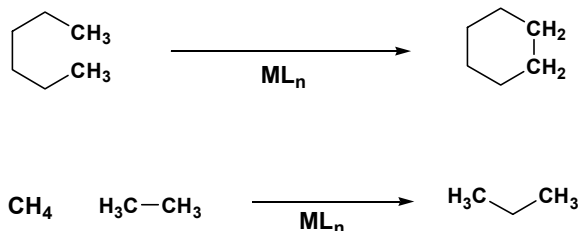


Direct Construction of Carbon-Carbon Bonds: A Brief Introduction

What chemists have always wanted to do:



The problem: no one has yet figured out what M is.

Consequently, chemists have resorted to exploiting functional groups (aldol, transition-metal catalysts, etc.) and the intrinsic reactivity of molecules (carbenes, radicals, pericyclic processes) to form carbon-carbon bonds.

When it comes to forming C-C bonds, though, it is worthwhile to strive for these idealized reactions, in order to streamline syntheses and reduce waste:

"Where possible, oxidation states of intermediates should regularly escalate during (convergent) assemblage process. The challenge is to involve active functionality, where possible, in the assemblage process." --David A. Evans (Frontiers in Chemistry Symposium, The Scripps Research Institute, 2004)

This review will cover the current state of the art in forming carbon-carbon bonds as directly as possible, without resorting to wasteful prefunctionalization, disposable functional groups and protecting groups. Ideally this involves cleavage of C-H bonds and direct coupling of the two carbon centers.

There are a number of useful reviews which discuss much of this work in further detail:

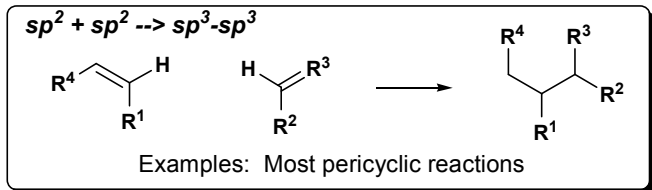
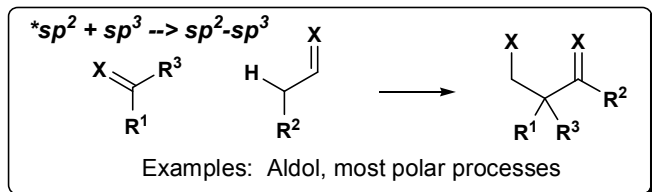
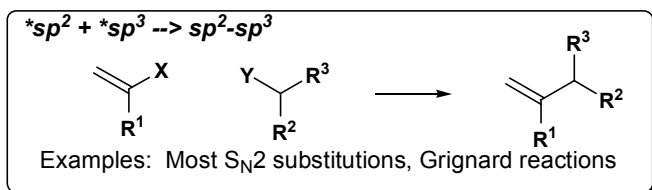
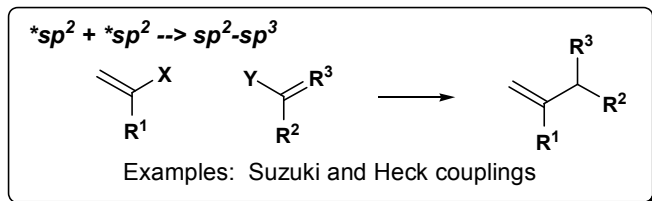
- D.C. Culkin, J.F. Hartwig. *Acc. Chem. Res.* **2003**, 36, 234.
 G. Dyker. *Angew. Chem. Int. Ed.* **1999**, 38, 1698.
 C.-H. Jun, J.H. Lee. *Pure Appl. Chem.* **2004**, 76, 577.
 F. Kakiuchi, N. Chatani. *Topics Organomet. Chem.* **2004**, 11, 45.
 F. Kakiuchi, S. Murai. *Acc. Chem. Res.* **2002**, 35, 826.
 M. Miura, M. Nomura. *Topics Curr. Chem.* **2002**, 219, 211.

Focus: Unusual reactivity involving a single-step formation of a C-C bond, ideally with one or both of the bonds broken being an unactivated C-H bond.

Definition of "activated" for the purpose of this review: a C-X bond which is easier to break than the corresponding C-H bond (i.e., prefunctionalization of the desired site for reactivity).

Disclaimer: Most of the following examples will involve cleavage of C-H bonds which are still activated electronically in some fashion by adjacent heteroatoms or conjugated π -systems. We will see some cases where this electronic activation is unnecessary.

Types of reactions **NOT** discussed in this review:

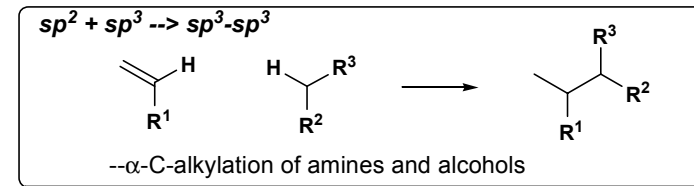
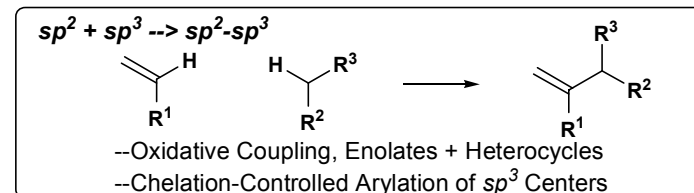
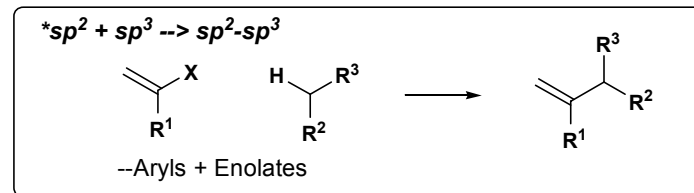
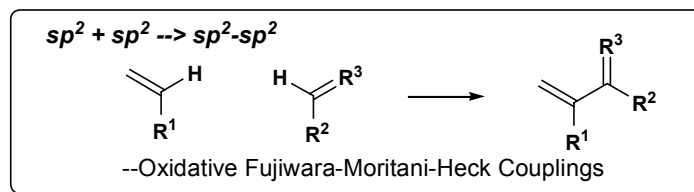
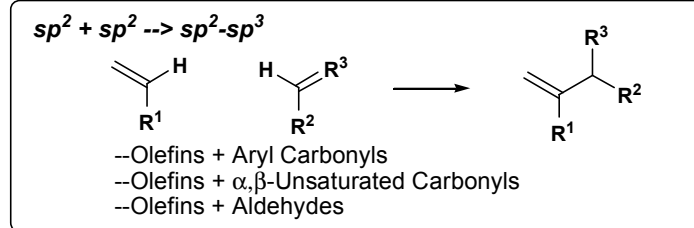


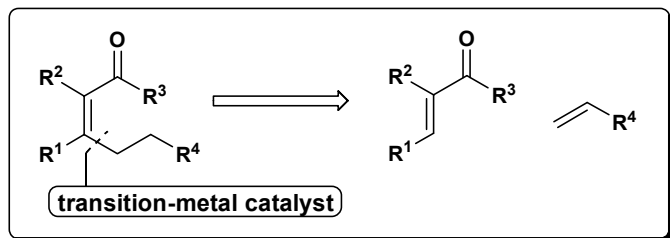
These kinds of reactions are well known and do not require further review. Instead, we will focus on different kinds of reactivities.

A NOTE ON NOTATION:

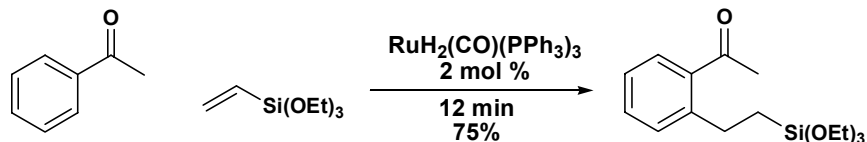
* = "disposable" activating group (e.g., halogen, OTf, OAc, etc.)

What **WILL** be discussed in this review:





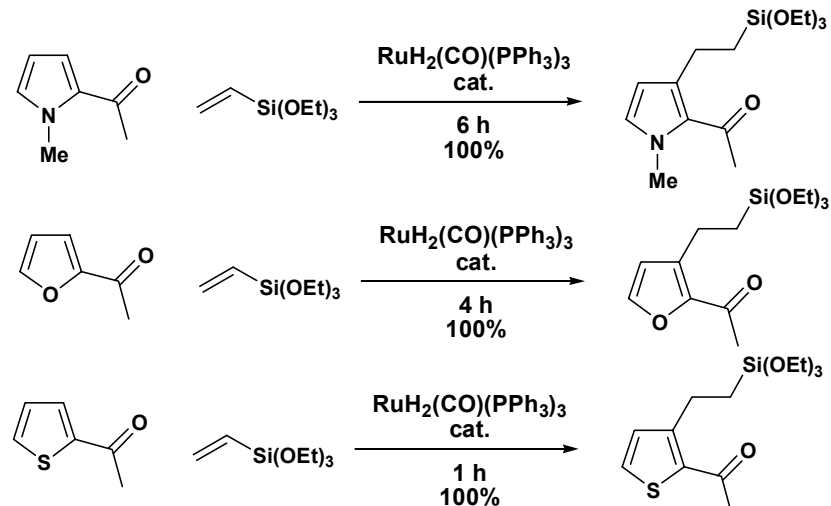
Prior to 1993, it was thought that the cleavage of C-H bonds was a thermodynamically and kinetically unfavorable process. Then came Shinji Murai:



S. Murai, et al. *Nature* **1993**, 366, 529-531.

The reaction is strongly regioselective for the *ortho*-position, suggesting the reaction proceeds through a chelated intermediate.

The reaction also works with a variety of heterocyclic ketones:

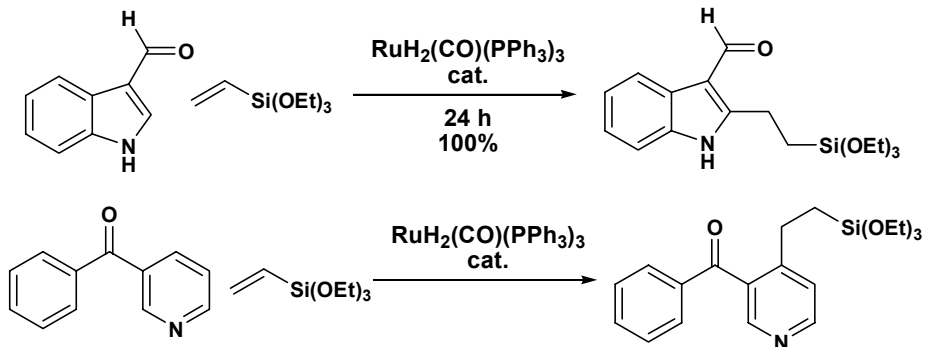


F. Kakiuchi, N. Chatani. *Topics Organomet. Chem.* **2004**, 11, 45-79.

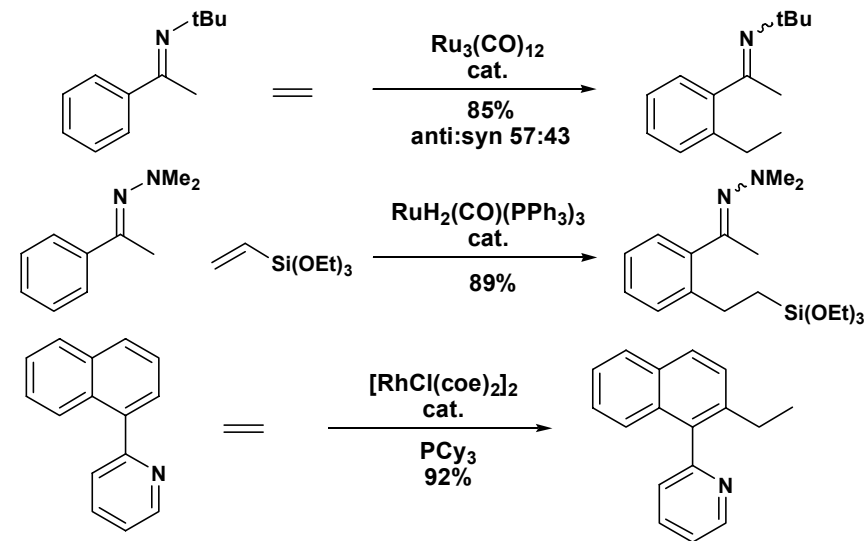
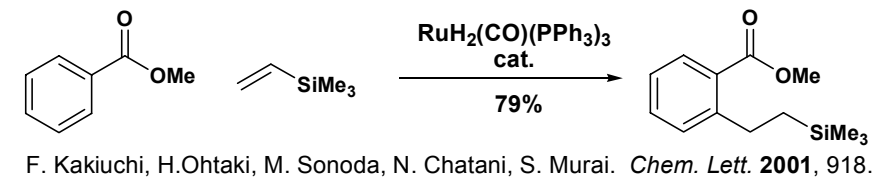
Run	Aromatic ketone	Olefin	Ketone/olefin/catalyst (mmol)	Time (h)	Product	Yield (%)	Product	Yield (%)
1			2 / 2 / 0.04	0.2		75,		8
2			2 / 6 / 0.04	90		<1,		94
3			2 / 4 / 0.04	4		(66)		
4		CH ₂ =CH ₂ (6 kg cm ⁻²)	2 / 12 / 0.04	2		100		
5			2 / 10 / 0.12	4		100		
6			2 / 10 / 0.12	33		96		
7			2 / 10 / 0.04	8		99		
8			2 / 2 / 0.04	6		100		
9			2 / 2 / 0.04	0.5		100		
10			2 / 2 / 0.04	0.5		100		
11			2 / 2 / 0.04	20		88		
12			2 / 2 / 0.04	4		100		
13			2 / 2 / 0.04	1		(90)		

The reactions were run in 3 ml of vigorously refluxing toluene (oil bath temperature 135 °C) as the solvent. For run 4, an autoclave was used. The yields of products were determined by gas chromatography and isolated yields are shown in parentheses. Structures of all products were established unequivocally by standard methods.

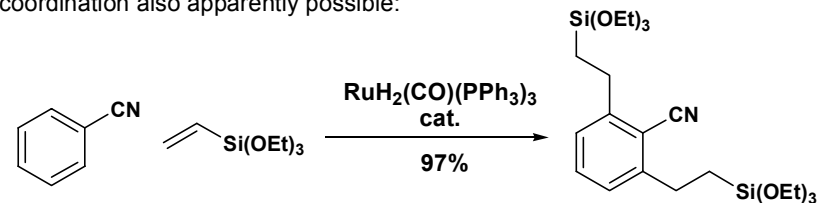
S. Murai, et al. *Nature* **1993**, 366, 529-531.



Other directing group substrates (note different catalysts):

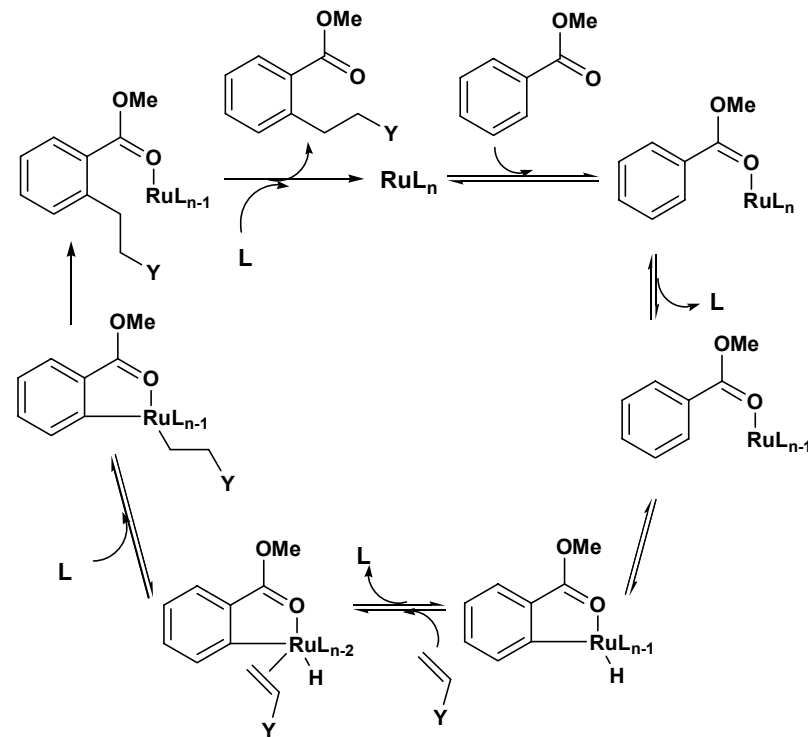


π -coordination also apparently possible:



F. Kakiuchi, N. Chatani. *Topics Organomet. Chem.* **2004**, 11, 45-79.

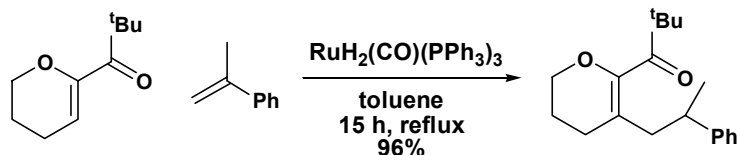
Mechanism still in some dispute, but kinetic isotope effect data suggest that C-H bond cleavage is **NOT** rate determining, but rather the C-C bond-forming step.



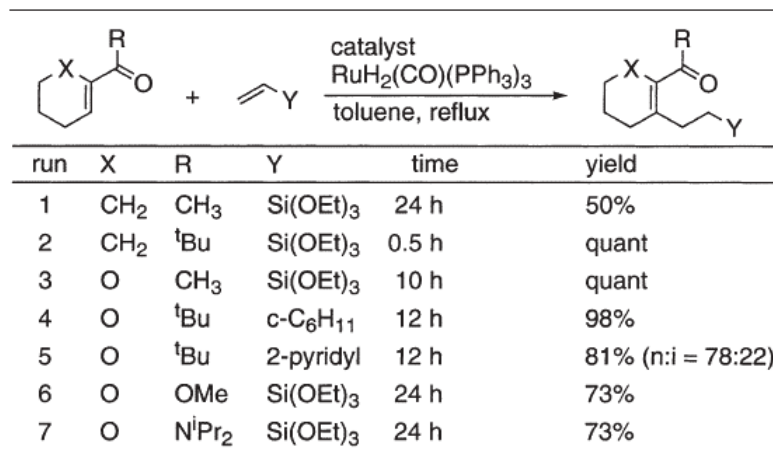
F. Kakiuchi, H. Ohtaki, M. Sonoda, N. Chatani, S. Murai. *Chem. Lett.* **2001**, 918.

Lesson #1: Chelation Control of C-H Bond Cleavage

C-H bonds not activated by electronic factors can still be selectively cleaved by catalysts placed next to the C-H bond by chelation with nearby heteroatom functional groups.

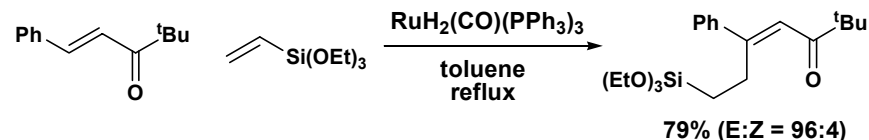
Related Substrate: α,β -Unsaturated Carbonyls

Reaction works with esters and amides, as well as non-dihydropyran systems:

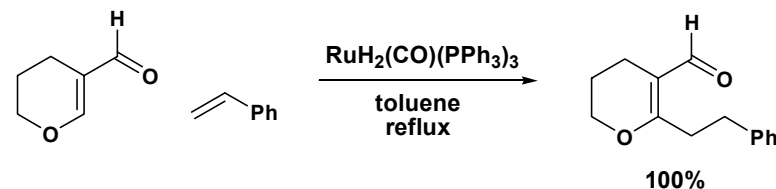


F. Kakiuchi, N. Chatani. *Topics Organomet. Chem.* **2004**, 11, 45-79.

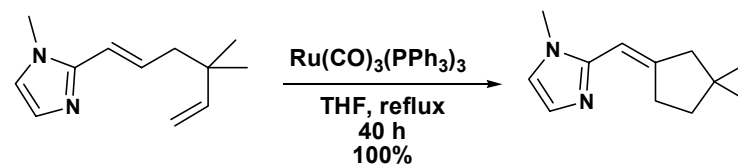
The reaction is also successful with acyclic systems:



Aldehydes are good substrates in limited cases, when a heteroatom is present γ to the carbonyl. Otherwise, the substrate undergoes decarbonylation.



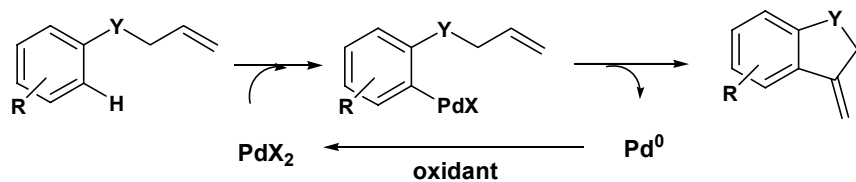
Intramolecular coupling also observed:



F. Kakiuchi, N. Chatani. *Topics Organomet. Chem.* **2004**, 11, 45-79.

Fujiwara-Moritani-Heck Oxidative Cyclization

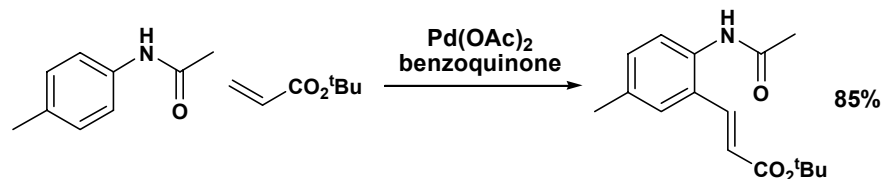
Heck cyclization reactions can occur without prefunctionalization of either the aryl or the olefin being coupled:



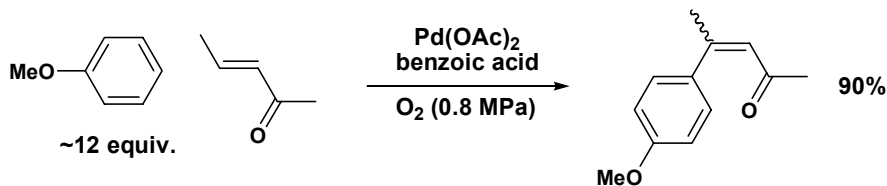
I. Moritani, Y. Fujiwara. *Tet. Lett.* **1967**, 1119.

Note how neither the olefin or arene has been preactivated.

Some examples:

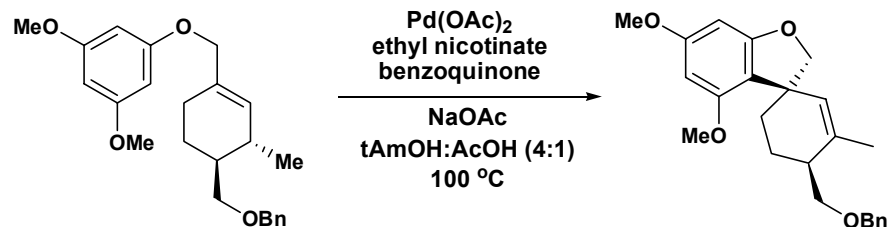


M.D.K. Boele, et al. *JACS* **2002**, 124, 1586.

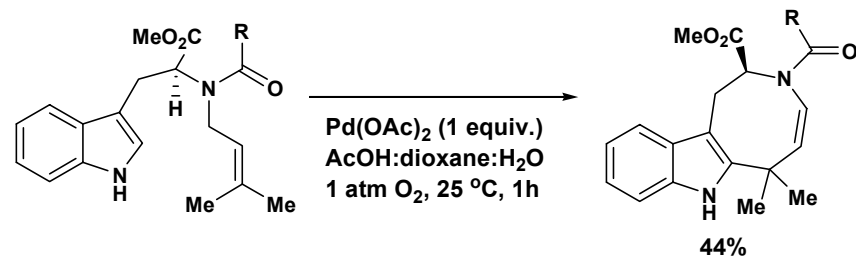


M. Dams, D.E. De Vos, S. Celen, P.A. Jacobs.
Angew. Chem. Int. Ed. **2003**, 42, 3512.

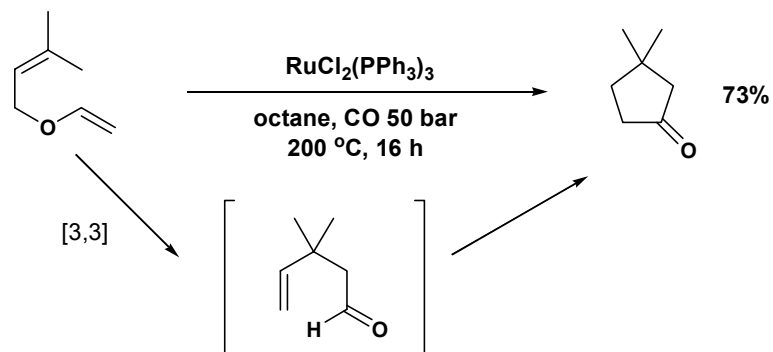
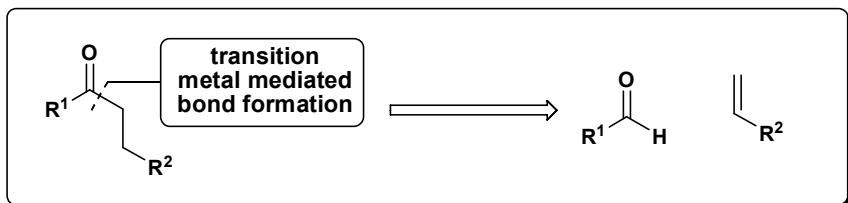
This method has been employed in more complex synthetic operations:



H. Zhang, E.M. Ferreira, and B.M. Stoltz.
Angew. Chem. Int. Ed. **2004**, 43, 6144.

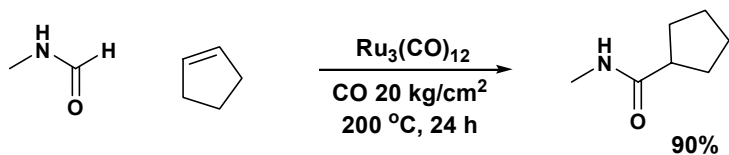
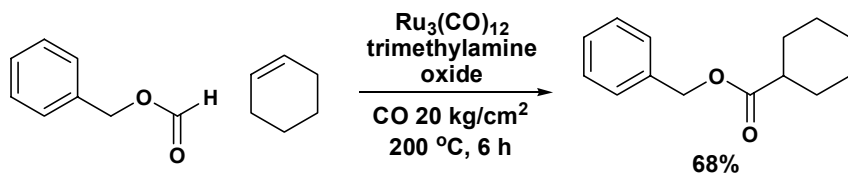


P.S. Baran, C.A. Guerrero, E.J. Corey. *JACS* **2003**, 125, 5628.
P.S. Baran, E.J. Corey. *JACS* **2002**, 124, 7904.

Hydroacylation: The Basic Retrosynthetic Disconnection

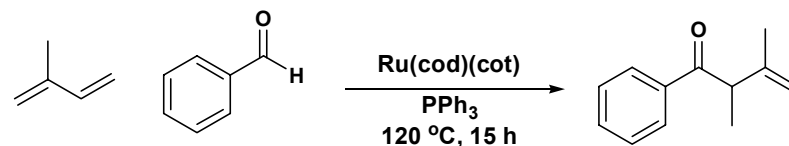
CO atmosphere necessary to suppress decarbonylation of the aldehyde.

The reaction also works on formyl esters and amides:

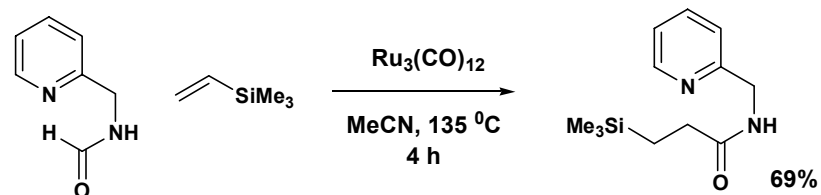
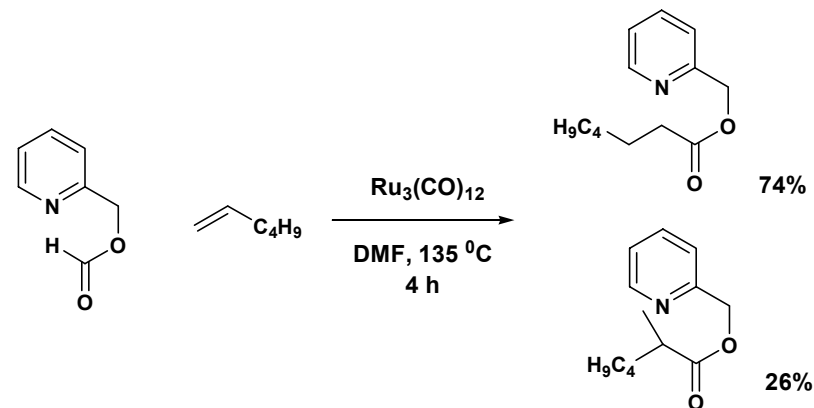


F. Kakiuchi, N. Chatani. *Topics Organomet. Chem.* **2004**, 11, 45-79.

Some hydroformylations can proceed without a CO atmosphere:

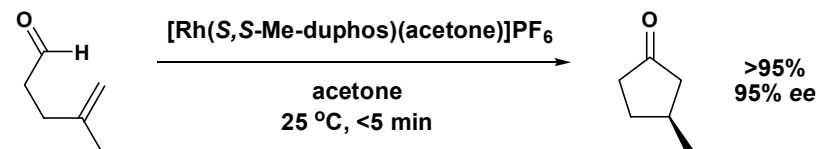


Another productive strategy involves chelation control:



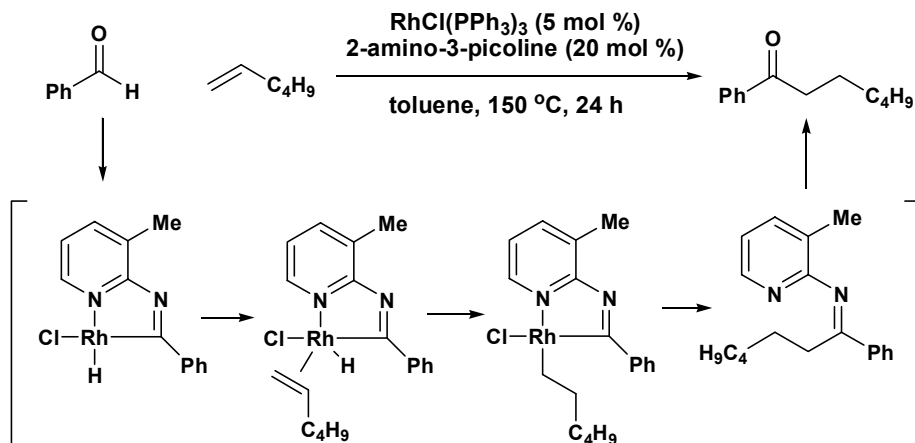
F. Kakiuchi, N. Chatani. *Topics Organomet. Chem.* **2004**, 11, 45-79.

It is possible to run this reaction asymmetrically with a chiral catalyst:



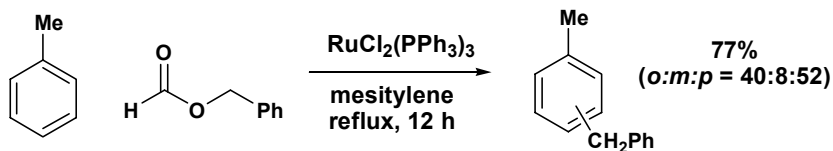
G. Dyker. *Angew. Chem. Int. Ed.* **1999**, 38, 1698.

Another strategy for avoiding decarbonylation involves going through an imine intermediate:



C.-H. Jun, J.H. Lee. *Pure Appl. Chem.* **2004**, *76*, 577.

One can also exploit the decarbonylation to one's advantage, albeit with poor site selectivity:



F. Kakiuchi, N. Chatani. *Topics Organomet. Chem.* **2004**, *11*, 45-79.

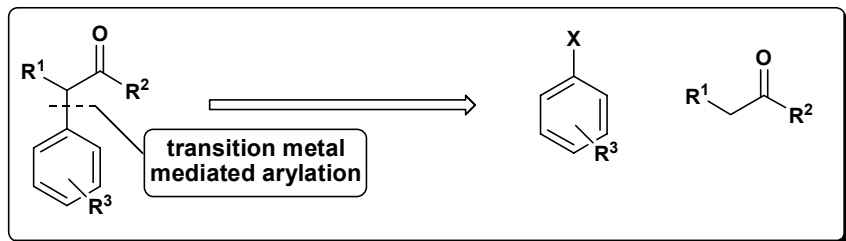
Lesson #2: The Aldehyde C-H Bond Is Readily Cleaved by Transition Metal Catalysts. This should lead one to at least one radically new transformation - the synthesis of ketones from aldehydes, a method which does not require changing the oxidation state of the carbonyl carbon. This should also encourage one to consider new possibilities for employing aldehydes in synthesis.

General Procedure of Ruthenium-Catalyzed Hydroesterification of Alkenes with Formates:

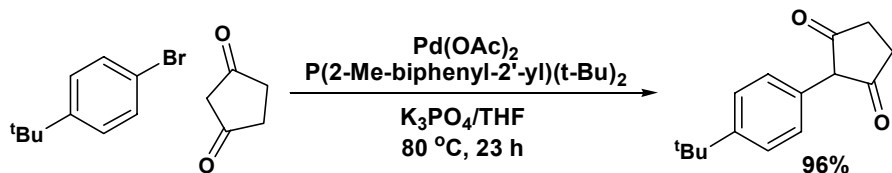
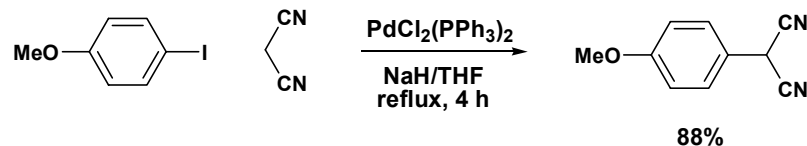
To a solution of 2-pyridylmethyl formate (54.8 mg, 0.4 mmol) in DMF (0.2 ml) was added 3,3-dimethyl-1-butene (101.0 mg, 1.2 mmol) followed by $\text{Ru}_3\text{CO}_{12}$ (12.8 mg, 5 mol %). The reaction mixture was stirred at $135\text{ }^\circ\text{C}$ for 3 h in a screw-capped vial. After removal of the solvent under the reduced pressure, the residue was purified by flash column chromatography on silica gel (15% EtOAc/hexane) to afford the (2-pyridylmethyl)-4,4-dimethyl pentanoate (Table 2, entry 3) as yellowish liquid: $^1\text{H NMR}$ (CDCl_3 , 250 MHz) δ 8.50 (d, 1H, $J = 4.4$ Hz), 7.61 (td, 1H, $J = 7.7, 1.4$ Hz), 7.26 (d, 1H, $J = 7.7$ Hz), 7.13 (m, 1H), 5.14 (s, 2H), 2.30 (m, 2H), 1.52 (m, 2H), 0.81 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 62.5 MHz) δ 174.4, 156.2, 149.8, 137.1, 123.2, 122.2, 67.1, 38.8, 30.4, 30.3, 29.4; IR (neat) 2959, 2870, 1741, 1595, 1475, 1145, 759 cm^{-1} ; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2$ 221.1417 (M^+), found 221.1413.

S. Ko, Y. Na, S. Chang. *JACS* **2002**, *125*, 750.

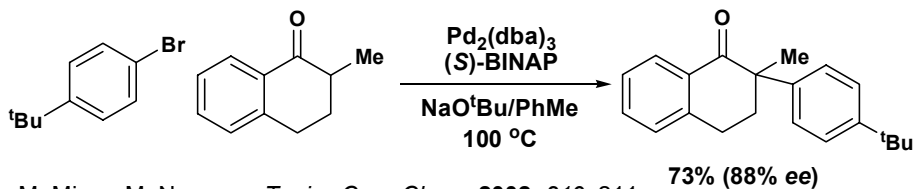
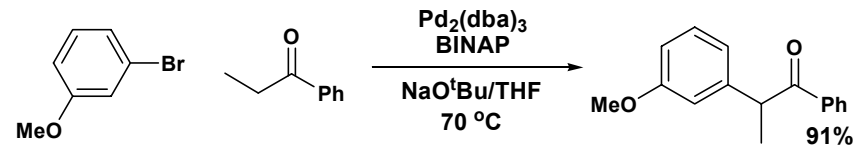
The Essential Retrosynthetic Disconnection:



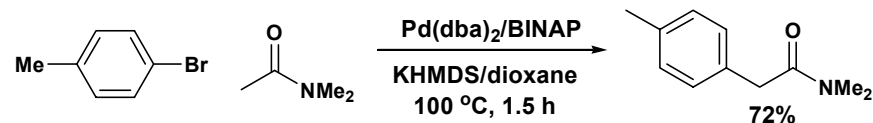
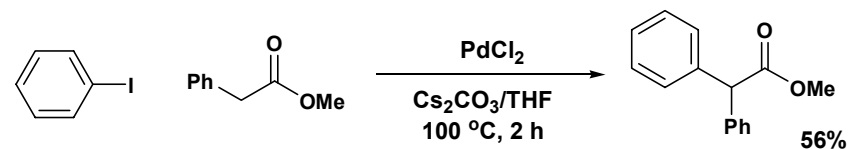
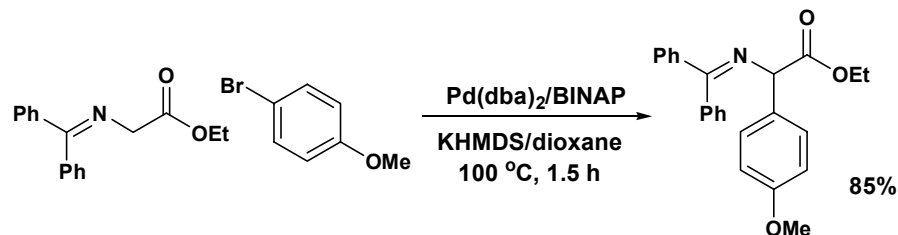
1,3-dicarbonyl substrates:



Buchwald, Miura and Hartwig groups have reported many successful examples of coupling with simple carbonyl compounds:

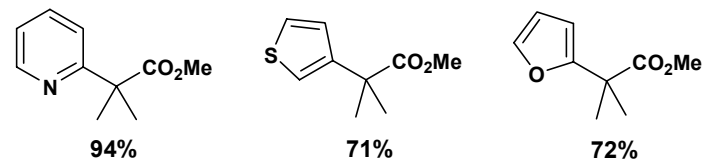
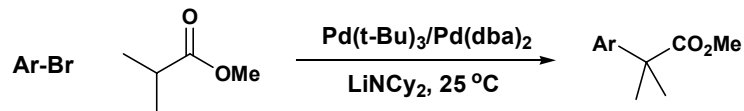
M. Miura, M. Nomura. *Topics Curr. Chem.* 2002, 219, 211.

Esters, amides and amino acids:

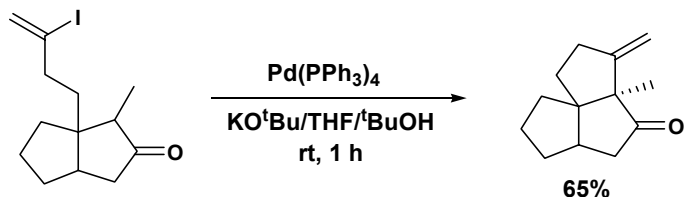
M. Miura, M. Nomura. *Topics Curr. Chem.* 2002, 219, 211.D.A. Culkin, J.F. Hartwig. *Acc. Chem. Res.* 2003, 36, 234.

A wide range of functional groups is tolerated about the aryl ring in the case of the amino acid substrate.

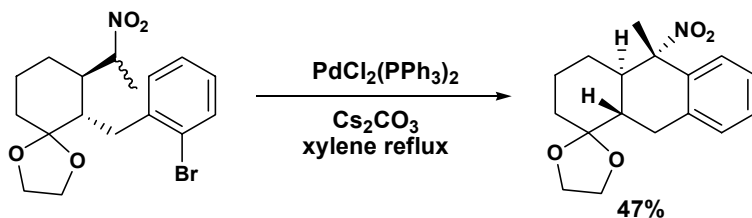
The reaction also works on a variety of heterocycles:

D.A. Culkin, J.F. Hartwig. *Acc. Chem. Res.* 2003, 36, 234.

This can work intramolecularly with vinyl iodides:

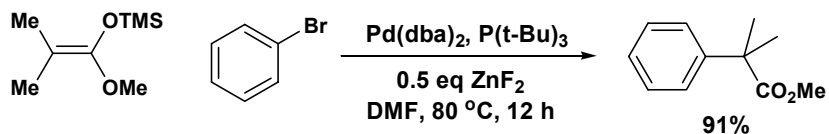


Nitro groups too:

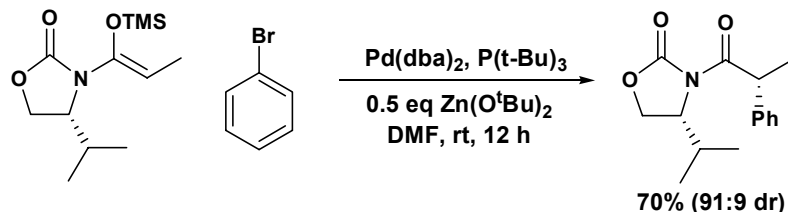


M. Miura, M. Nomura. *Topics Curr. Chem.* **2002**, 219, 211.

Hartwig has recently disclosed a modified procedure involving silyl enol ethers:

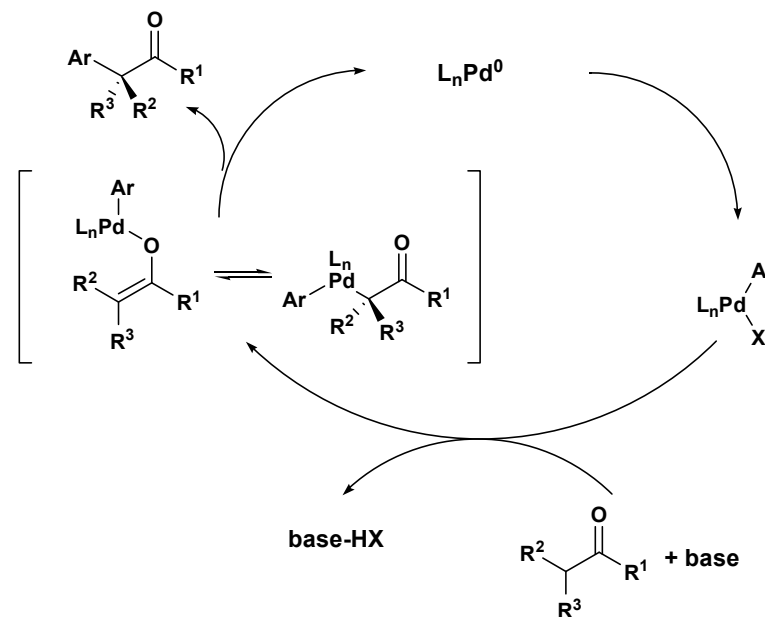


The reaction tolerates a wide range of aryl and ester substituents. It also works well with the Evans auxiliary:



X. Liu, J.F. Hartwig. *JACS* **2004**, 126, 5182.

A plausible mechanism for this reaction:



D.A. Culkin, J.F. Hartwig. *Acc. Chem. Res.* **2003**, 36, 234.

Typical experimental procedure for aryl-enolate coupling:

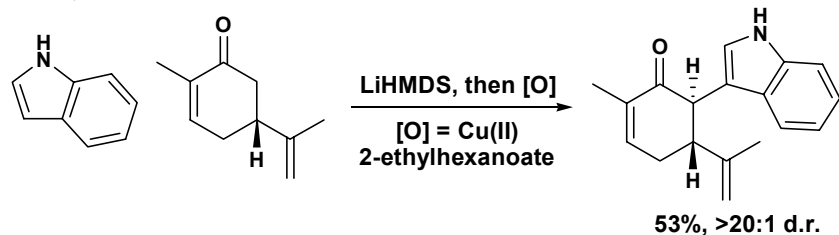
A typical procedure for Eq. (4) [15] is as follows. An oven-dried, resealable Schlenk tube containing a stirbar is capped with a rubber septum, evacuated, and cooled under argon. The tube is then charged with $\text{Pd}(\text{OAc})_2$ (2.3 mg, 0.01 mmol), the ligand (6.9 mg, 0.022 mmol), the 1,3-diketone (1.2 mmol), and K_3PO_4 (490 mg, 2.3 mmol). The septum is replaced, and the tube is again evacuated and backfilled with argon. Solvent (3 ml) and the aryl bromide (1.0 mmol) are sequentially injected, and the septum is replaced with a Teflon screw cap under a flow of argon. The tube was sealed, and the mixture is stirred and heated for the time specified. The mixture is then diluted with MeOH and filtered. The filtrate is concentrated and chromatographed.

from M. Miura, M. Nomura. *Topics Curr. Chem.* **2002**, 219, 211.

Oxidative Coupling of Heterocycles to Enolates

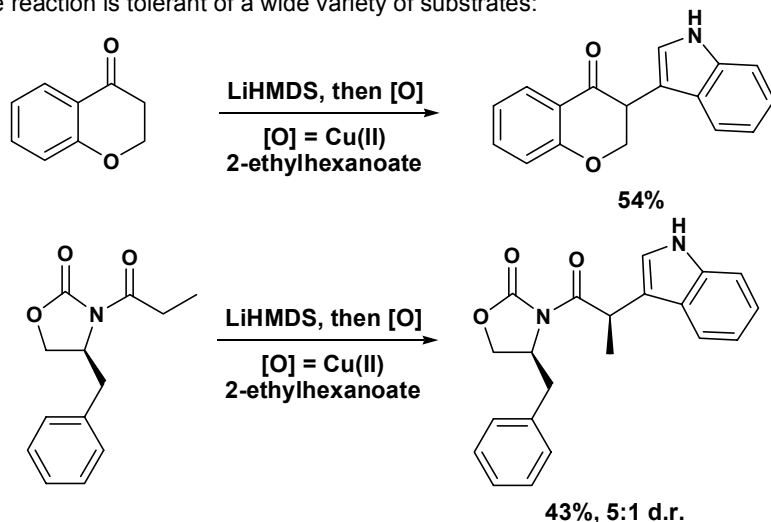
The oxidative coupling of enolates to form 1,4-diketones is known in the literature, but sporadically employed (see the 1995 Evans group seminar on oxidative coupling of enolates by Chuck Scales for further review).

Baran and colleagues have adapted this method for the direct coupling of heterocycles to enolates:



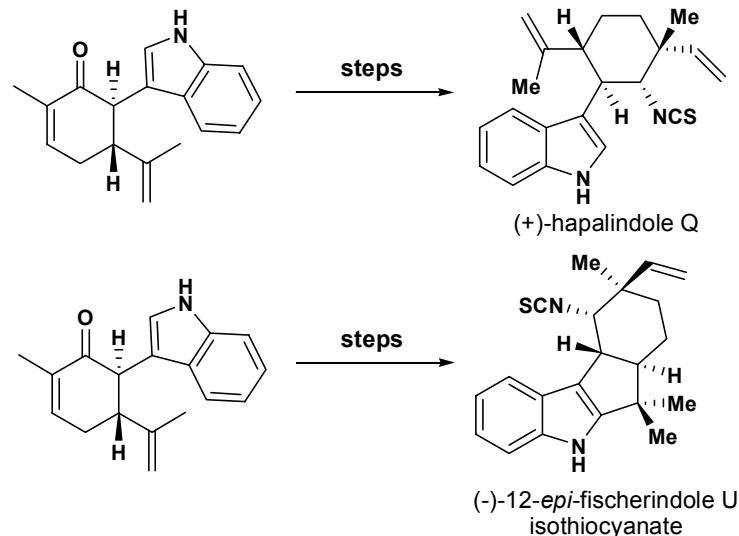
The reaction does not require prefunctionalization of the heterocycle prior to coupling, a distinct advantage over transition-metal-mediated methods. Regioselectivity appears to be directed towards the site of greatest electronic density on the heterocyclic ring.

The reaction is tolerant of a wide variety of substrates:

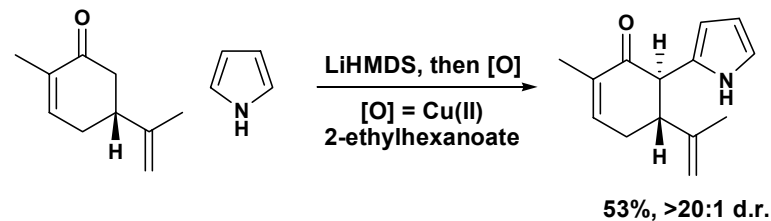


P.S. Baran, J.M. Richter. *JACS* 2004, 126, 7450.

This reaction has been applied in enantioselective total syntheses of hapalindole Q and 12-*epi*-fischerindole U isothiocyanate:



Oxidative coupling with pyrroles has also been observed:

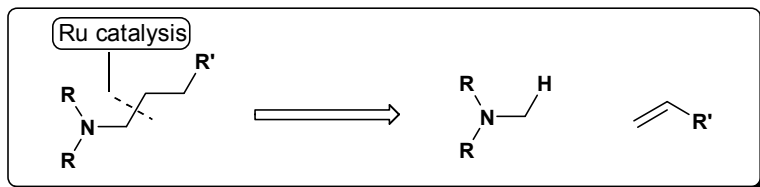


P.S. Baran, J.M. Richter, D.W. Lin. *Angew. Chem. Int. Ed.* 2004, in press.

Although it is generally accepted in the literature that enolate couplings go through radical intermediates, the high diastereoselectivity of the couplings observed with pyrrole and indole suggest that a Cu(II)-mediated mechanistic pathway may be involved.

The previous slides present relatively well-established methodologies for the formation of sp^3 - sp^2 bonds. Now we venture off the edge of the map into uncharted waters. Warning - here be dragons...

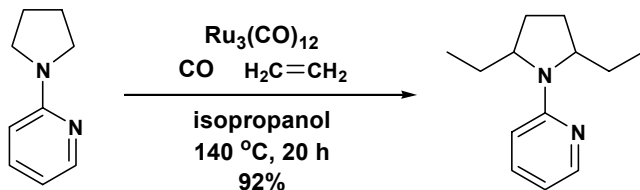
α -C-Alkylation of Amines: The Basic Retrosynthetic Disconnection



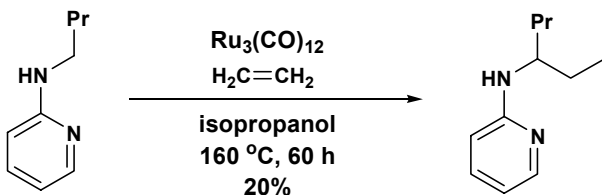
OK, this is cheating a little bit - formation of an sp^3 - sp^3 center. But it's similar to previous methodology, and illustrates another important lesson:

Lesson # 3: Electronic Activation of sp^3 Bonds by Adjacent Heteroatoms.

The presence of an adjacent heteroatom with lone pairs can activate an sp^3 C-H bond for cleavage by transition metal catalysts.



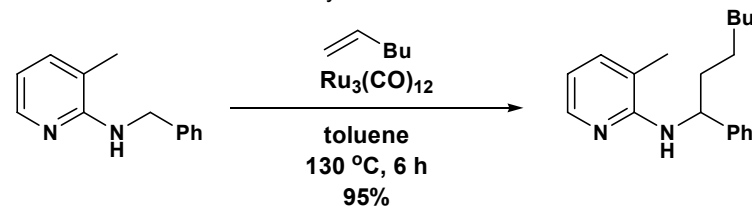
This reaction works well with cyclic amines, less so with acyclic ones:



N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai. *JACS* **2001**, *123*, 10935.

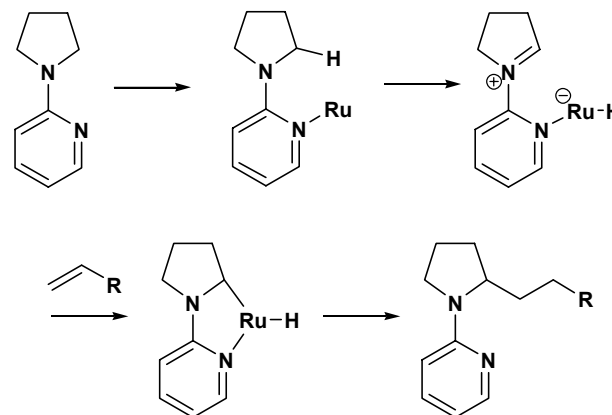
The presence of the pyridine ring is essential - acylamines and acylimines do not work as well.

The reaction also works with benzylic amines:



C.-H. Jun, D.-C. Hwang, S.-J. Na. *J. Chem. Soc., Chem. Comm.* **1998**, 1405.

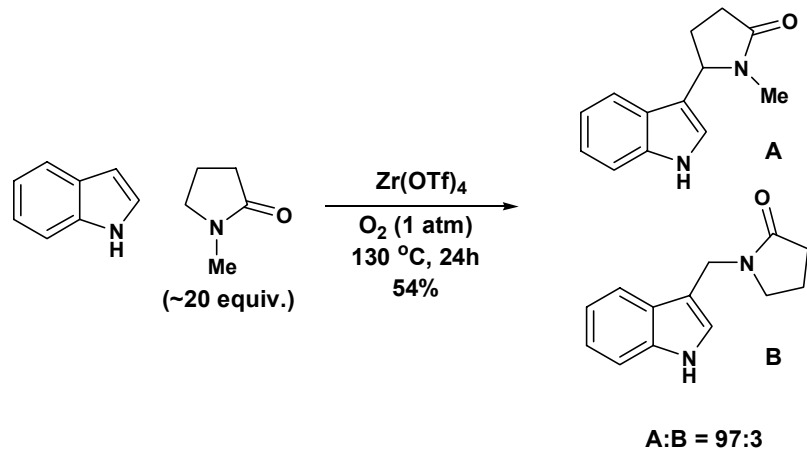
Murai and colleagues have proposed a plausible mechanism for this reaction, involving an acylimine intermediate:



N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai. *JACS* **2001**, *123*, 10935.

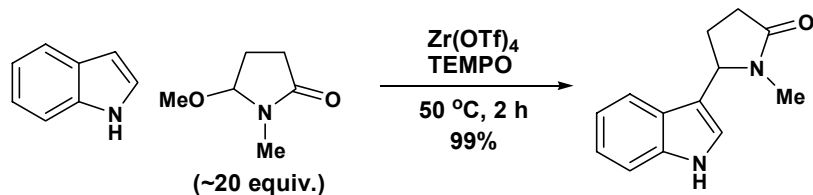
The presence of the acylimine intermediate is somewhat counterintuitive. However, other recently-reported reactions suggest that this is a plausible pathway (*vide infra*).

Tsuchimoto and colleagues have recently reported a method for the direct coupling of heterocycles to amines:



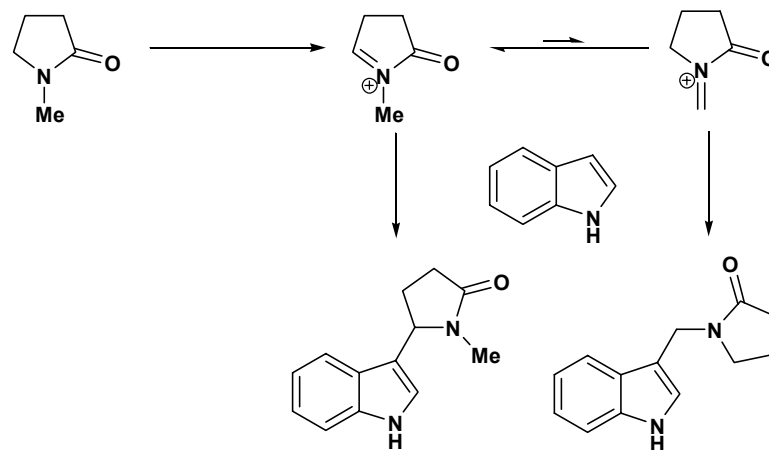
The reaction also works with thiophenes, pyrroles, and oxazolidinones, although yields generally range from 14% to 28%.

Interestingly, Tsuchimoto and colleagues also invoke an acyliminium intermediate, based on the following result:



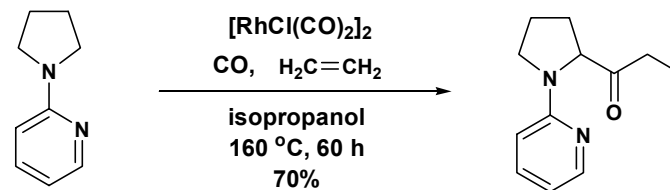
T. Tsuchimoto, T. Ozawa, R. Negoro, E. Shirakawa, T. Kawakami. *Angew. Chem. Int. Ed.* **2004**, 43, 4231.

This immediately lends credence to the idea that amines activate adjacent C-H bonds electronically for removal by oxidizing agents:



T. Tsuchimoto, T. Ozawa, R. Negoro, E. Shirakawa, T. Kawakami. *Angew. Chem. Int. Ed.* **2004**, 43, 4231.

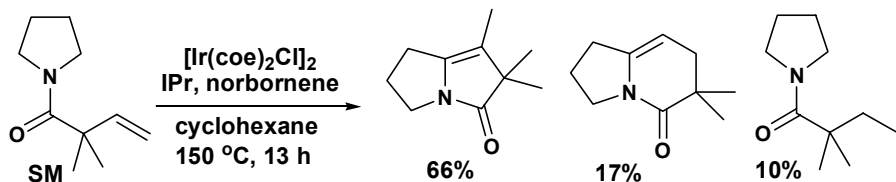
A related transformation: three-component α -C-carbonylation of amines:



N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishiii, F. Kakiuchi, S. Murai. *JACS* **2000**, 122, 12882.

The proposed mechanism is similar to that for the α -C-alkylation reaction, with an additional carbonylation step.

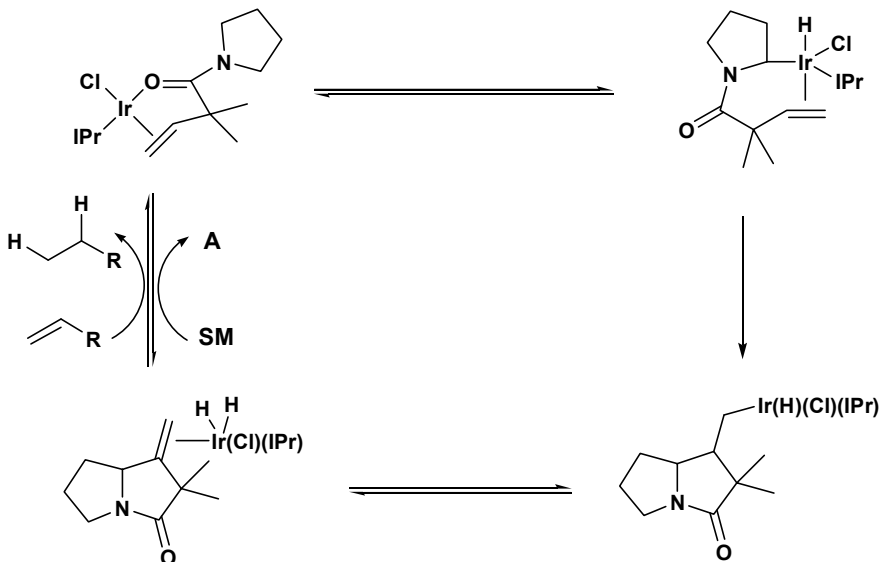
Dalibor Sames and colleagues have recently disclosed a method for intramolecular cyclization of an amide onto an olefin at the α -C position next to the nitrogen.



IPr = N,N'-bis(2,6-diisopropylphenyl)-imidazolyl carbene

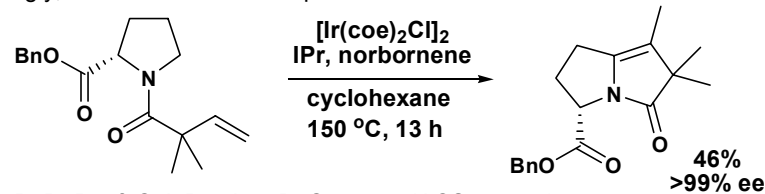
The norbornene additive is present to suppress formation of the reduced side product C.

The following mechanism has been proposed. It should be observed that the critical step in this cycle is the fact that alkene insertion (and thus C-C bond formation) is favored over β -hydride elimination (which would simply regenerate the alkene).



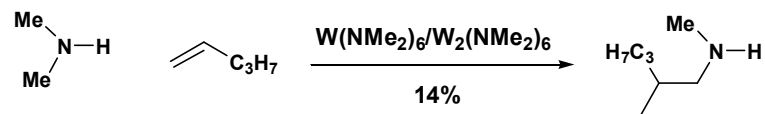
B. DeBoef, S.J. Pastine, D. Sames. *JACS* **2004**, 126, 6556.

Amazingly, the reaction works on proline derivatives!



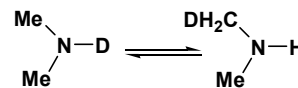
B. DeBoef, S.J. Pastine, D. Sames. *JACS* **2004**, 126, 6556.

A final remarkable example involving dimethylamine is over 20 years old!



This observation is accompanied by the observation that a number of similar metal amide complexes catalyze hydrogen-deuterium exchange on the methyl groups of dimethylamine, suggesting that insertion into the C-H bond is quite facile:

catalyst	% H-D exchange ^c	insertn (turnovers) ^d
Ti(NMe ₂) ₄	0 ^e	0.0
Zr(NMe ₂) ₄	37	0.0
Hf(NMe ₂) ₄	0 ^e	
Nb(NMe ₂) ₅	67	4.5
Ta(NMe ₂) ₅	26	0.3
W(NMe ₂) ₆	57	7.0
Sn(NMe ₂) ₄	0 ^e	0.0



^a All runs in evacuated sealed tubes 14 h at 160 °C.
^b Catalyst was 2:1 adduct of W₂(NMe₂)₆/W(NMe₂)₆ prepared by method of Chisholm.¹⁷ ^c Percent decrease in 1243-cm⁻¹ band. All runs contained 0.25 mmol of catalyst and 12.5 mmol of Me₂ND in 5 mL of decalin.
^d Yield of hexylmethylamines in mol/mol of catalyst. All runs contained 0.25 mmol of catalyst, 12.5 mmol of 1-pentene, and 12.5 mmol of dimethylamine in 5 mL of decalin. ^e None detected under conditions where as little as 3% exchange could be observed.

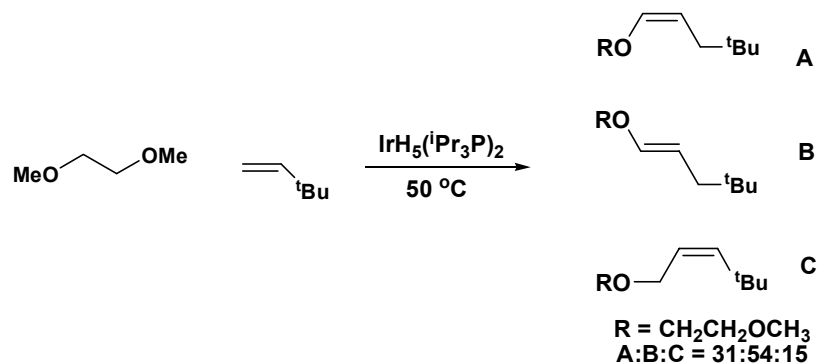
W.A. Nugent, D.W. Overall, S.J. Holmes. *Organometallics* **1983**, 2, 161.

This observation suggests the following important lesson:

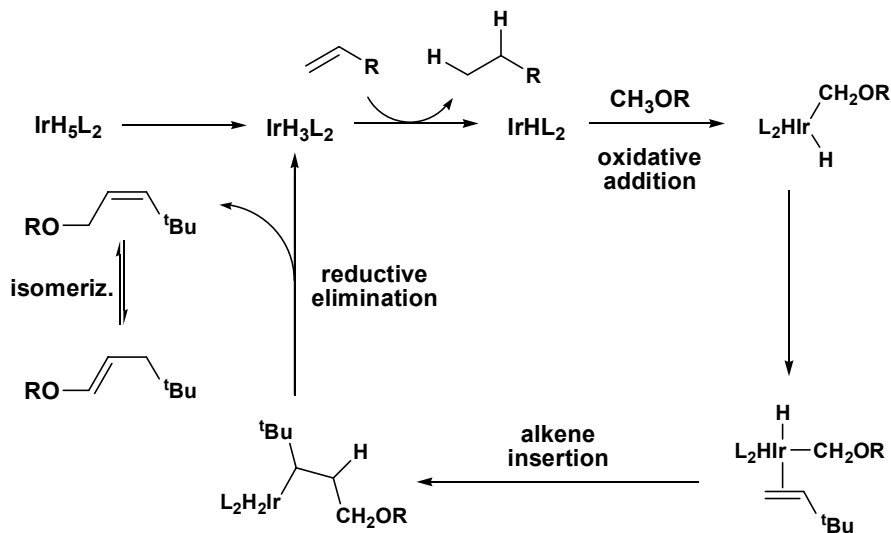
Lesson # 4: Cleavage of C-H Bonds, even sp^3 Bonds, is Easy.

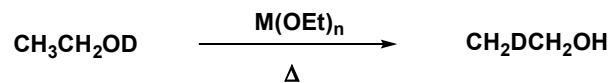
Transition metal catalysts clearly can insert easily into C-H bonds. The real challenge is to trap the resulting C-M bond in a productive fashion, i.e. formation of a C-C bond.

Activation of C-H Bonds α and β to Oxygen

 Some papers also suggest that C-H bonds α and β oxygen are primed for cleavage.


The authors suggest the following mechanism:

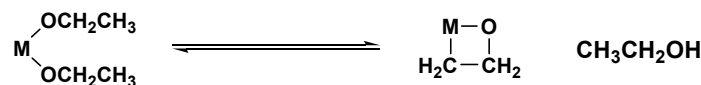

 Y. Lin, D. Ma, X. Lu. *Tet. Lett.* **1987**, 28, 3249.

 Nugent and colleagues have also reported an isotope scrambling catalyzed by metal alkoxides on ethanol. Deuterium exchange is observed exclusively at the β carbon:


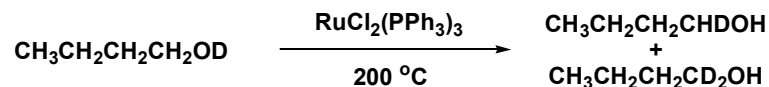
catalyst	temp, °C	% H-D exchange ^c	distributn of ² H label, ^b %		
			CH ₂ D	CD ₂ H	CD ₃
Ti(OEt) ₄	180	0 ^e			
Zr(OEt) ₄	200	14	5	25	70
Nb ₂ (OEt) ₁₀	200	18	27	41	32
Ta ₂ (OEt) ₁₀	180	9			
Ta ₂ (OEt) ₁₀	200	23	28	39	33
Ta ₂ (OEt) ₁₀	220	47			
Ta ₂ (OEt) ₁₀ + C ₂ H ₅ N ^d	200	55	38	39	23
Ta ₂ (OEt) ₁₀ + Et ₃ N ^d	200	50			
W(OEt) ₆	200	0 ^{e,f}			

^a All runs involved 0.5 mmol of catalyst in 50 mmol of ethanol-*d* for 14 h in evacuated glass tubes. ^b Relative areas of *d*¹, *d*², *d*³ resonances (at δ 0.98, 0.96, and 0.94, respectively) in the 61.4-MHz ¹H-decoupled ²H NMR. ^c Percent of starting OD incorporated into methyl group determined by area of OH resonance in 90-MHz ¹H NMR. ^d Run additionally contains 2.0 mmol of amine additive. ^e Catalyst decomposed to white insolubles; no exchange detected under conditions where 1% exchange could be observed. ^f Ethanol was disproportionated to diethyl ether and H₂O.

Nugent invokes the formation of an oxametallocyclobutane intermediate in this reaction:


 W.A. Nugent, D.W. Overall, S.J. Holmes. *Organometallics* **1983**, 2, 161.

As Nugent notes, the formation of multiply-deuterated products suggests that this process is facile and rapid.

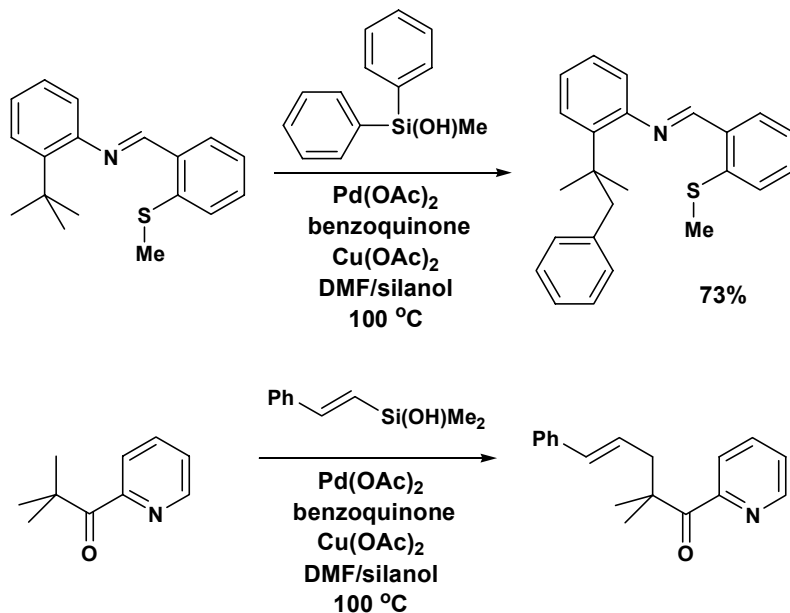
 Other transition metals can catalyze deuterium exchange at the α carbon of alcohols:

 Y. Sasson, J. Blum. *J. Chem. Soc., Chem. Comm.* **1974**, 309.
 S.L. Regen. *J. Org. Chem.* **1974**, 39, 260.

Even more intriguing than electronic activation of C-H bonds is insertion into totally unactivated C-H bonds. In these cases, the strategy of choice is the chelation strategy mentioned in Lesson # 1:

Lesson # 1 (Rephrased): Activation of C-H Bonds by Proximity

When faced with a totally unactivated C-H bond, even these can be cleaved by transition metal catalysts which are placed in proximity to the C-H by by intramolecular chelation effects.

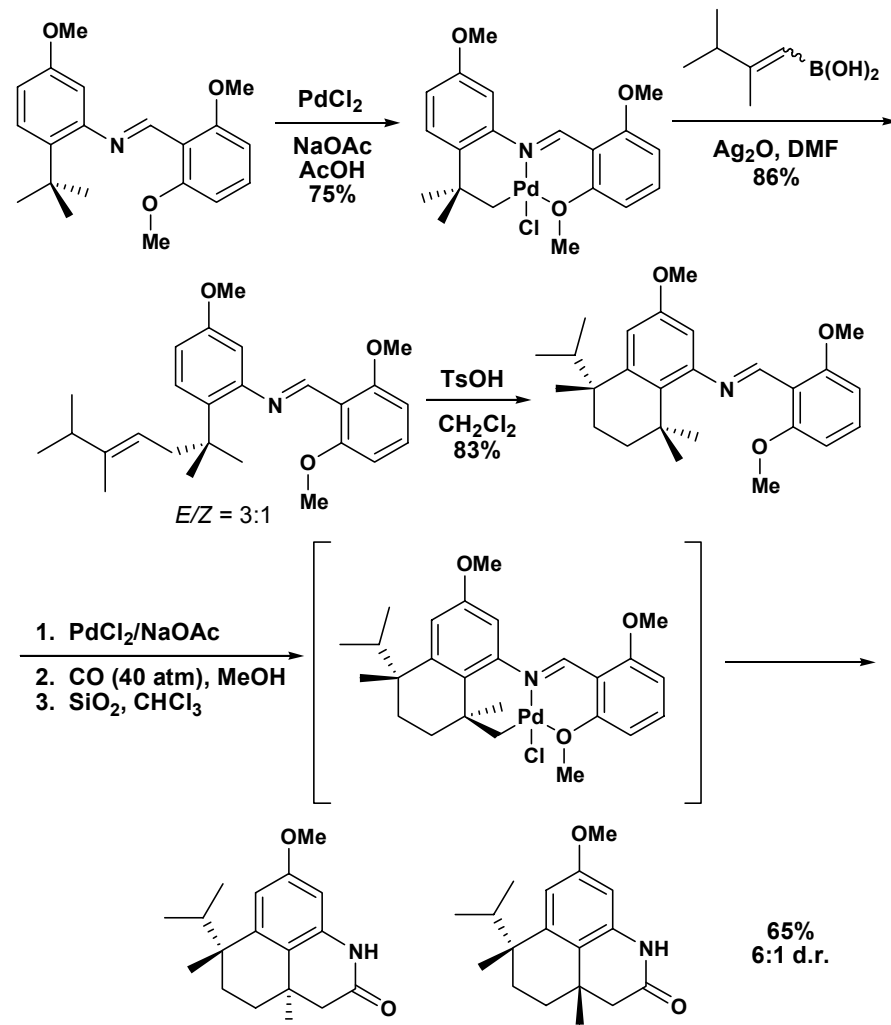
This strategy is employed elegantly by Dalibor Sames and colleagues, who have recently reported the insertion of an sp^2 center into an unactivated sp^3 C-H bond:



B. Sezen, R. Franz and D. Sames, *JACS* **2002**, *124*, 13372.

The critical feature of this reaction is the use of an sp^2 nitrogen to chelate the Pd catalyst and position it for the oxidative addition into the unactivated C-H bond. Particularly exciting is the use of an imine to guide the reaction - this suggests the potential utility of imines in chelation-control C-H bond cleavage.

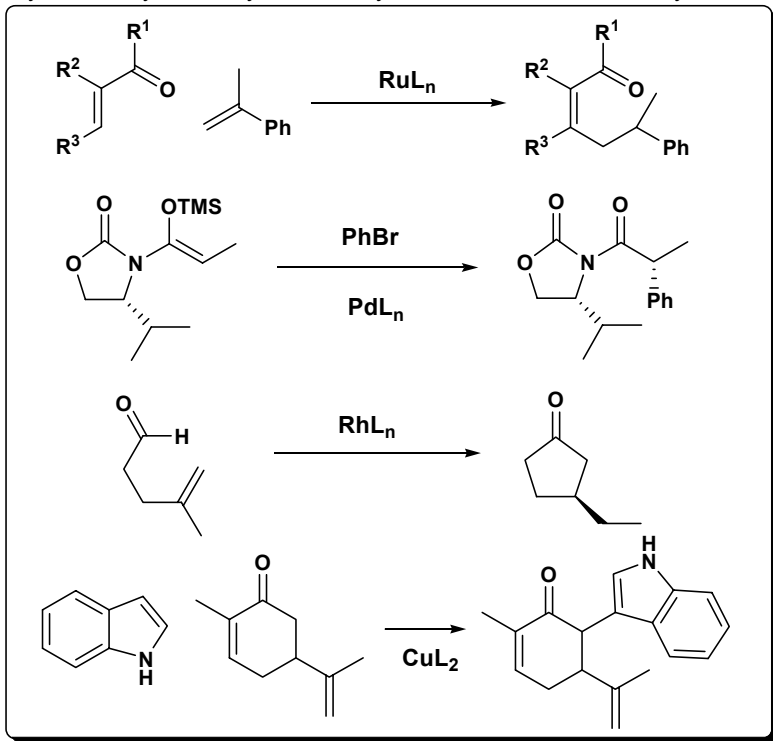
Sames and colleagues have successfully deployed this strategy in their studies towards the synthesis of teleocidin B-4:



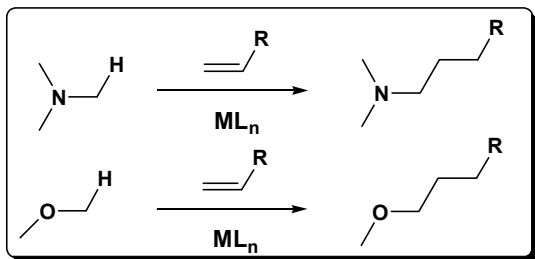
B.D. Dangel, K. Godula, S.W. Youn, B. Sezen, D. Sames. *JACS* **2002**, *124*, 11856.

Outlook

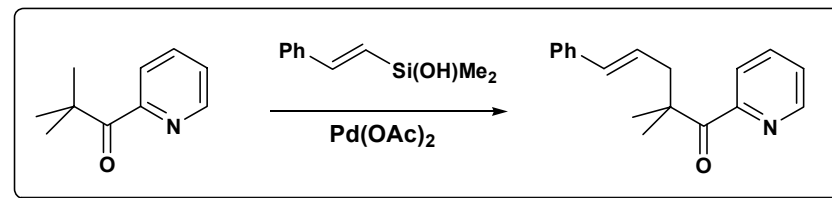
The diversity of new coupling reactions involving carbonyl compounds suggest that carbonyl chemistry has not yet been fully mined for unusual reactivity:



Further studies aimed at understanding the factors which govern activation of C-H bonds α to heteroatoms also offer great promise for revolutionary new transformations.

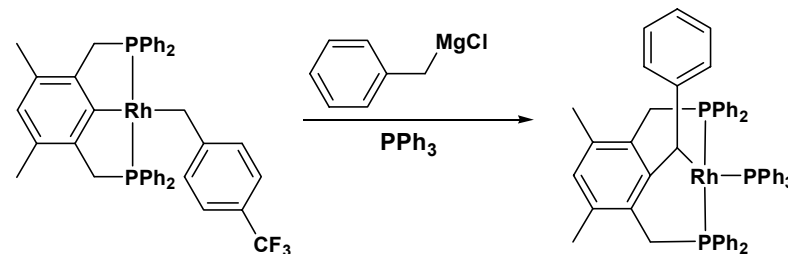


Chelation control to direct catalysts to otherwise unactivated C-H bonds represents a third exciting avenue of work:



A Final Note:

The organometallic literature is littered with examples of amazing bond cleavage and bond-forming reactions. The trouble is that most of these reactions occur in the context of forming stable organometallic complexes which are unable to turnover and produce product:



R. Cohen, M.E. van der Boom, L.J.W. Shimon, H. Rosenberg, D. Milstein, *JACS* **2000**, *122*, 7723.

So if you're looking for the reactions of tomorrow, a good place to look for their embryonic beginnings are in the organometallic journals of today...