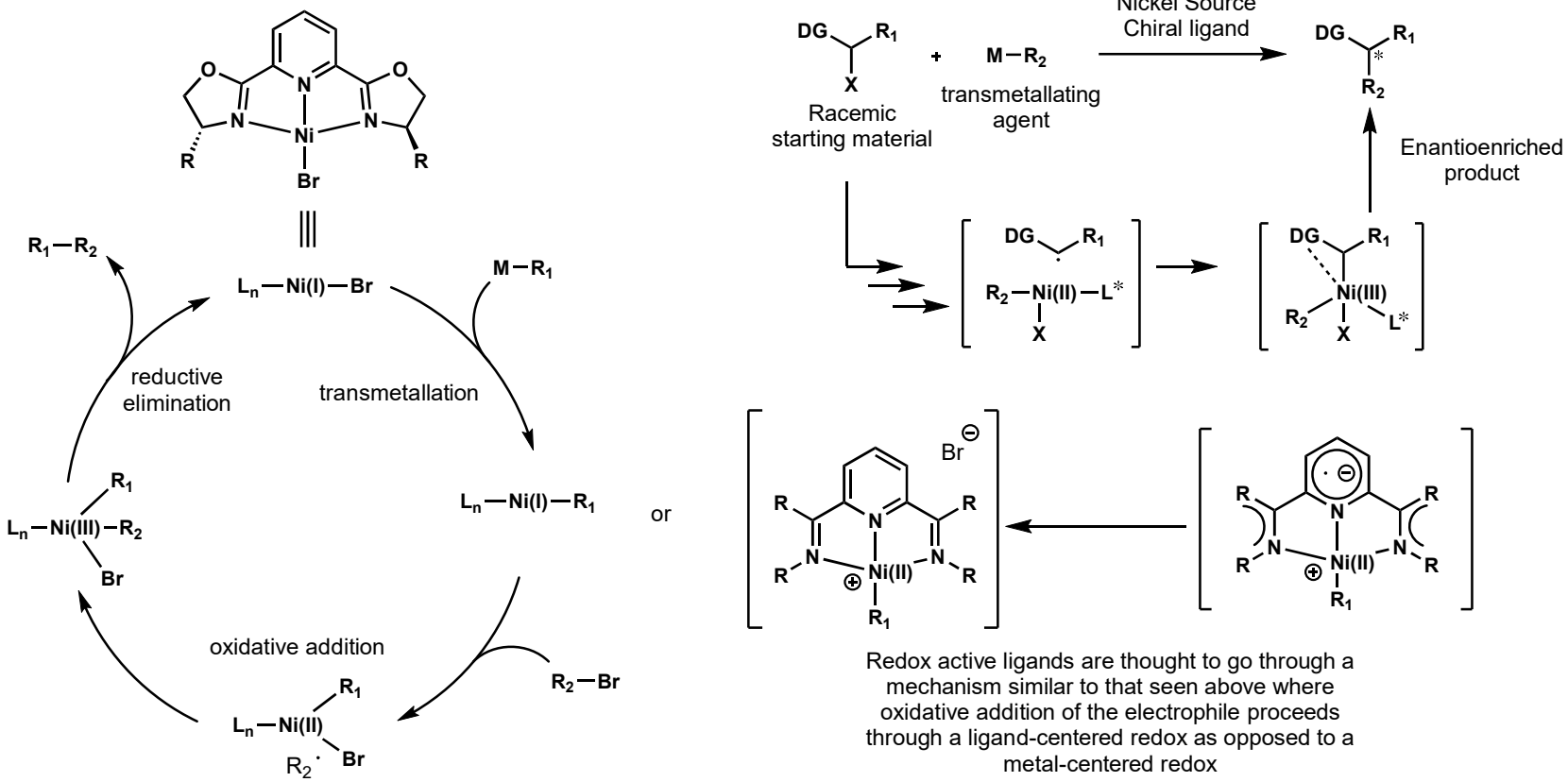


Chem. Lett. **1992**, 21, 691–694; *J. Am. Chem. Soc.* **1998**, 120, 11186–11187; *J.Am. Chem. Soc.* **2002**, 124, 4222–4223; *J. Am. Chem. Soc.* **2003**, 125, 14726–14727; *J. Am. Chem. Soc.* **2013**, 135, 624–627; *Angew. Chem. Int. Edn* **2009**, 48, 2656–2670; *J. Am. Chem. Soc.* **2008**, 130, 8156–8157; *J. Am. Chem. Soc.* **2005**, 127, 4594–4595

Proposed Mechanisms for C(sp^3)-C(sp^3) Cross-Couplings

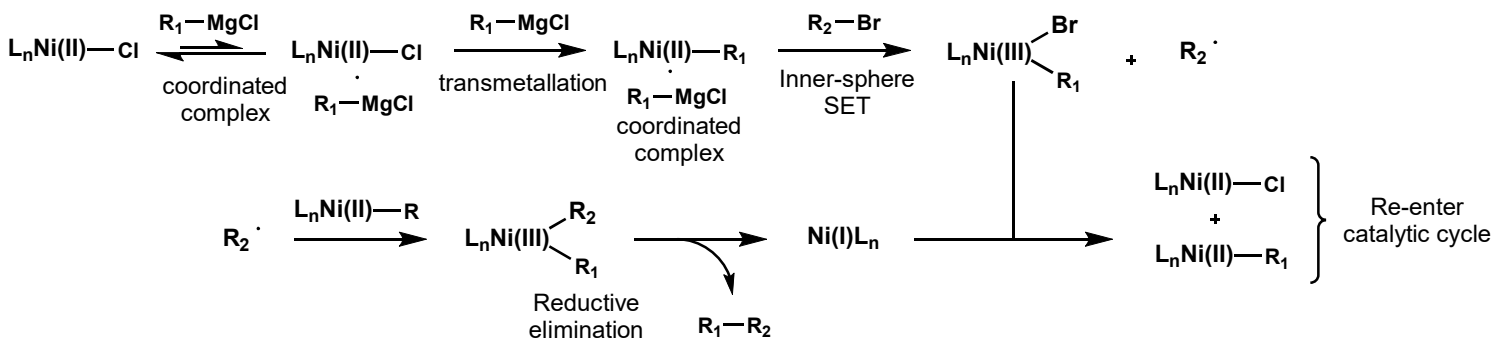
Robert Demoret

Fu-type Cross-Coupling mechanism



Redox active ligands are thought to go through a mechanism similar to that seen above where oxidative addition of the electrophile proceeds through a ligand-centered redox as opposed to a metal-centered redox

Ni-pincer Complex Mechanism



J. Am. Chem. Soc. **2011**, 133, 15362–15364 ;*J. Am. Chem. Soc.*, **2006**, 128 (40), pp 13175–13183; *J. Am. Chem. Soc.,* **2013**,135, 12004–12012; Nature, **2014** 509, 299–309

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Reductive Cross-Coupling

Robert Demoret

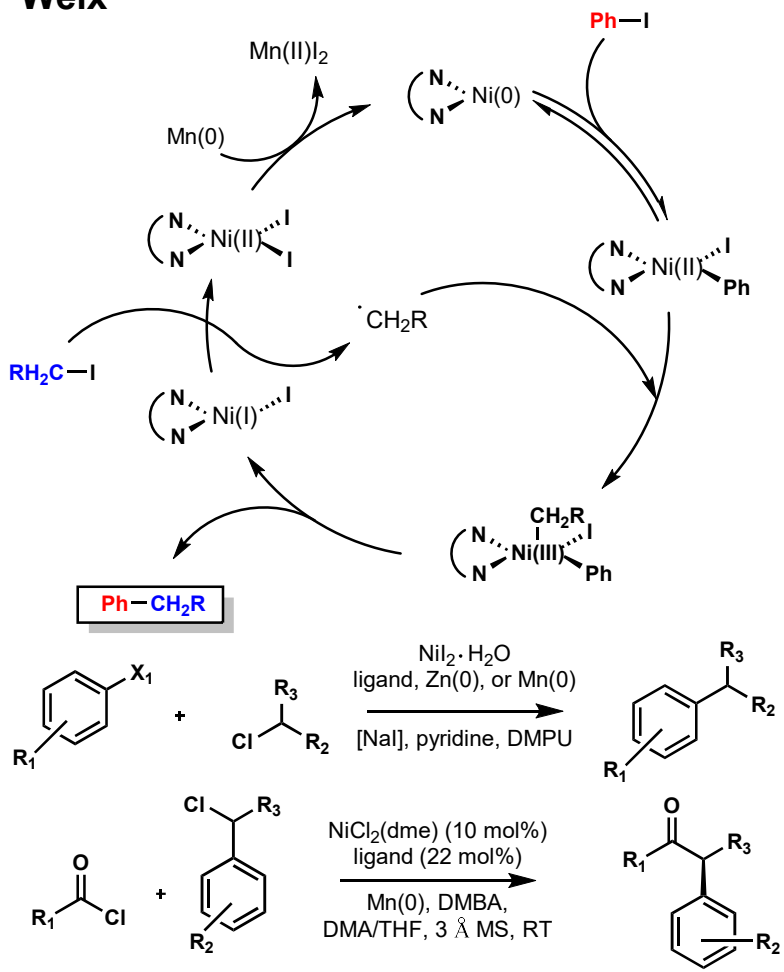
Reductive cross-coupling joins two electrophilic components, and mitigates homo-dimerization, without the formation of a stoichiometric organometallic species.

This method circumvents the need for any nucleophilic reagents which can be costly, unstable, and/or cause undesired side reactions, but the difficulty is differentiating between the two electrophiles and preventing homodimerization.

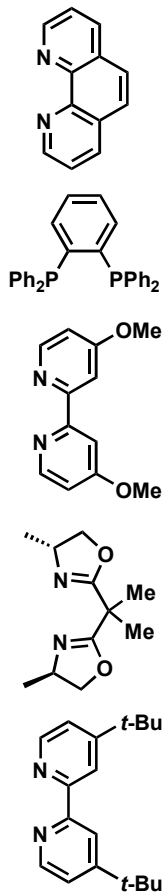
This method utilizes all of the available oxidation states of nickel and matches the properties of the electrophilic halides to the capabilities of the catalyst which avoids side reactions.
- Aryl haildes more readily undergo polar oxidative addition (Ni(0)/Ni(II))
- Alkyl radicals are more stable than aryl radicals (Ni(I)/Ni(III)).

This method has also been rendered asymmetric by the Reisman group through the use of chiral ligands.

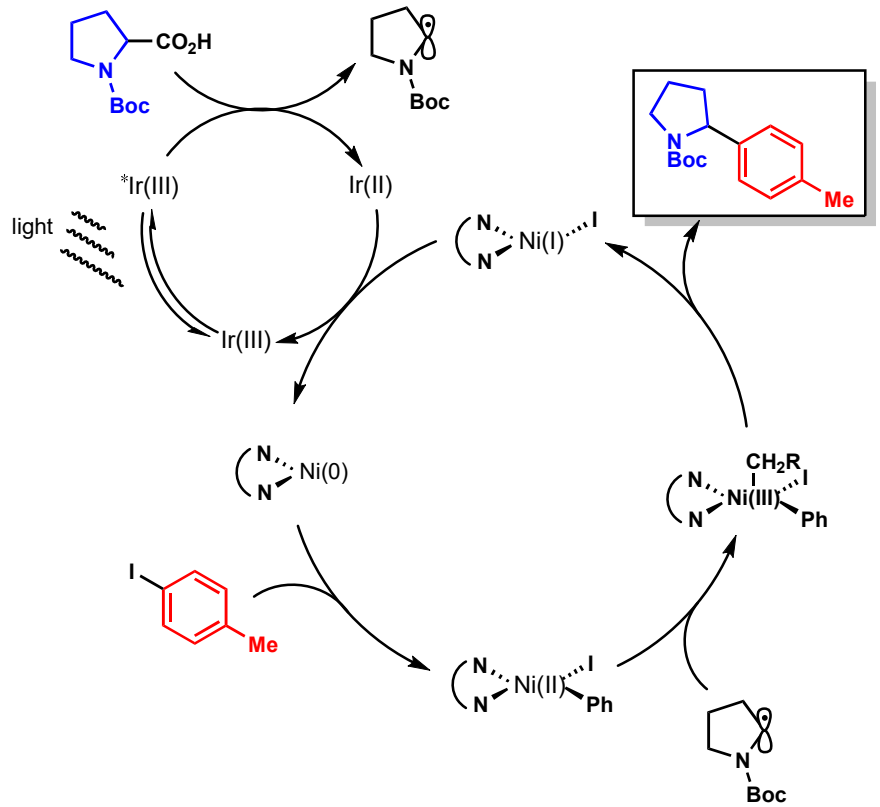
Weix



Ligands



MacMillan



J. Am. Chem. Soc. **2013**, 135, 16192-16197; | *J. Am. Chem. Soc.* **2013**, 135, 7442-7445

C-H Activation

Robert Demoret

The difficulty with C-H activation lies in the selective activation of a specific C-H bond in the presence of chemically similar C-H bonds.

Itami et. al uses decarbonylative coupling of aryl and heteroaryl esters and (benz)oxazoles with an air stable nickel pre-catalyst.

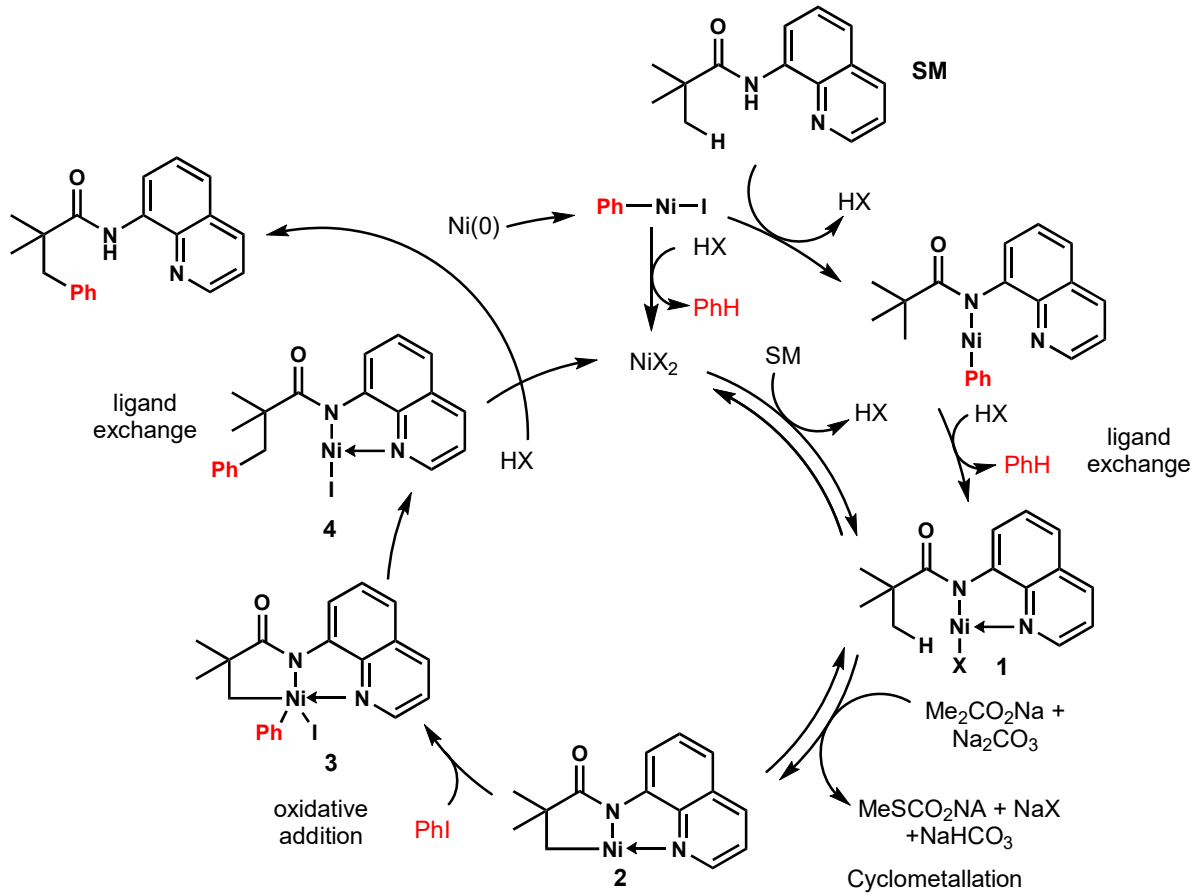
Chatani and co-workers reported the first example of a nickel catalyzed chelation-assisted C-H activation with the aid of a directing group.

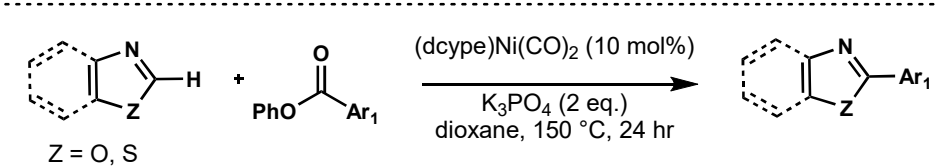
A proposed mechanism for the reaction is shown to the right:

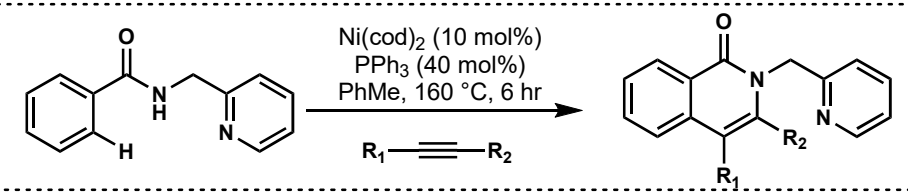
- Coordination of the amide to the Ni center followed by ligand exchange with the concomitant generation of HX gives the Ni complex **1**, which undergoes reversible cyclometalation to give **2**, probably via a concerted-metallation-deprotonation mechanism.

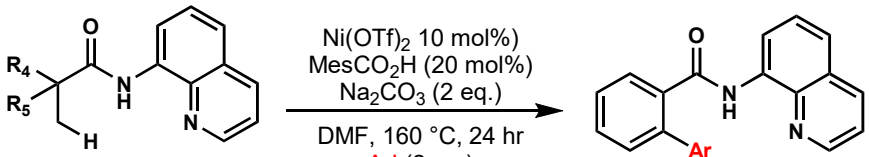
- The oxidative addition of iodobenzene gives the high valent Ni(IV) complex **3**. The Ni(IV) complex **3** undergoes reductive elimination to give **4** which, on protonation, affords the desired arylation product with the regeneration of Ni(II).

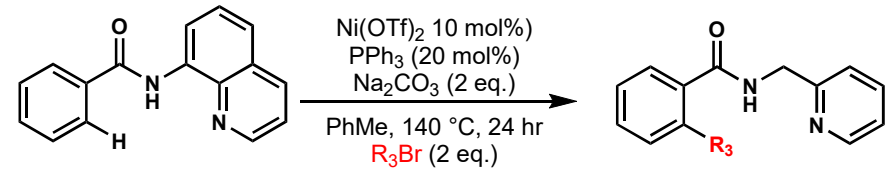
It should be noted that nickel(II) - (IV) catalytic cycles are very rare.











J. Am. Chem. Soc. **2012**, 134, 13573–13576; *J. Am. Chem. Soc.* **2014**, 136, 898-901

Heck Reaction

Robert Demoret

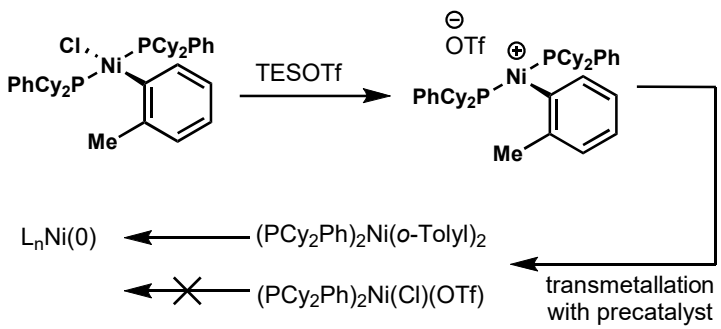
Computational work with Pd and Ni proposes lower energy barriers for oxidative addition and migratory insertion for Ni in contrast to to faster β-hydride elimination and catalyst regeneration for Pd.

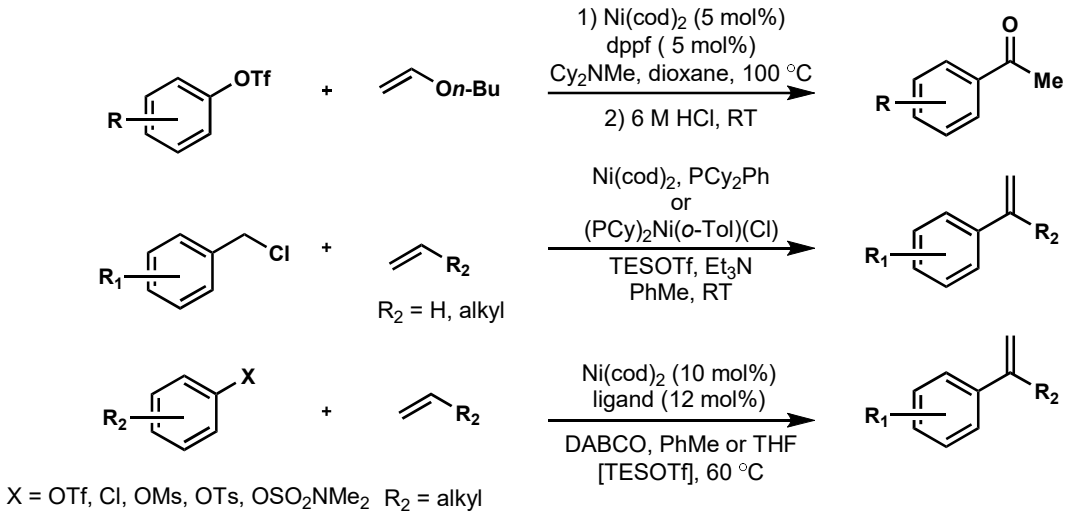
Skyrdstrup and coworkers developed a general method for the coupling of electronically biased enol ethers and aryl triflates to generate methyl ketones.

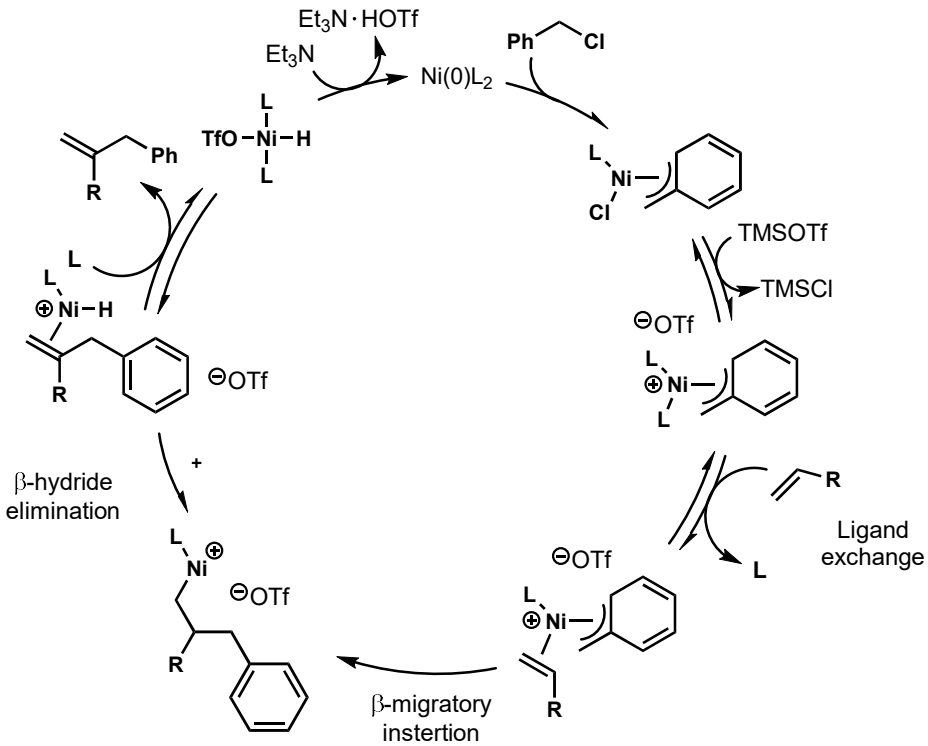
Regio-selectivity is one of the key issues for the heck reaction for electron rich alkenes.
- This issue can be overcome by employing a cationic Ni species after oxidative addition through dissociation of a the halide as opposed to the ligand itself
- This mechanism (shown below) is now commonly employed for the Heck reaction

The other major issue with the Heck reaction occurs with electronically unbiased olefins which tend to give a mixture of branched and linear isomeric products depending on which position of the olefin the metal inserts.
- Jamison and co-workers overcame this problem by employing a nickel catalyzed cationic Heck pathway that utilizes the fact that the shorter Ni-ligand bond lengths make steric differentiation between a proton and an alkyl substituent feasible.

Jamison's group then developed an air stable Ni precatalyst which obviates the need for a glovebox and also showed that COD is a noninnocent ligand in the heck reaction.







Organometallics, **2004**, 23, 2114–2123; *J. Am. Chem. Soc.* **2013**, 135, 1585-1592

Reductive Coupling

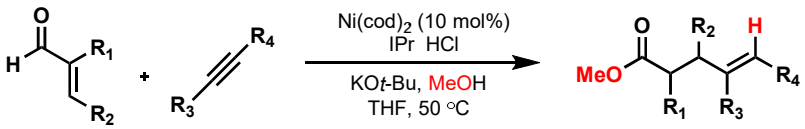
Robert Demoret

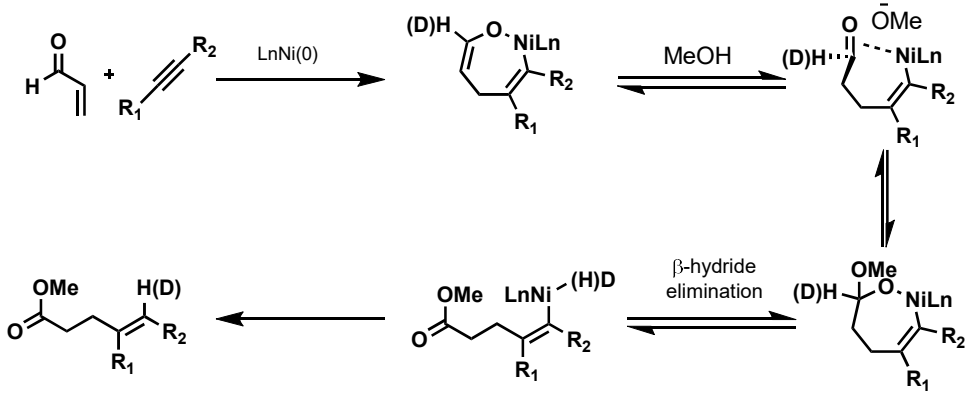
Reductive coupling involves the joining of two π-components with a reducing agent to form a new C-H σ-bond.

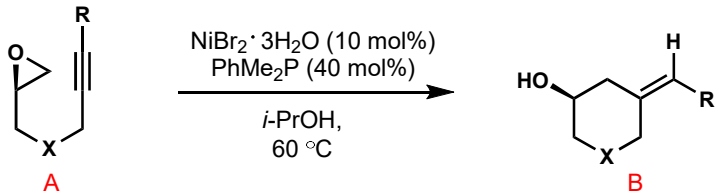
The reaction is thought to proceed through an oxidative cycloaddition followed by σ-bond metathesis with the reducing agent and subsequent reductive elimination.

The major developments in this field include the discovery of milder reducing agents as well as tuning the regioselectivity of the reactions.

Montogomery and co-workers were able to use MeOH to facilitate an internal redox during the coupling of enals with alkynes





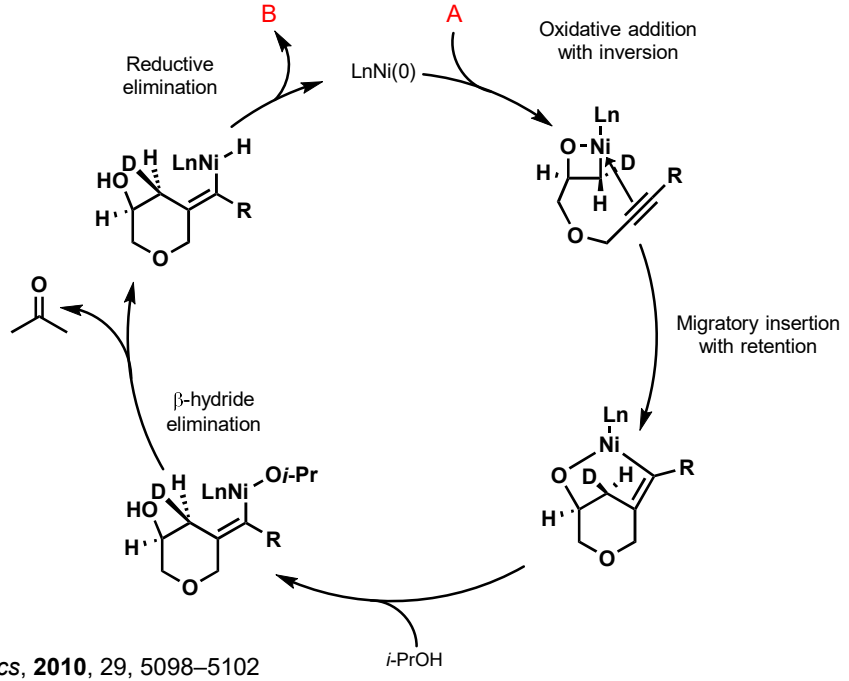


X = O, NBn, CH_2

Jamison and co-workers have also shown that *i*-PrOH can also act as a mild reductant.

Most notably, they were able to perform this transformation under very mild conditions without the use of $Ni(cod)_2$.

Recent studies by Beletskaya and co-workers have shown that phosphine ligands are capable of reducing $Ni(acac)\bullet H_2O$ salts to the active Ni(0) species *in situ* without any special precautions or handling procedures.



J. Am. Chem. Soc., **2008**, 130, 469-471; *Org. Lett.*, **2011**, Vol. 13, No. 15; *Organometallics*, **2010**, 29, 5098–5102

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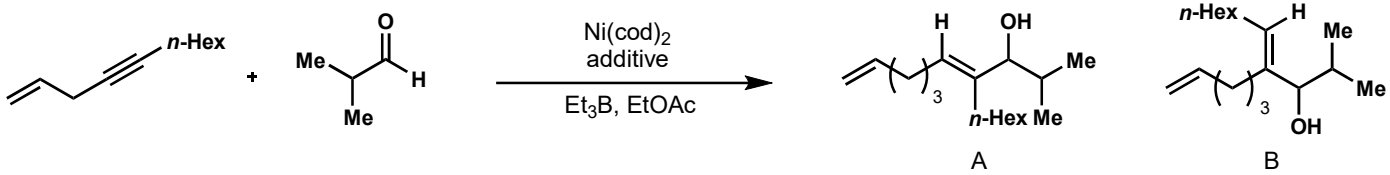


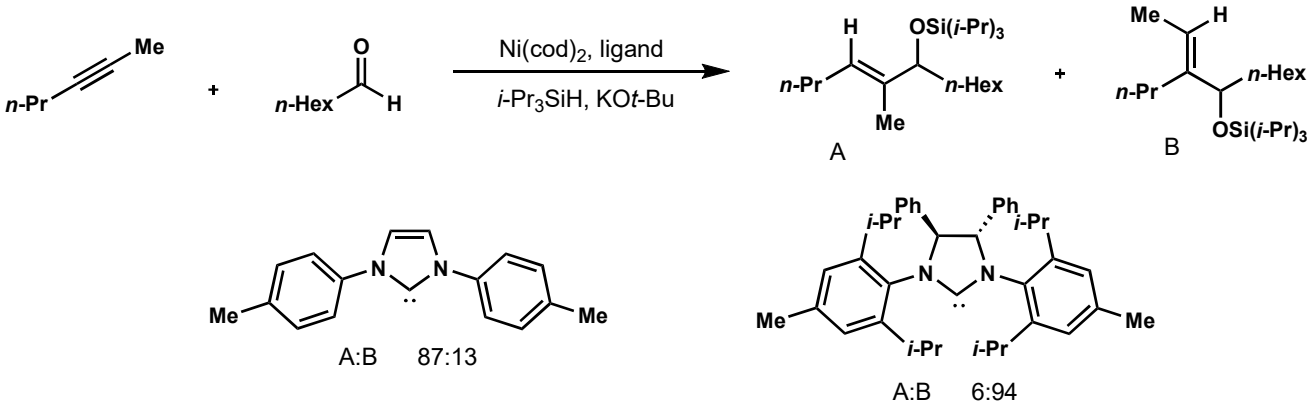
Additive	A:B
None	>95:5
PBu_3	1:1
PCy_3	5:95

In order to tune the regioselectivity of the reductive coupling Montgomery and co-workers utilized a pendant alkene which could act as a ligand to the Ni after coordination of the alkyne.

The ligand sphere could then be altered by adding different phosphine ligands which in turn changed the entire course (mechanism) of the reaction as was proven by Jamison and co-workers.

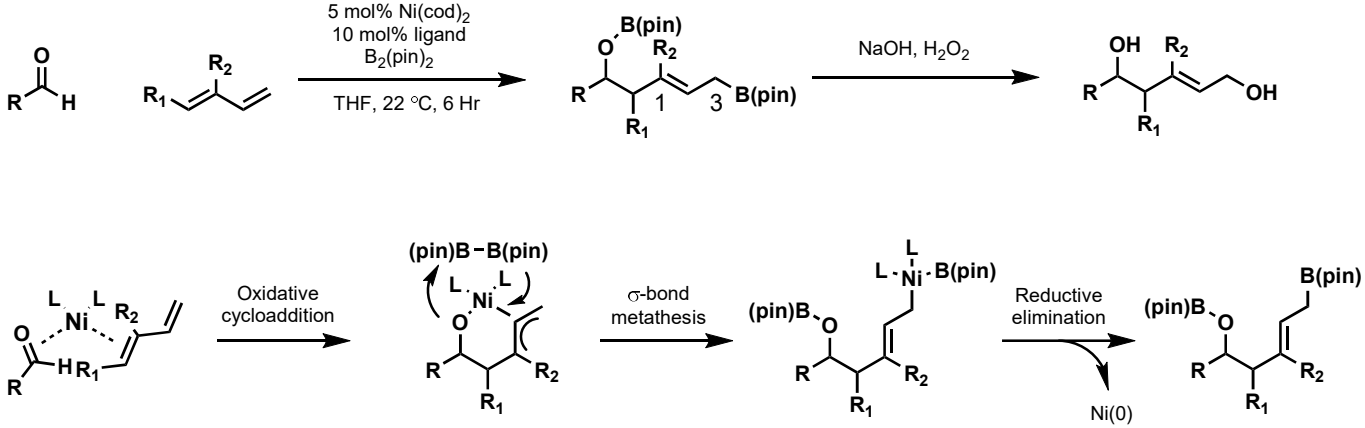
Montgomery and co-workers also showed that the regioselectivity of the oxidative cycloaddition could be influenced through the use of bulky NHC ligands.

By switching to a bulky NHC ligand, the alkene repositions itslef in such a manner to reduce the steric hinderance, which in turn changes the regioselectivity of the reaction



Recent work by Morken and coworkers has shown that dienes can undergo regioselective oxidative cycloaddtion into aldehydes followed by regioselective transmetallation, which is influenced by the ligand being employed.

PCy_3 ligands result in the allyl borylation at position 3, but the employment of $P(SiMe_3)_3$ results in borylation at position 1. This is thought to be an electronic as opposed to a steric effect becasue $P(SiMe)_3$ has the same cone angle as $P(t\text{-}Bu)_3$. $P(SiMe_3)_3$ is thought to act as an electron acceptor which may facilitate reductive elimination prior to allyl isomerization.

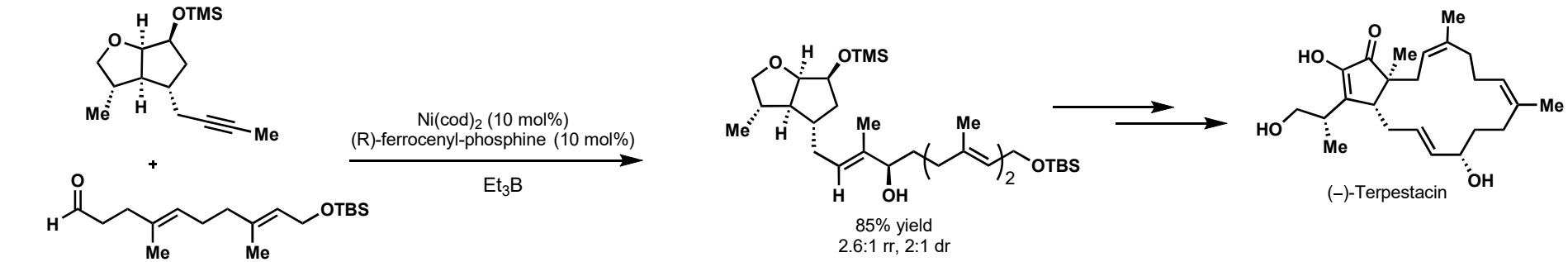


J. Am. Chem. Soc., **2004**, 126 (47), pp 15342–15343; *J. Am. Chem. Soc.*, **2010**, 132, 6304–6305; *J. Am. Chem. Soc.* **2008**, 130, 16140–16141; *J. Am. Chem. Soc.*, **2010**, 132, 7576–7577

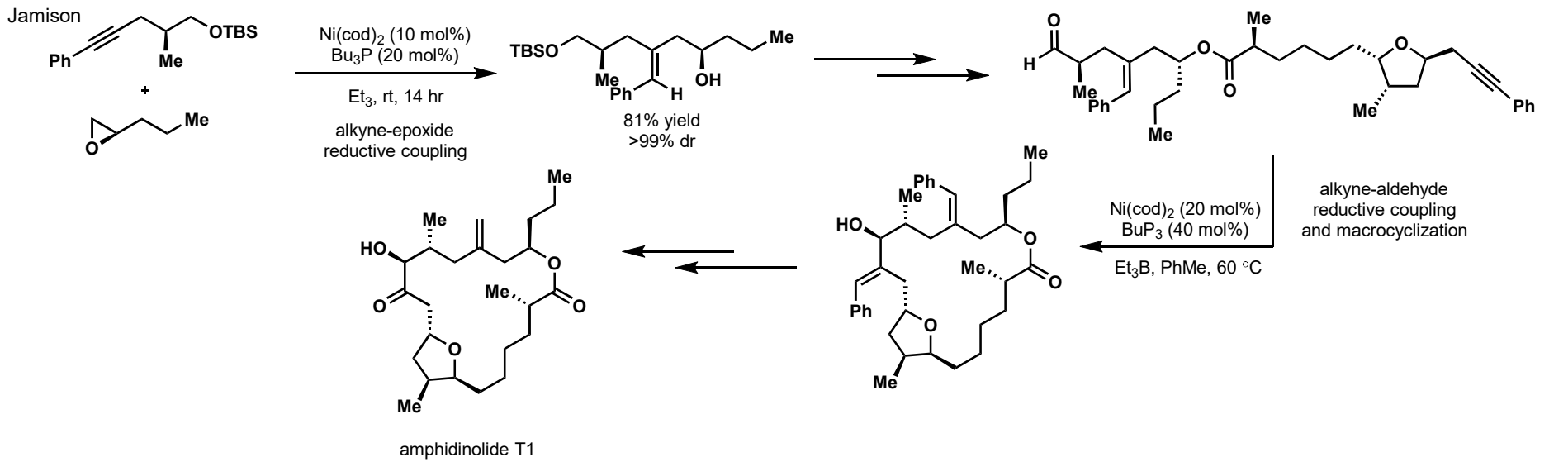
Nickel in Total Synthesis

Robert Demoret

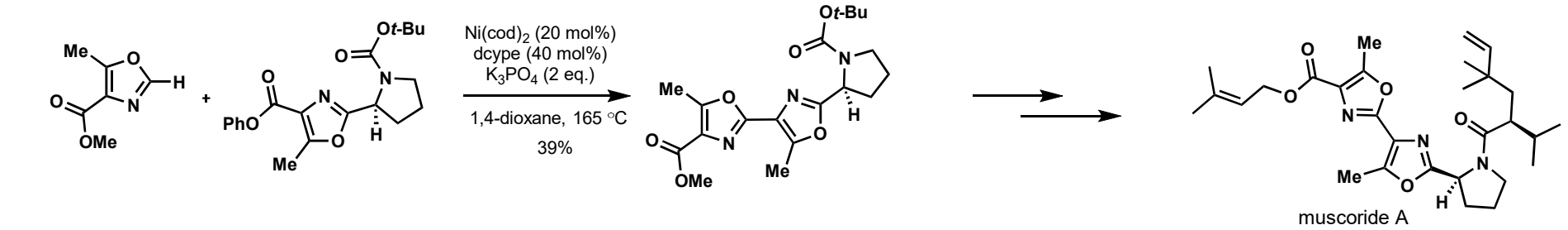
Jamison



Jamison



Itami



J. Am. Chem. Soc. 2003, 125, 11514-11515; J.Am. Chem. Soc. 2004, 126, 998-999; J. Am. Chem. Soc. 2012, 134, 13573-13576