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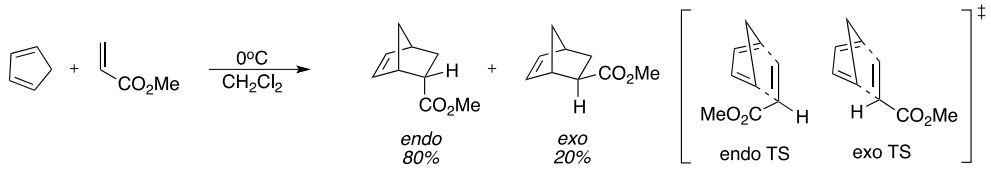
Topic: Selective Catalysis

1. Key Definitions

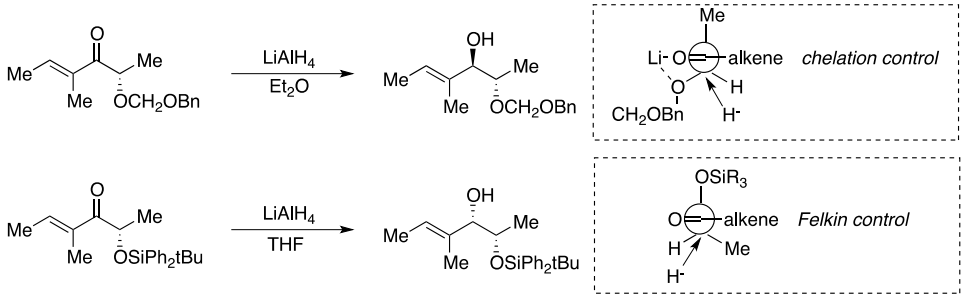
1.1. **Diastereoselectivity**: preferential formation of one *diastereomer* over another

1.1.1. Type A: simple diastereoselectivity – selectivity inherent to a reaction process



Sauer *ACIE* **1967**, *6*, 16

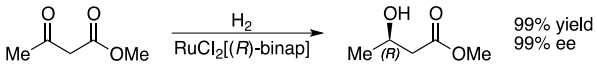
1.1.2. Type B: induced diastereoselectivity – selectivity promoted by existing stereocentres



Overman *Tet. Lett.* **1982**, *23*, 2355

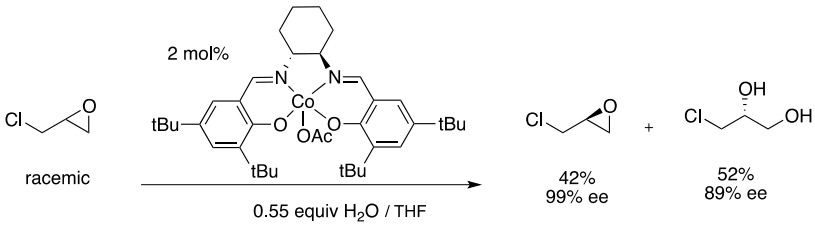
1.2. **Enantioselectivity**: preferential formation of one *enantiomer* over another

1.2.1. Type A: generation of a new chiral center



Noyori *JACS* **1987**, *109*, 5856

1.2.2. Type B: enantiodiscrimination – selective reaction of one enantiomer over another



Jacobsen *Science* **1997**, *277*, 936 & *JACS* **2002**, *124*, 1307

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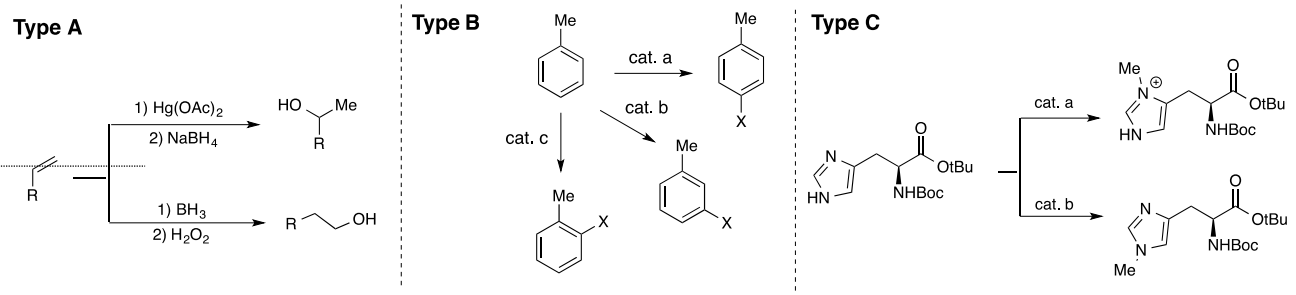
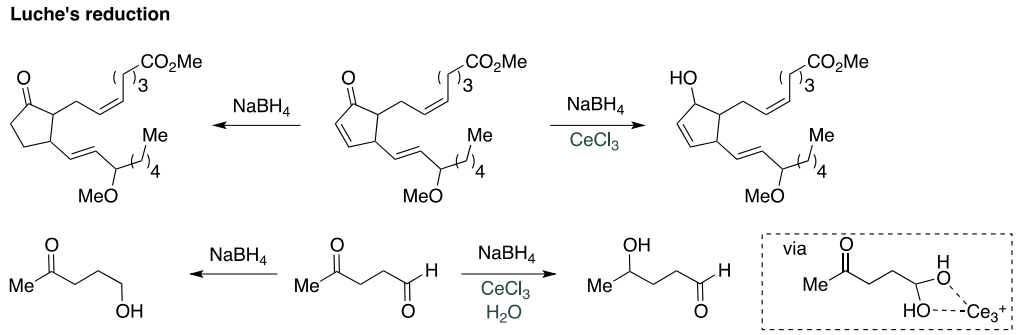
1.3. **Regioselectivity**: A regioselective reaction is one in which one position of bond formation or cleavage occurs preferentially over all other possible positions.



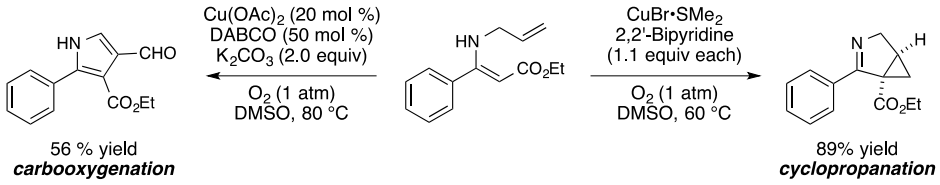
Trost *Science* **1983**, *219*, 245

1.4. **Chemoselectivity** is the preferential reaction of a chemical reagent with one functional group over others.



Yudin *ACIE* **2010**, *49*, 262

1.5. **Product-selectivity** is when two or more distinct products (which are not regio- or stereoisomers) can be preferentially produced from a common starting material. This area of research is currently gaining interest within the synthetic community.



Chiba *JACS* **2011**, *133*, 13942

2. Selective catalysis

2.1. Why selective catalysis?

- The object of selective catalysis is to streamline synthetic processes, reducing the need for protecting groups and thereby increasing the efficiency and speed of synthesis.
- Biological systems often show an amazing combination of stereo-, regio-, and chemoselectivity, providing motivation and inspiration for synthetic chemists.
- Chemists can predict selectivity by using metrics including redox potential, pKa, HSAB, and A (steric) values.

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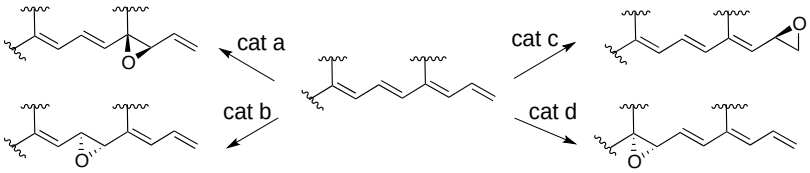
In the case shown below, for example, it would be ideal to have 4 distinct catalysts to perform both chemo- and enantioselective catalysis:



Sharpless *ACIE* **2002**, *41*, 2024

2.2. The underlying principle

The rationale and physical organic chemistry concepts behind asymmetric catalysis apply equally to catalytic divergent synthesis:

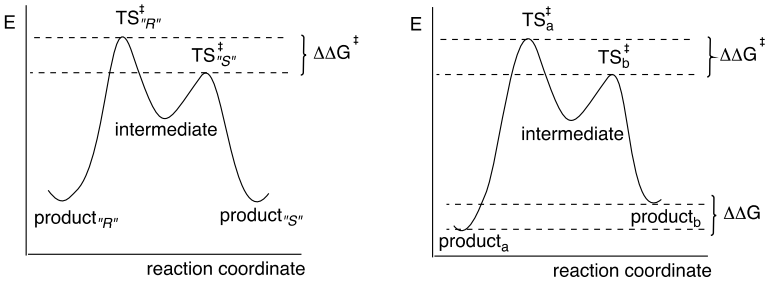


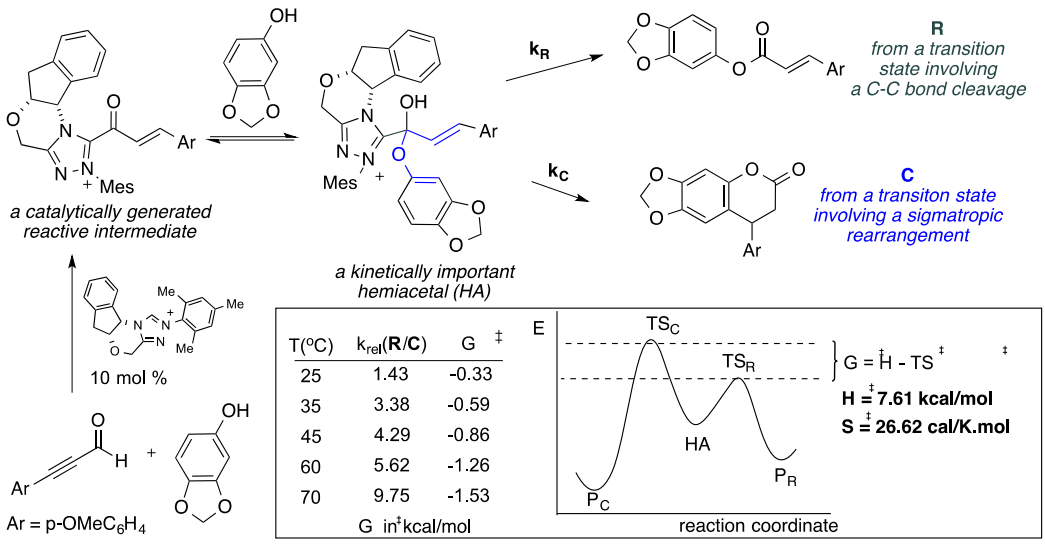
Fig. A) A generic energy diagram for an enantioselective reaction

Fig. B) A generic energy diagram for a catalytic diveregent synthesis

Bode *ACIE* **2012**, *51*, 10954

2.3. Energetic factors in the selectivity

Partition experiments can help to elucidate the energetic factors behind the competing pathways. This may allow for direct measurement of the relative energy of the two pathways by measuring the product ratio (***k_{rel}***) over a range of temperatures.



Bode *ACIE* **2011**, *50*, 1673

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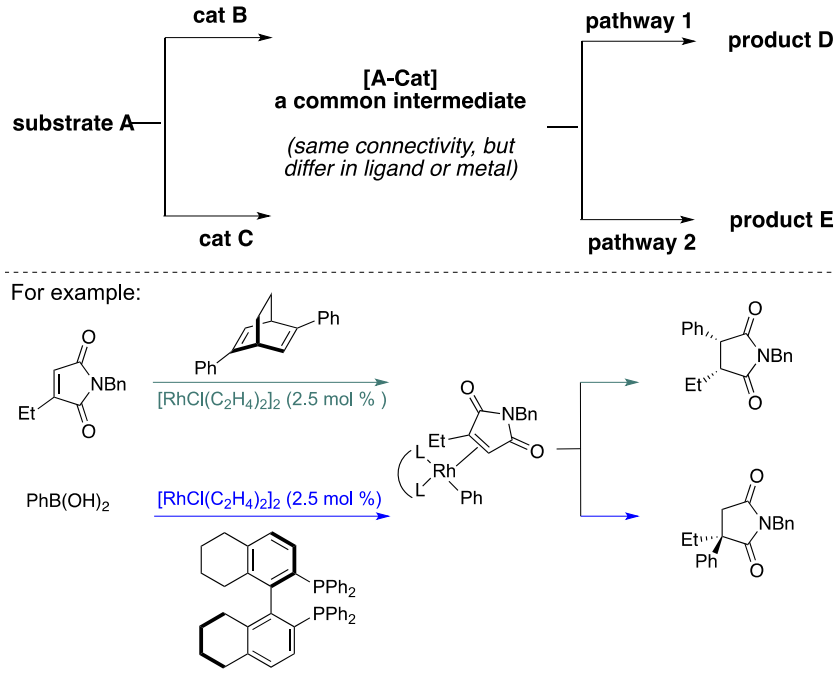
3. Classes of catalytic divergent synthesis

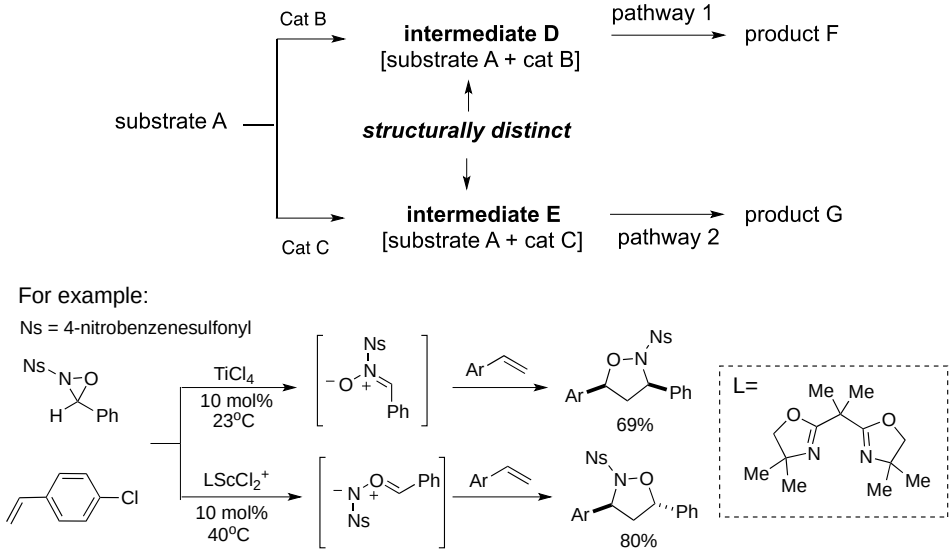
We propose two classes of catalytic divergent synthesis, which differ in their mechanistic nuances:

Class A: Divergence from a common reaction intermediate:



Hayashi *JACS* **2006**, *128*, 5628

Class B: Divergence arising from two available pathways with distinct catalyst-substrate complexes



Yoon *ACIE* **2010**, *49*, 930

4. Types of selectivity

- **Innate selectivity**: the selectivity comes from a substrate-controlled process.
- **Catalyst-controlled selectivity**: a catalyst, a ligand, or an additive induces the selectivity.

Innate selectivity can be viewed as similar to the traditional "background rate" in asymmetric catalysis. Catalytic divergent synthesis may involve overcoming this intrinsic barrier in favor of the desired pathway.

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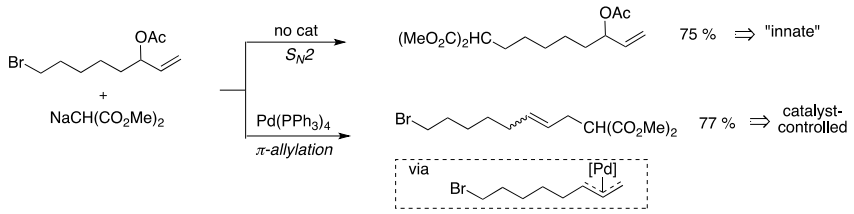
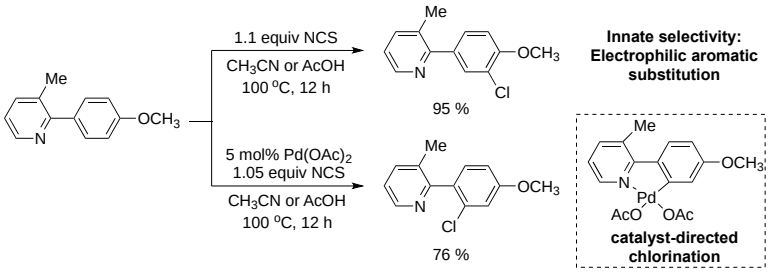


Trost *Science* **1983**, *219*, 245

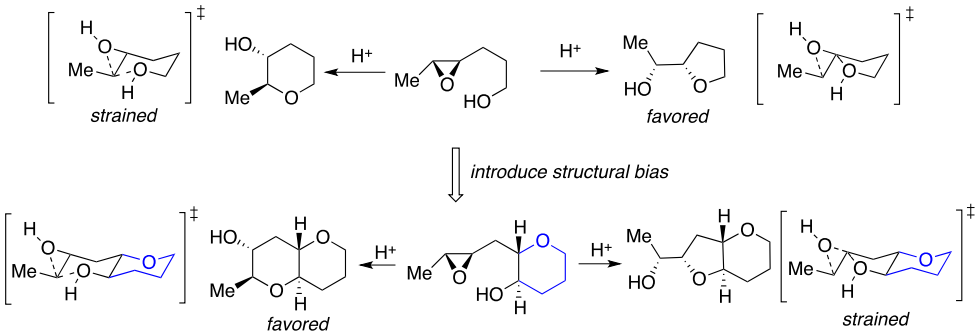


Sanford *Org. Lett.* **2006**, *8*, 2523

5. Methods to achieve selectivity (either regio-, chemo-, or product-selectivity)

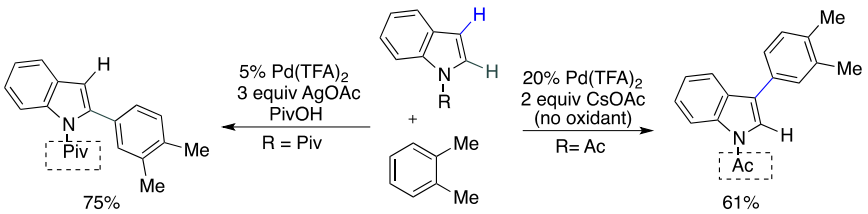
5.1. Substrate modification (***substrate-controlled selectivity***)

5.1.1. Circumvent the intrinsic preference of reaction pathway by altering the substrate



Jamison *Science* **2007**, *317*, 1189

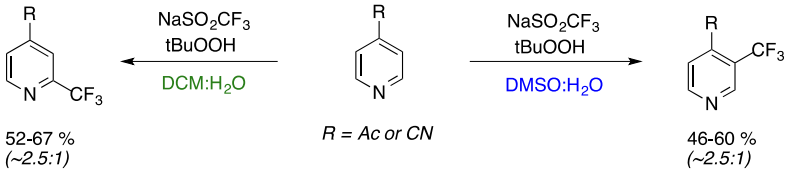
5.1.2. Introduction of a directing group



Fagnou *JACS* **2007**, *129*, 12072

5.2. Modification of the reaction conditions such as solvent, pH, temperature, etc.

5.2.1. Solvent effects



Baran *PNAS* **2011**, *108*, 14411

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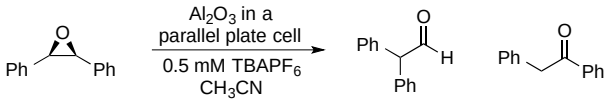
5.2.2. The use of excitation energy or electric field

The site selectivity of the rearrangement of *cis*-stilbene oxide, catalyzed by Al_2O_3 deposited on Si electrodes, can be controlled by a field-dipole effect. In this case, selectivity ($\Delta\Delta G^{\ddagger}$) is a function of electric field strength (E) and the difference in chemical potential ($\Delta\mu$).

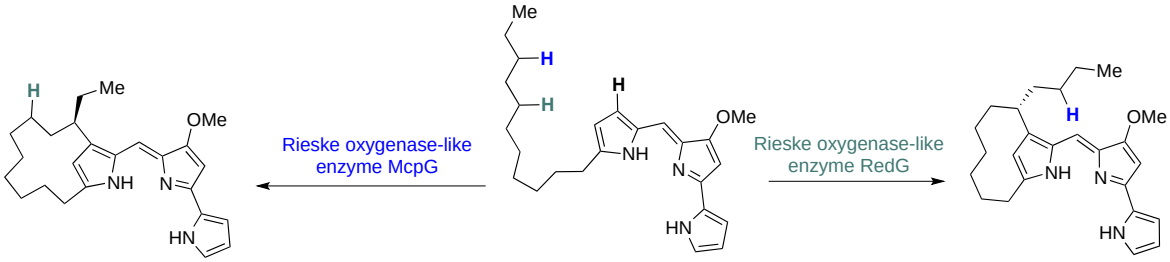


Without electric field:	1	4
With electric field:	17	1

Kanan *JACS* **2012**, *134*, 186

6. The use of enzyme catalysis (a type of catalyst-controlled selectivity)

Enzymatic processes can impart an exquisite level of site- and/or stereoselectivity.



Metacycloprodigiosin undecylprodigiosin Streptorubin

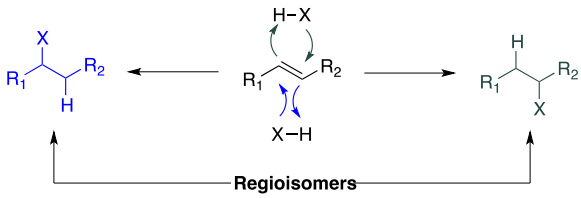
Challis *Nature Chem* **2011**, *3*, 388

7. Regioselective Catalysis

7.1. Definitions and Key Principles

Regioisomer: The positional isomers formed from different locations of bond formation/cleavage.

Note: The term "*regiospecific*" to refer to a reaction that is 100% regioselective is discouraged, and has no correlation to the difference between "stereoselective" and "stereospecific"



IUPAC Gold Book (http://goldbook.iupac.org/)

Regioselectivity control in reactions of non-aromatic pi-systems depends on electronic and steric factors - charged intermediates and polarized transition states dictate the relative position of nucleophile and electrophile.

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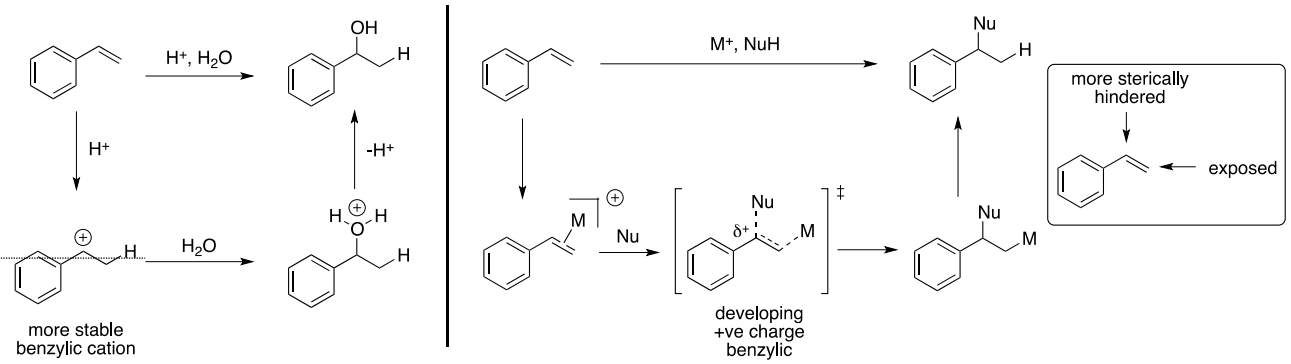
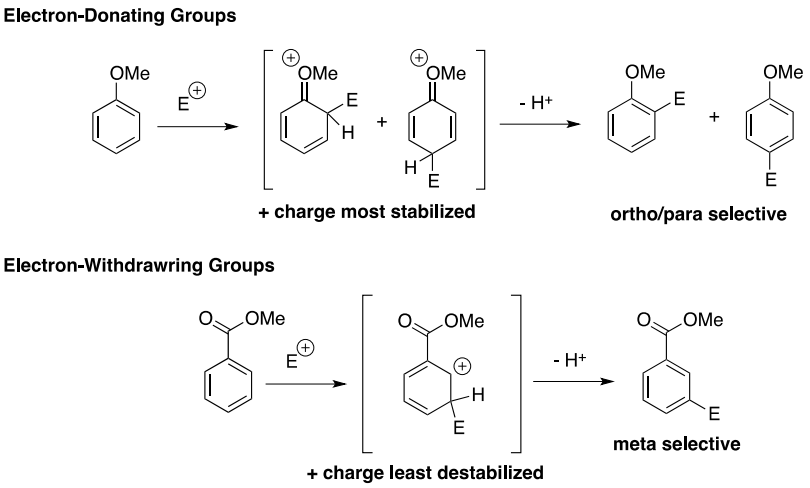


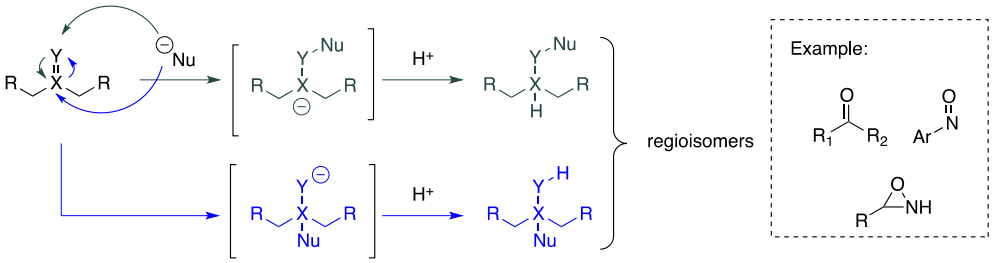
Clayden, et al. Organic Chemistry, Oxford Uni. Press. 2011

The regioselectivity of aromatic substitution reactions is heavily influenced by the electron distribution of the conjugated pi-system. This is perfectly demonstated by the regioselectivity of the Friedel-Crafts reaction:



Clayden, et al. Organic Chemistry, Oxford Uni. Press. 2011

It is worth mentioning that issues of regioselectivity are not often encountered in reactions of strongly dipolar functional groups. For example, the hypothetical green carbonyl attack shown below would lead to a regioisomeric product, but this product is not formed due to the inversion of polarity this would require.



For example, see MacMillan *JACS* **2003**, *125*, 10808 & Maruoka *JACS* **2006**, *128*, 6046

7.2. Regioselective Functionalization of Alkenes and Alkynes

Catalytic regioselective reactions can be designed to modulate regioselectivity in several ways. Careful tuning of several factors, including catalyst and ligand choice, can help to overcome even strong inherent substrate selectivity.

The traditional Tsuji-Wacker oxidation of allylic carbamates, for example, gives a nearly 1:1 ratio of aldehyde and ketone products. This is likely because the electronic bias of the bond formation is counteracted by the sterics of the neighbouring group, leading to poor selectivity in the intermolecular attack of water on the Pd-activated alkene:

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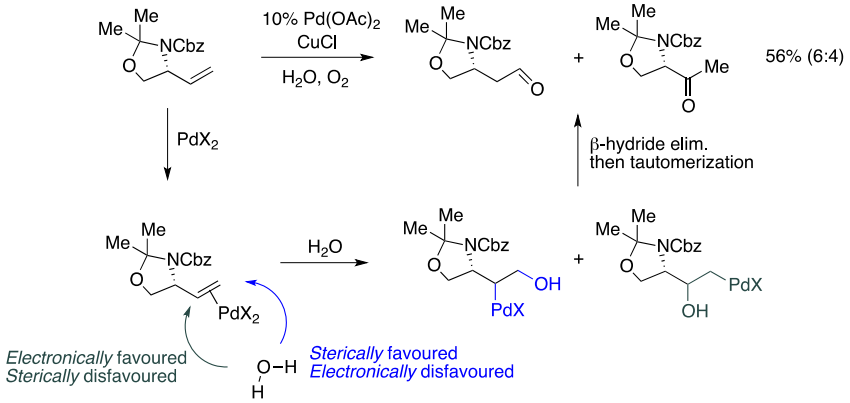
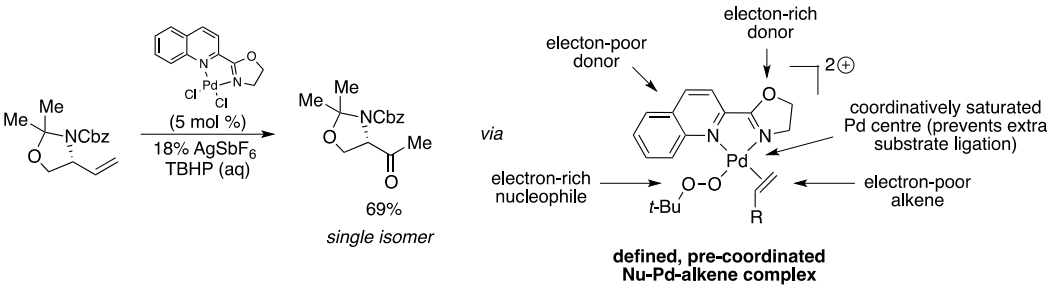


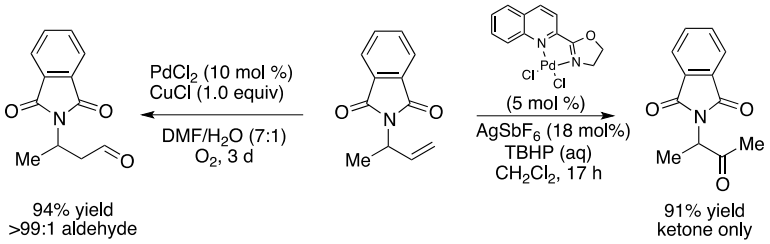
However, Sigman has designed a new ligand/oxidant combination that renders this reaction remarkably selective, showcasing design elements that could have general implications for Pd-catalyzed activation of alkenes.

These include the use of electronically asymmetric ligands to pre-organize both reactants, a complexed nucleophile to ensure intramolecular addition (*via* migratory insertion), and a cationic metal to maximize the reactivity and electronic bias in the transition state. These factors combine to precisely control the site of attack.



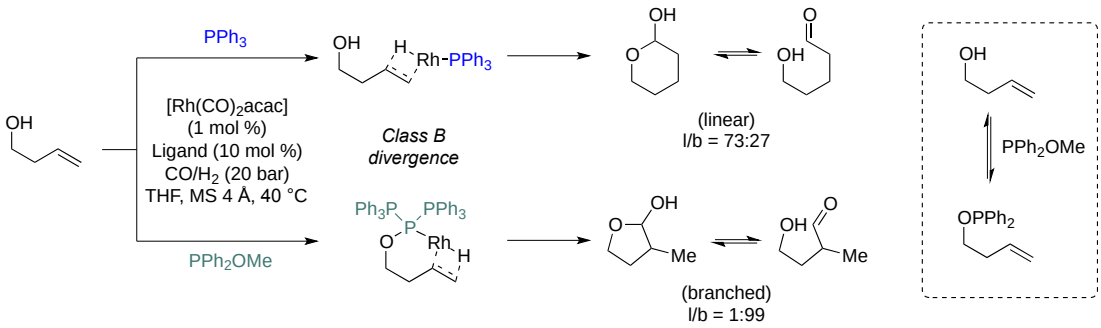
Sigman, *Acc. Chem. Res.* **2012**, *45*, 874

Through tuning of conditions, this catalyst system can achieve either ketone- or aldehyde-selectivity.



Aldehyde selective: Feringa, *JACS*, **2009**, *131*, 9473 & Ketone selective: Sigman, *JACS*, **2011**, *133*, 8317.

Another example of a selectivity-controlled reaction of alkenes is hydroformylation *via* the use of scaffolding ligands. These bind covalently and reversibly to the substrate, leading to a temporarily intramolecular transformation that can lead to dramatically improved and reversed selectivity with substrates such as homoallylic alcohols. In this case, PPh_2OMe serves not only as a catalytic directing group for Rh but also as an electrophile for the alcohol. A ligand unable to bind to the substrate, such as PPh_3, leads to the linear product through the "innate" pathway.



Breit *ACIE* **2008**, *47*, 7346 & Tan *JACS* **2008**, *130*, 9210 for similar approach

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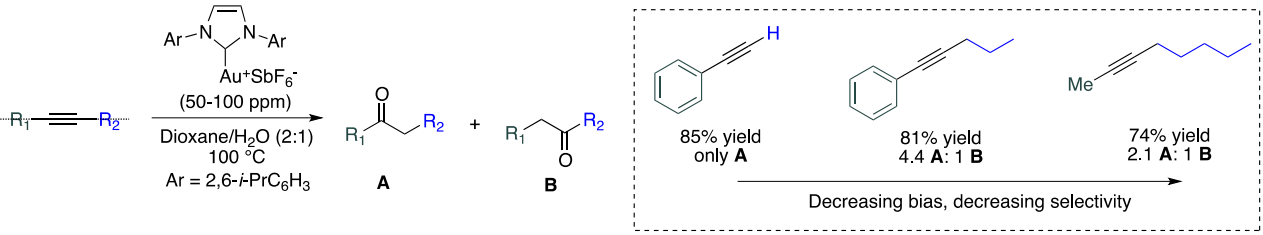
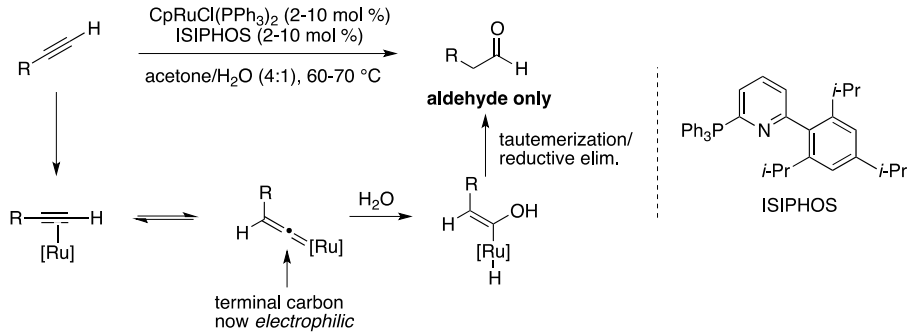
Catalytic hydration of alkynes is typically under Markovnikov control, since the transition states are highly polarized and require hard nucleophiles. Recently, gold-catalysts have emerged as promising catalysts for this process. However, the powerful influence of the inherent selectivity is clear, as seen in the examples below:



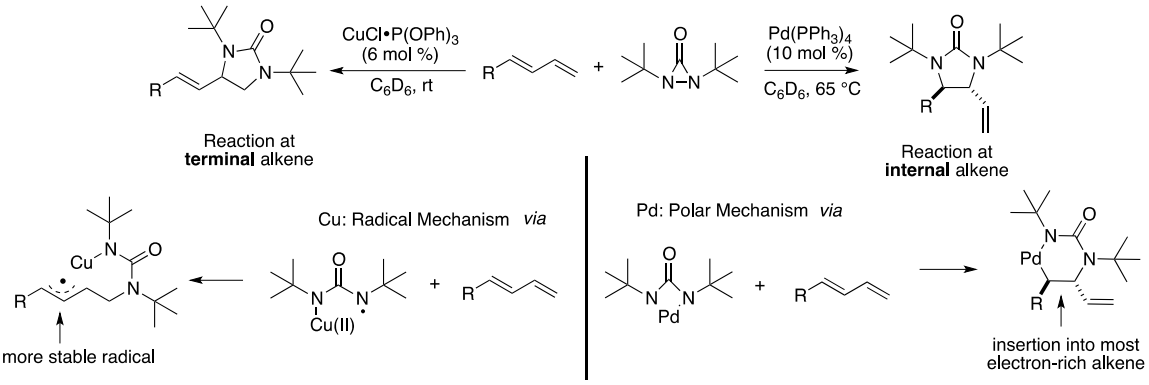
Nolan *JACS* **2009**, *131*, 448

In order to reverse the selectivity, an alternative mechanism is required. Hydration of terminal alkynes catalyzed by Ru complexes leads very selectively to anti-Markovnikov products (aldehydes), especially under the influence of ligands recently developed by Hintermann:



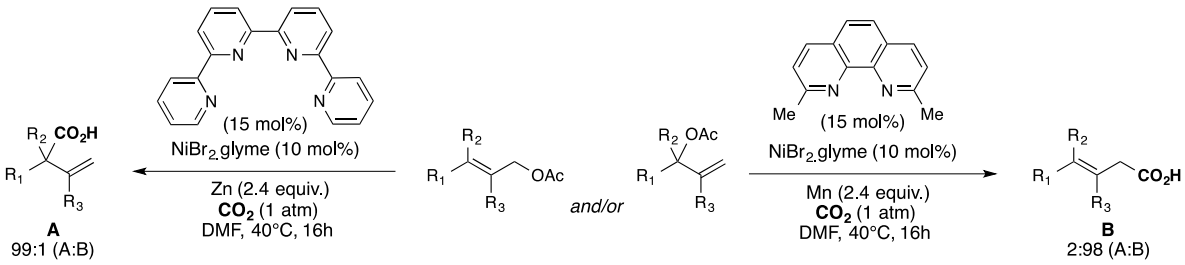
Catalyst: Hintermann *JACS*, **2011**, *133*, 8138 & Mechanism: Wakatsuki *ACIE* **1998**, *37*, 2867

Regioselectivity can be altered by appropriate catalyst choice – palladium and copper-catalyzed diamination of dienes proceed with differing internal/terminal selectivity, due to differences in the mechanisms involved.



Pd-Catalyzed: Shi *JACS*, **2007**, *129*, 762; Shi *JACS*, **2010**, *132*, 3523 Cu-Catalzyed: Shi *OL*, **2007**, *9*, 2589.

The ligand environment around the metal can also play an important role. Martin has reported a Ni-catalysed protocol for the carboxylation of allyl esters with carbon dioxide, where the regioselectivity of the substitution is controlled by the choice of ligand and reductant.



Martin *JACS* **2014**, *136*, 17702

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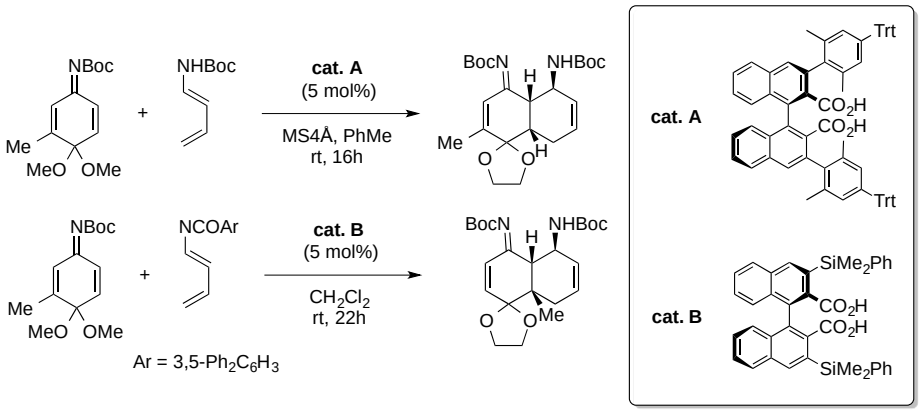
7.3. Regioselective Cycloaddition Reactions

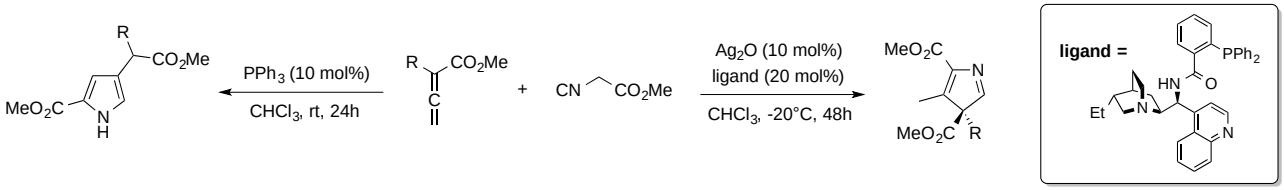
Uncatalysed [4+2] and [3+2] cycloaddition processes typically feature inherent selectivity based on the electronic properties of the components involved. However, this inbuilt selectivity is rarely complete, and is often challenging to control. However, catalytic methods for divergent regioselective cycloaddition reactions have begun to emerge.

For example, Maruoka has reported the site-divergent Diels-Alder reaction of quinone imine ketals, where catalyst modulation can be used to redirect the regioselectivity of the process to the unfavoured dienophile.



Maruoka *ACIE* **2015**, *54*, 4617

Catalyst system regiocontrol has also been showcased in [3+2] cycloadditions. Recent work by Zhao showcased a divergent synthesis of 1H and synthetically challenging 3H pyrroles from allenoates and activated isocyanides, by phosphine and silver catalysis respectively.



Zhao *JACS* **2015**, *137*, 628

7.4. Regioselective Functionalization of Arenes

There are three main methods for the regioselective functionalization of arenes:

1) Reagent-controlled reactions
2) Chelation-assisted directing-group controlled reactions
3) Catalyst-controlled reactions

While by modern methods nearly any substitution pattern can be achieved on nearly any arene, these are typically achieved by applying a variety of different chemistries to the starting material at hand, exploiting the inherent reactivity of the specific arene involved. General regiocontrol in arene substitution remains an area of intense investigation.

7.4.1. Reagent-Controlled Reactions

Reactions of monosubstituted alkylbenzenes (an *o/p* directing group) typically favour formation of the *para* isomer because of the steric hindrance around the *ortho* position. However, judicious choice of reagents can lead to reversal of regioselectivity- in this case the “naked” iodonium provided by Barluenga’s reagent is guided to the ortho position by pre-complexation with the trifluoroacetamide.

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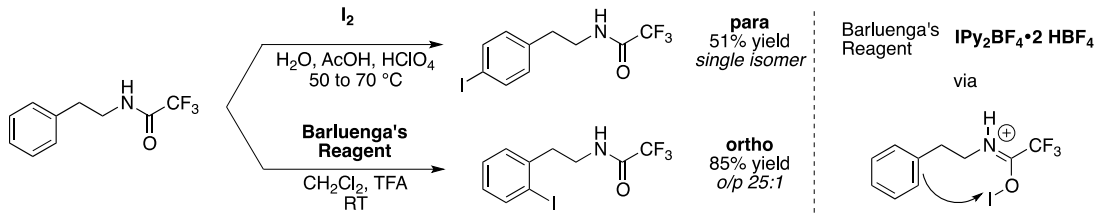
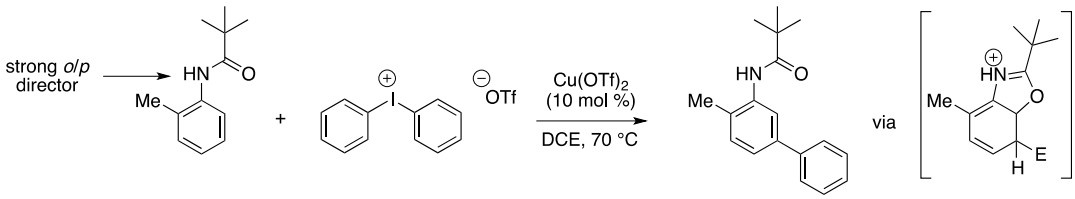


Ortho-selective: Barluenga *ACIE* **2007**, *46*, 1281 & *Para*-selective: US2003/225266 A1, **2003**

Especially interesting are examples where the expected regioselectivity can be overridden. Cu-catalyzed reactions of pivanilides with diaryliodonium salts are highly *meta*-selective, despite the nitrogen group being a strong *o/p* director. Note that $Cu(OTf)_2$ is required to activate the electrophile but plays no role in the selectivity - reactions without copper at higher temperature give the same *meta* regioisomer.

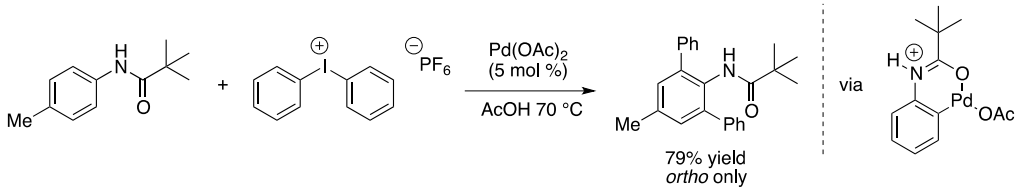


Gaunt *Science* **2009**, *323*, 1593 (for discussion on role of $Cu(OTf)_2$, see Gaunt *ACIE* **2011**, *50*, 463)
For the mechanism, see Wu *JACS* **2011**, *133*, 7668

7.4.2. Chelation-Assisted Directing Group-Controlled Reactions

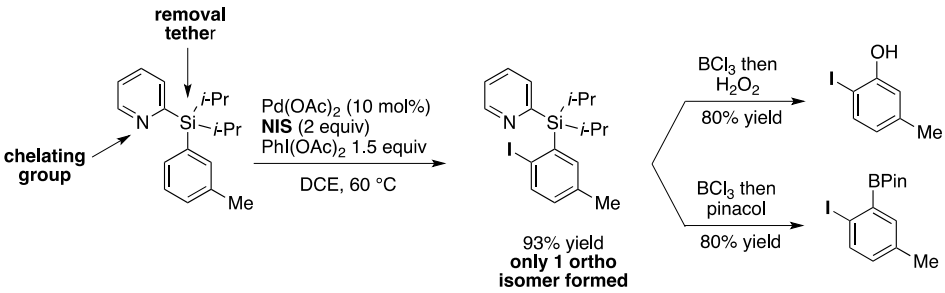
Many reactions take advantage of the coordinating ability of the functional groups on the arene to direct functionalization of adjacent positions.

This is especially common for Pd-catalyzed reactions, where the directing group also helps stabilize high oxidation state intermediates. In the example below, the pivanilide group directs *ortho*-palladation of the aromatic ring. Note that consecutive alkylations/arylations are hallmarks of electrophilic substitutions where the product is more nucleophilic than the starting material. Also, contrast this example with the copper-catalyzed reation just above - this will reinforce the importance of directing groups and changes in mechanism.



Daugulis *ACIE* **2005**, *44*, 4046

The main drawback of using directing groups is that their presence in the molecule is often permanent, limiting the overall generality of the process. A new trend is the use of directing groups that can be converted into a range of new products:



Gevorgyan *ACIE* **2010**, *49*, 8729

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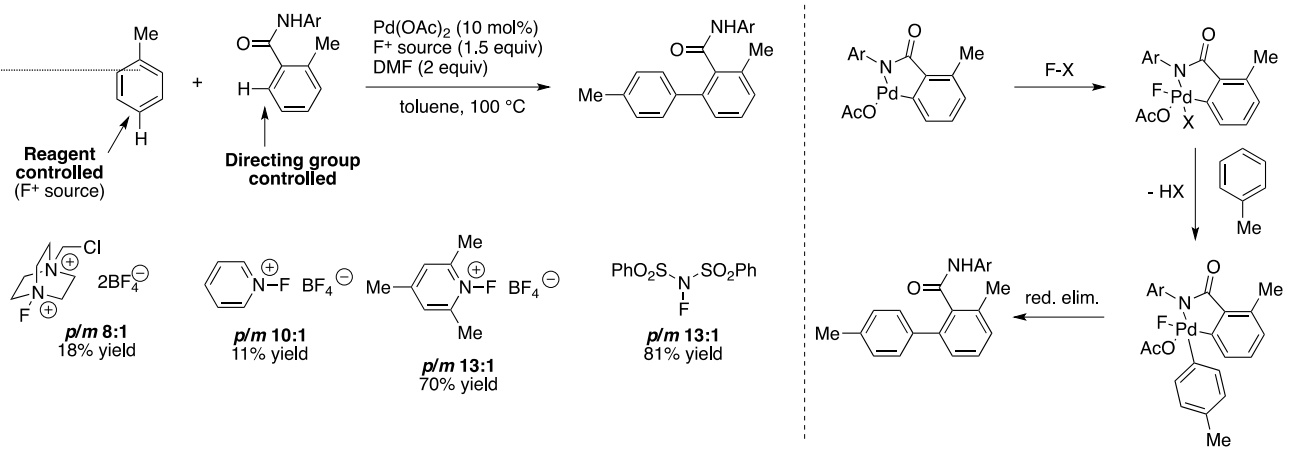
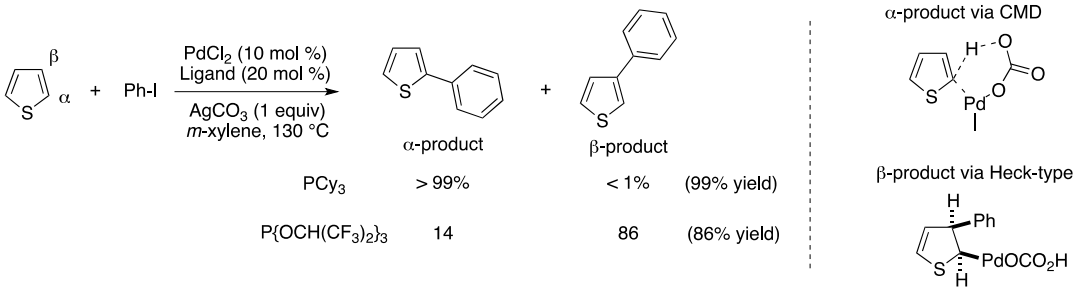
Different types of regioselectivity can work together to make for highly selective reactions. In the example below, a **chelating group** places the Pd catalyst in the *ortho* position relative to the amide. The resulting Pd(IV) intermediate is attacked by the toluene solvent in a **reagent controlled** fashion - this is an electrophilic palladation that favours the *para* position of the nucleophile for steric reasons.



Yu *JACS* **2011**, *133*, 13864

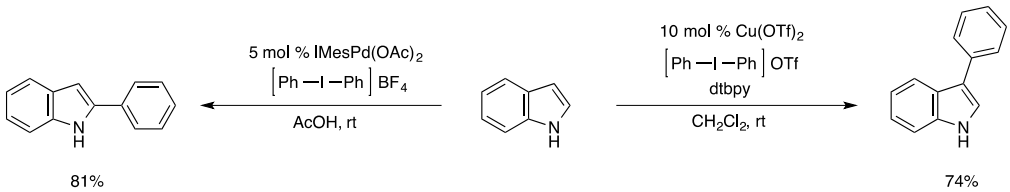
7.4.3. Catalyst-Controlled Reactions

This is a emerging, competitive area, potentially representing a step toward ideal regioselectivity in the functionalization of arenes. The Pd-catalyzed reaction of thiophenes with aryl iodides can be tuned to give either regioisomer simply by altering the ligand. This has been calculated to be a result of a change in mechanism in the product-determining step: electron-rich phosphines favour CMD-based direct arylation, while electron-poor phosphites allow a Heck-type carbopalladation.



Itami *ACIE* **2010**, *49*, 8946 (for the mechanism, see Fu *CEJ* **2011**, *17*, 13866)

Functionalization of indoles has been of long-standing interest in the field of direct arylations. Recent advances in the area include the discovery of catalyst-controlled reactions that can control the C2/C3 regiochemistry by altering the metal catalyst.



Sanford *JACS* **2006**, *128*, 4972; Gaunt *JACS* **2008**, *130*, 8172

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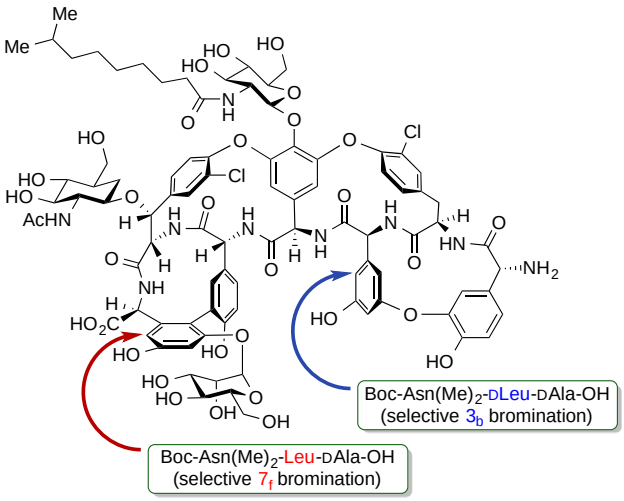
Catalyst-controlled regioselectivity of this type has also been demonstrated in more complex systems. Miller has shown that sequence modulation of a peptide allows for site-selective bromination of the antibiotic teicoplanin. This area is of particular interest as selective functionalization of such systems is both synthetically challenging and presents an important means for developing new, bacteria-resistant antibiotics.

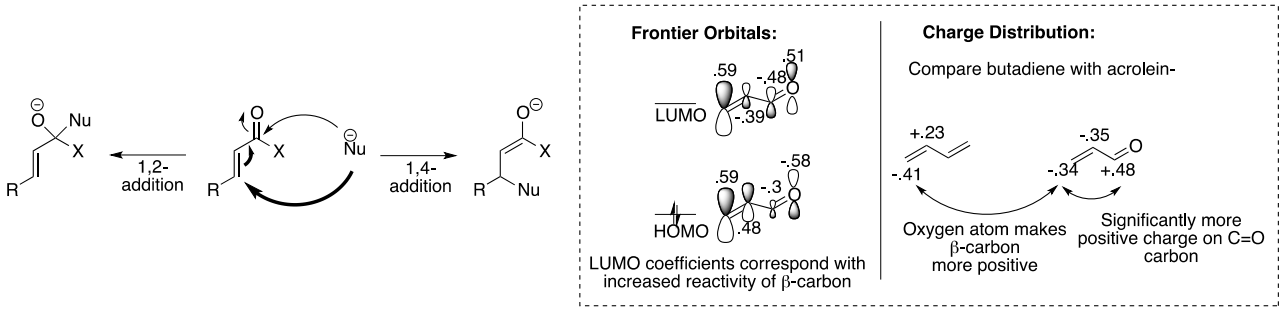


Conditions:
peptide
n-bromophthalimide (1.1 equiv.)
H2O/MeOH (1:1), rt, 1.5h

Miller, *JACS*, **2013**, *135*, 8415

8. Regioselective α,β-unsaturated carbonyl reactions

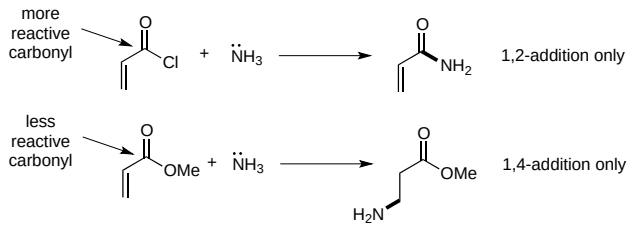
1,2- vs 1,4-Addition: *α,β*-unsaturated carbonyl compounds are *ambident* electrophiles - nucleophiles can attack either the C=O or C=C bond.



LUMO calculations: Houk, *JACS*, **1973**, 4094. Charges: Tidwell, *JOC*, **1994**, 4506

8.1. Substrate-controlled selective addition to α,β-unsaturated carbonyl reactions

The selectivity is determined by a combination of the nature of the leaving group and nucleophile:



Fleming, *Molecular Orbitals and Organic Chemical Reactions*, **2010**, p 188

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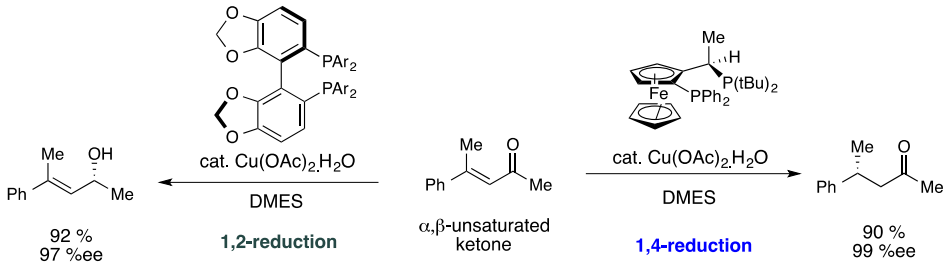
8.2. Catalyst-controlled selective reduction or addition to α,β-unsaturated carbonyls

- Ligand modification can alter the selectivity of reduction due to "subtle and complex interactions between the substrate, solvent, and bulky ligands".

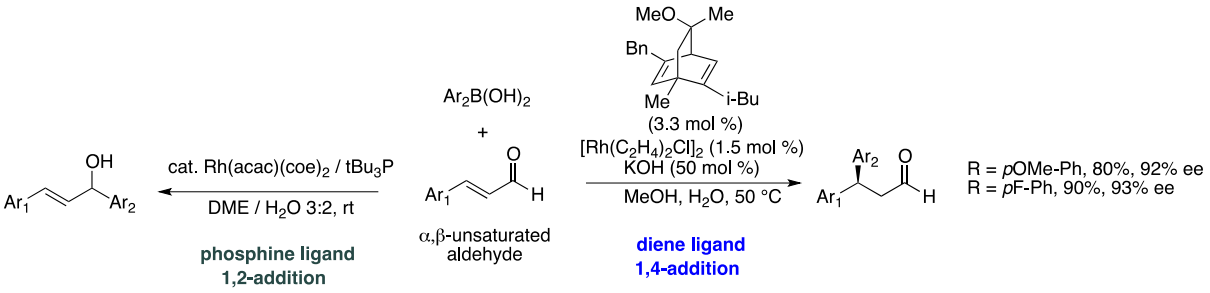


(Dimethylethoxysilane = DMES).

Lipshutz *Tetrahedron* **2012**, *68*, 3410

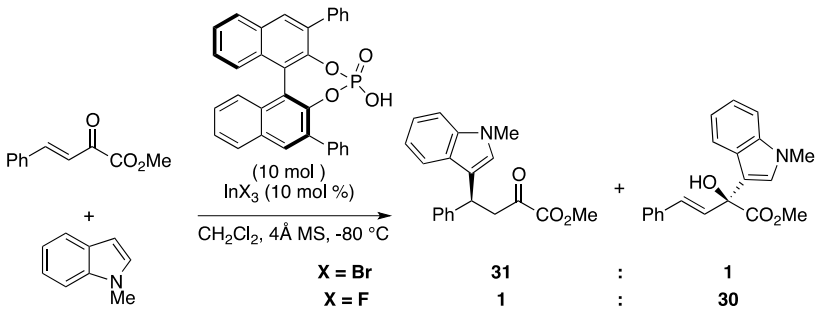
For selective non-metal-catalyzed 1,4-reduction, see MacMillan *JACS* **2005**, *127*, 32 & List *JACS* **2006**, *128*, 13368

- Diene ligands can provide exquisite chemo- and enantioselectivity - additions to unsaturated aldehydes proceed by 1,4-addition. This is in stark contrast to Rh/phosphine catalysis, which furnishes the 1,2-addition product exclusively.



Carreira *JACS* **2005**, *127*, 10850 & Miyaura *JOC* **2000**, *65*, 4450

- Changing counterion can switch the preference for selective 1,2- vs 1,4-conjugate addition.



Luo *ACIE* **2011**, *50*, 6610

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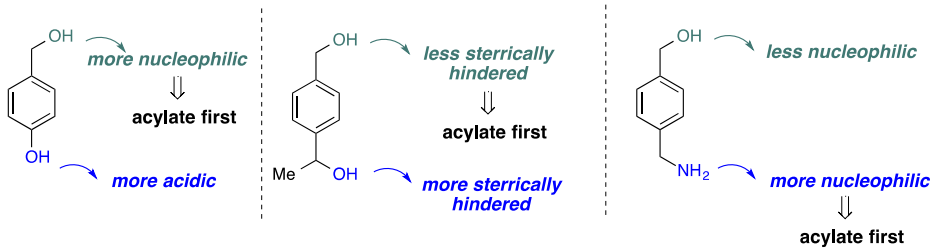
9. Chemoselective functionalization of nucleophiles

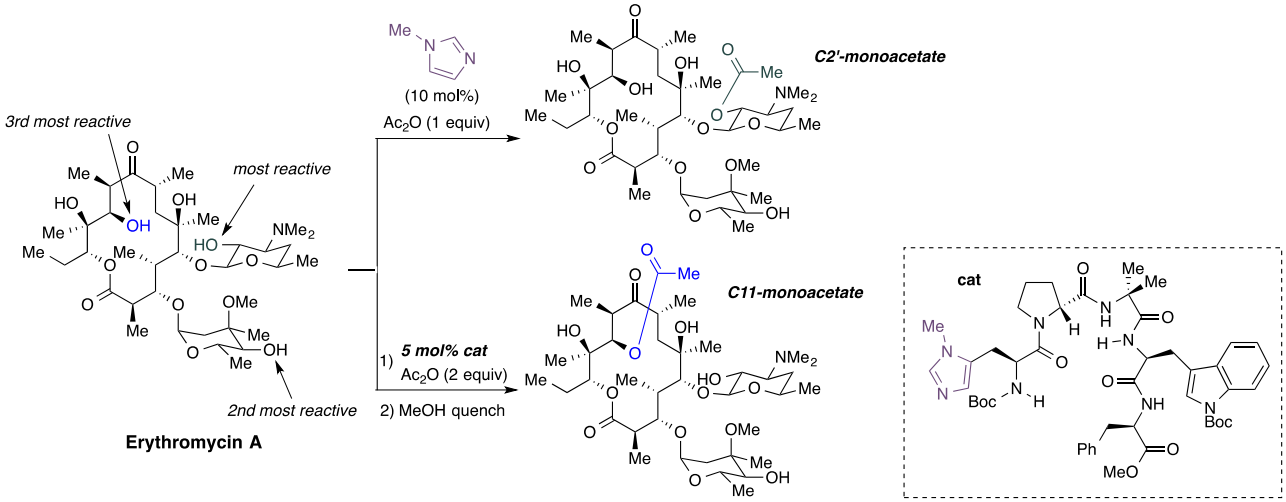
9.1. Selective acylation reactions

Selective acylation strategy concerns how to override inherent preferences of innate relative acidity, sterics, or nucleophilicity.



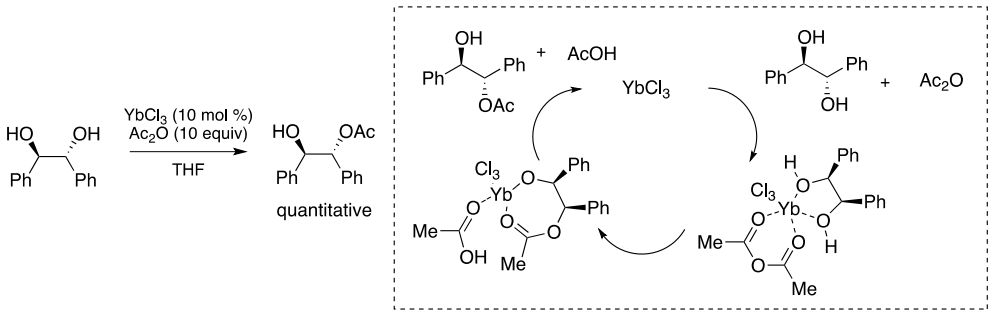
Melman *OBC* **2004**, *2*, 1563

Selective acylation of alcohols using peptide-based catalysts:



Miller *ACIE* **2006**, 45, 5616

9.1.1. Chemoselective mono-acylation of diols by Yb catalysts



Clarke *JOC* **2002**, *67*, 5226

9.1.2. Selective O-acylation in the presence of amines

- Catalytically generated acyl azoliums have been long known to preferentially acylate alcohols and water over amines. This chemoselectivity can be utilized to acylate hydroxyl groups in the presence of amino groups. Catalytic amidation reaction may be achieved when HOAt or imidazole is used.

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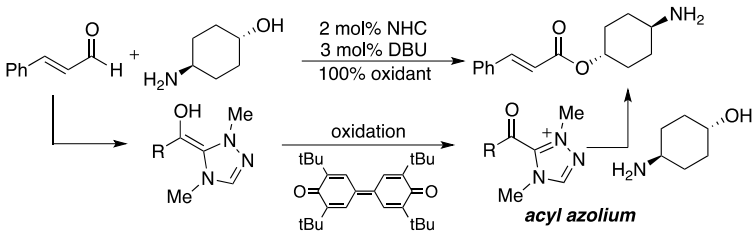
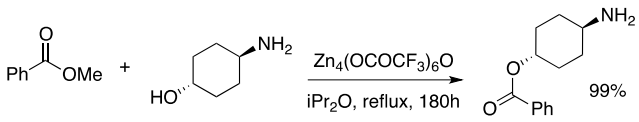


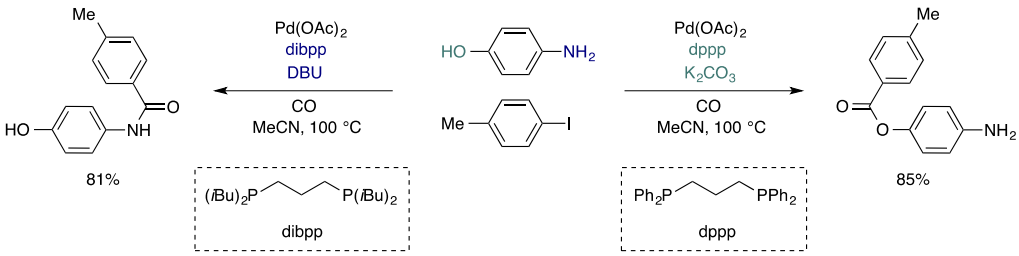
Studer *JACS* **2010**, *132*, 1190

- Polymeric Zn catalysts allow for selective acylation of the hydroxyl group over the amine due to the enhanced oxophilicity of the Zn ions.



Mashima *JACS* **2008**, *130*, 2944

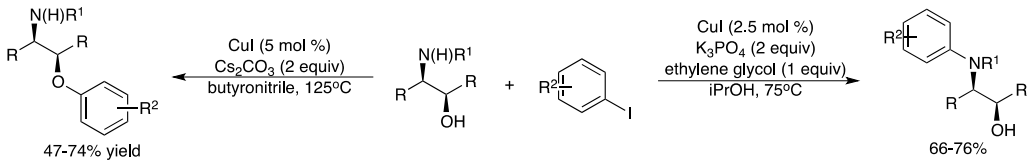
- In the carbonylation reaction below, amino phenols act as nucleophiles. Ligand and base selection is the key to the selective acylation. The excellent selectivity was realized for 4- and 3-amino phenols, while 2-amino phenol gives only the amide.



Alper *JACS* **2014**, *136*, 16970

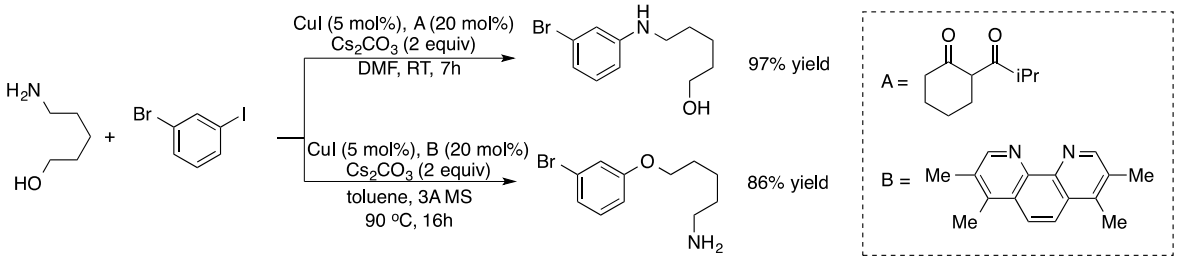
9.2. Selective O- vs. N-arylation

- Selective Buchwald-Hartwig amination of 1,2 aminoalcohol (simple amines and alcohols do not work). The selectivity arises from the relative tightness of chelation, depending on reaction conditions and additives.



Buchwald *OL* **2002**, *4*, 3703

- Buchwald has also designed ligands specifically for the purpose of reacting selectively with amines and alcohols. The anionic nature of ligand **A** attenuates the electrophilicity of Cu(I) and favors coordination of amine. The Cu(I) complex with **B** is much more electrophilic and favors binding of alcohol.



Buchwald *JACS* **2007**, *129*, 3490

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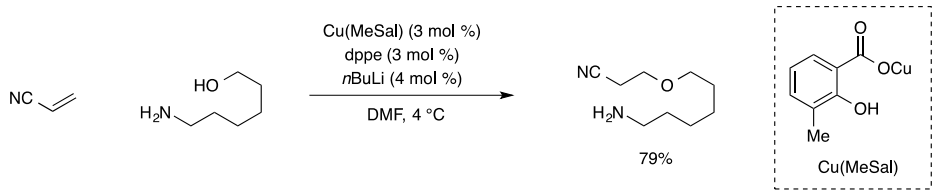
9.3. Selective 1,4-addition of O- vs. N-nucleophiles

A cooperative catalyst system (soft Lewis acid and hard Brönsted base) enables the selective 1,4-addition of oxygen nucleophiles to acrylonitrile.



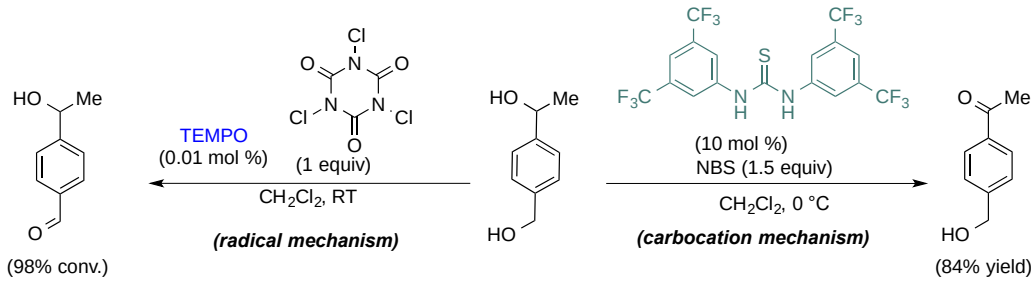
Ohshima *ACIE* **2014**, *53*, 1611

9.4. Chemoselective oxidation and reduction reactions

9.4.1. Chemoselective oxidation

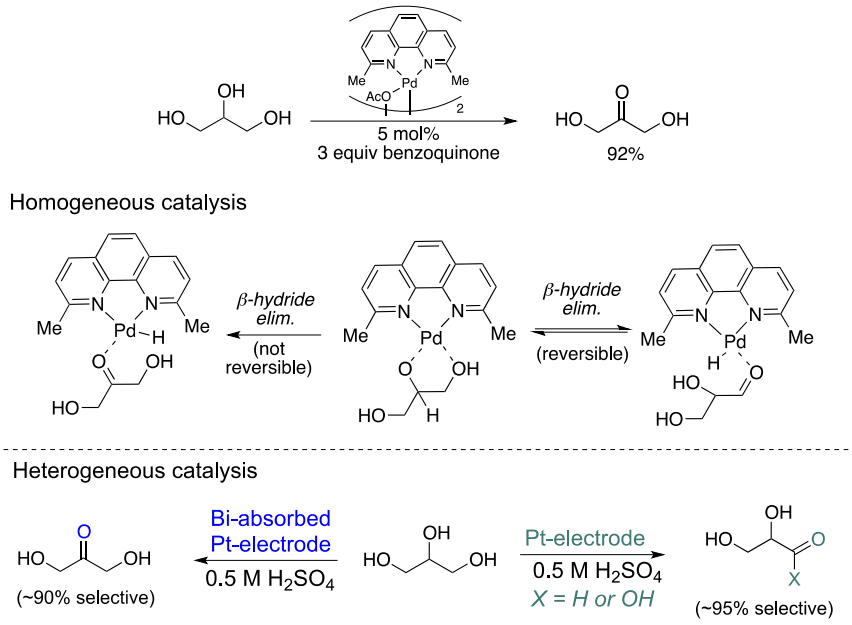
Depending on the mechanism, selective oxidation reactions may reinforce or override innate steric or nucleophilic preference (similar to the cases above).

- *Innate steric preference*. The catalyst reinforces innate chemoselectivity to achieve complete oxidation of primary over secondary alcohol.



Giacomelli *OL* **2001**, *3*, 3041 & Mukherjee *JOC* **2012**, *77*, 1592

- Selective oxidation of secondary alcohols over primary may be achieved either by employing Pd and benzoquinone, or by heterogeneous catalysis.



Waymouth *ACIE* **2010**, *49*, 9456 & Koper *ACS Catal.* **2012**, *2*, 759

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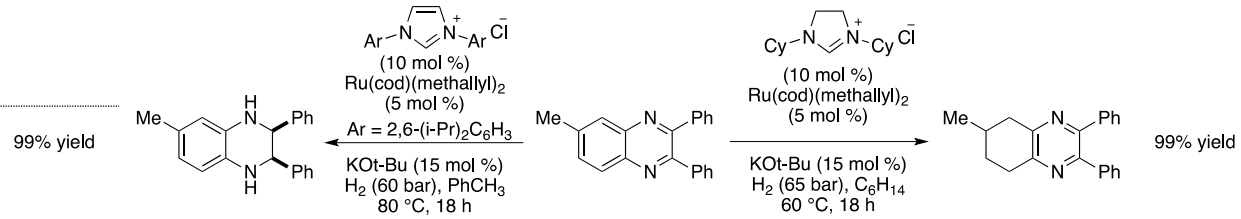
9.4.2. Chemoselective hydrogenation

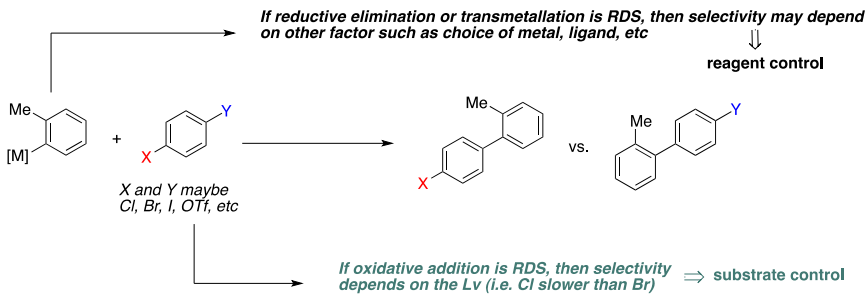
Chemoselective hydrogenation of heteroaromatic systems can also be achieved through proper choice of ligand (steric and/or electronic factors can play a role).



Glorius *ACIE* **2011**, *50*, 3803

10. Chemoselective arene functionalization

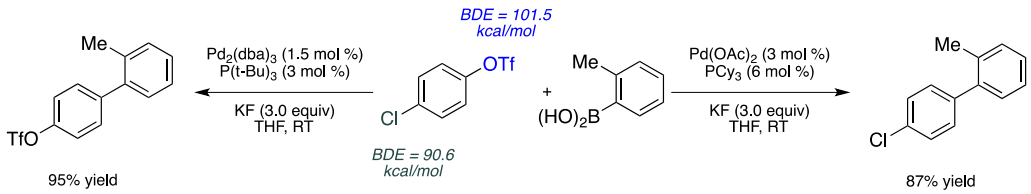
Bond	Bond Strenth (in kcal/mol)
C-C	90
C-O	92
C-N	85
C-F	115
C-Cl	84
C-Br	72
C-I	58



Blanksby and Ellison *Acc. Chem. Res.* **2003**, *36*, 255 & Bordwell *Acc. Chem. Res.* **1988**, *21*, 456

10.1. C-X substitution

- Chemoselective Suzuki-Miyaura cross-couplings can be achieved through catalyst choice - monoligated Pd (favored with PtBu) favors C-Cl insertion, while bisligated Pd (the active species with PCy_3) favors C-OTf insertion.



Fu *JACS* **2000**, *122*, 4020

For rationale: Houk and Schoenebeck *JACS* **2010**, *132*, 2496 & Schoenebeck *ACIE* **2011**, *50*, 8192

- Altering the ligand and Pd sources can affect the chemoselectivity of cross-coupling reactions. In the first case below, a working hypothesis postulates that the more bulky ligand directs an oxidative addition towards the less hindered *para* position, while oxidative addition is irreversible at the *ortho* position for a system with a less bulky ligand system.

- The second example shows how changing the catalytic metal from Pd to Cu switches the selectivity of an amination process.

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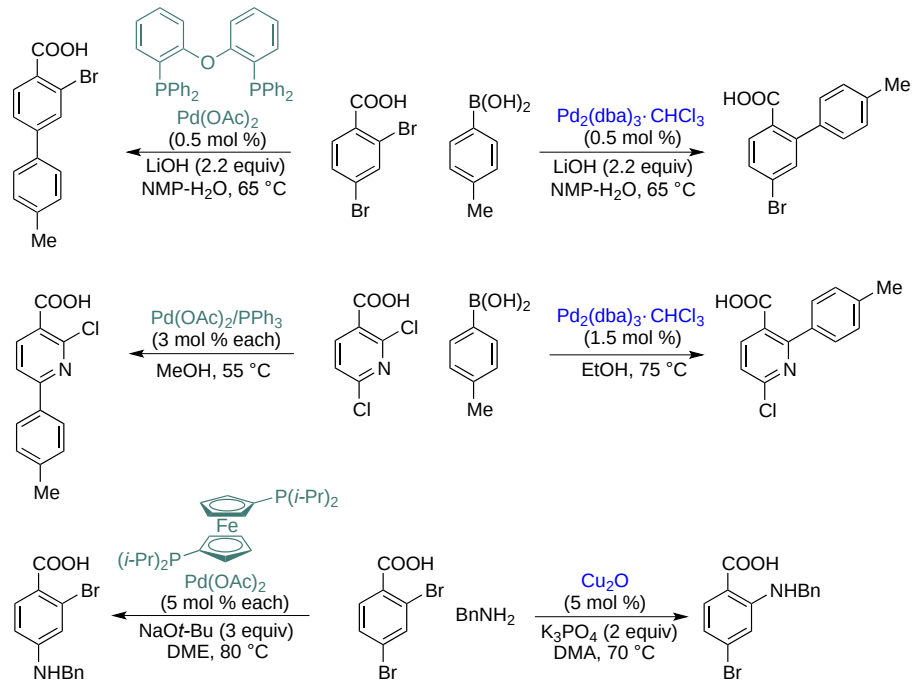


Houpis *OL* **2008**, *10*, 5601, *JOC* **2010**, *75*, 6965, & *Adv. Synth. Catal.* **2011**, *353*, 538

10.2. C-H functionalization

Parameter: kinetics (rate) vs. thermodynamics (bond strength or pKa)

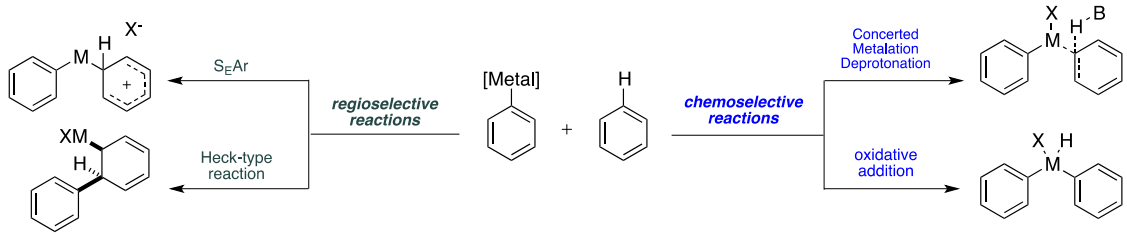
Rates of C-H oxidation normally follow:
tertiary C-H > ethereal C-H ≈ benzylic C-H > secondary C-H > primary C-H.

These are general rules, dependent upon electronic factors and not steric bias.

Bond	BDE (kcal/mol)	pKa
C_{Methyl}-H	105	48
$C_{Isopropyl}$-H	99	51
$C_{tertbutyl}$-H	97	53
C_{allyl}-H	89	43
C_{phenyl}-H	113	43
C_{vinyl}-H	111	50
HCC-H (ethyne)	133	25

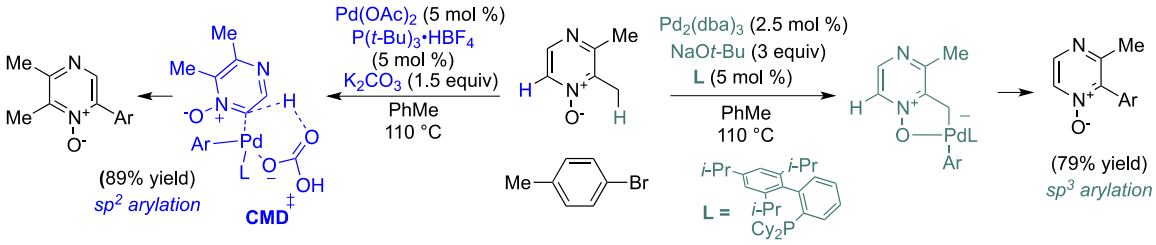
Baran *Acc. Chem. Res.* **2012**, *45*, 826 & Sanford *Acc. Chem. Res.* **2012**, *45*, 936

- Aryl C-H functionalization: depending on the mechanism, formal classification of C-H bond functionalization may change



Ackermann *ACIE* **2009**, *48*, 9792

- Altering the base and the Pd source may allow for selective C-H bond activation by selective deprotonation at a different site.



Fagnou *JACS* **2008**, *130*, 3266 & *Tetrahedron* **2009**, *65*, 3155

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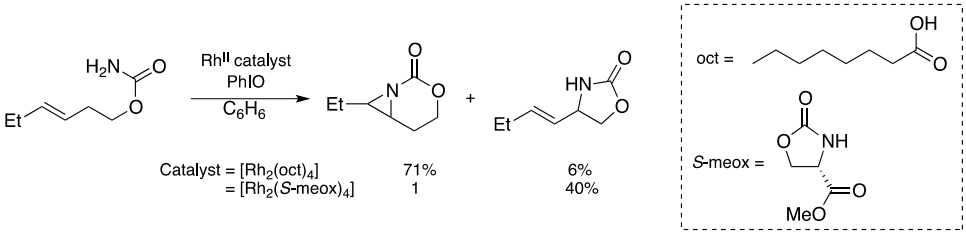
10.3. Chemoselective alkane functionalization

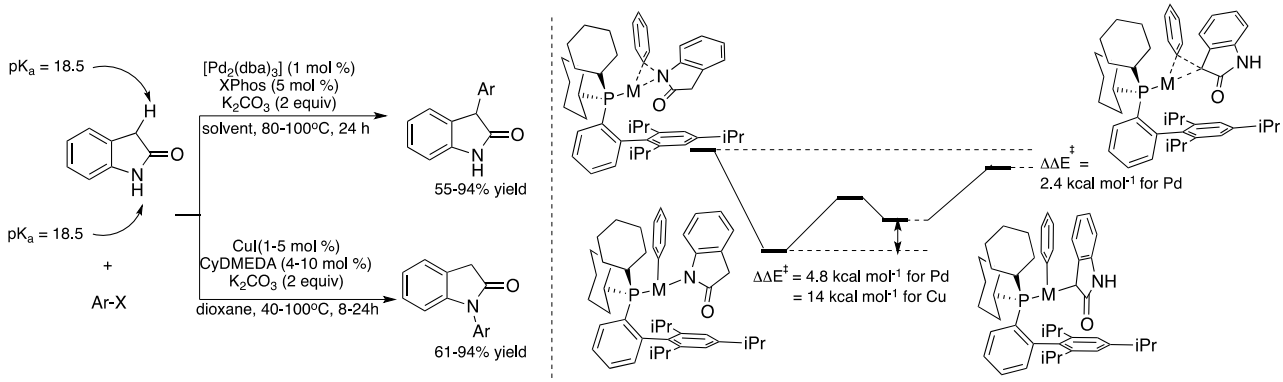
- Depending on ligand choice, aziridination or allylic C-H oxidation can take place. Typically, carboxylate ligands tend to furnish aziridine adducts, and carboximidates give allylic C-H oxidation products.



Hayes *Chem. Comm.* **2006**, 4501

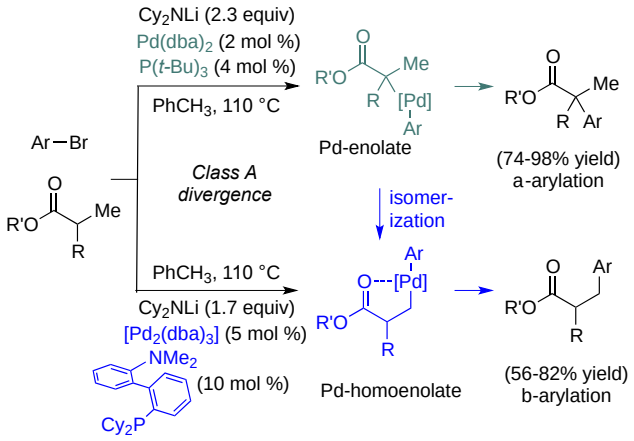
In the example below, two protons show equivalent acidity, and catalyst choice generates different products:

- N-arylation is favored for Cu as the M-N complex is significantly lower in energy (14 kcal/mol) than the corresponding M-C complex.
- C-arylation is favored for Pd as equilibrium takes place between the M-C and M-N complexes. The outcome then follows the Curtin-Hammett situation – reductive elimination from M-C complex is lower in energy by 2.4 kcal/mol.



Buchwald *JACS* **2008**, *130*, 9613

Hartwig described the catalytic generation of palladium enolate, which undergoes reductive elimination to give the *α*-arylated product (top). Recently, ligand-controlled Pd catalyzed *β*-arylation by electron-withdrawing aryl halides (bottom) has been reported. Detailed kinetic and DFT studies revealed that *β*-arylation was kinetically favorable for certain ligands, but not for P(*t*Bu)$_3$ due to the stabilization of the metal from the ligand's backbone.



Hartwig *JACS* **2001**, *123*, 8410 & Clot and Baudoin *ACIE* **2010**, *49*, 7261

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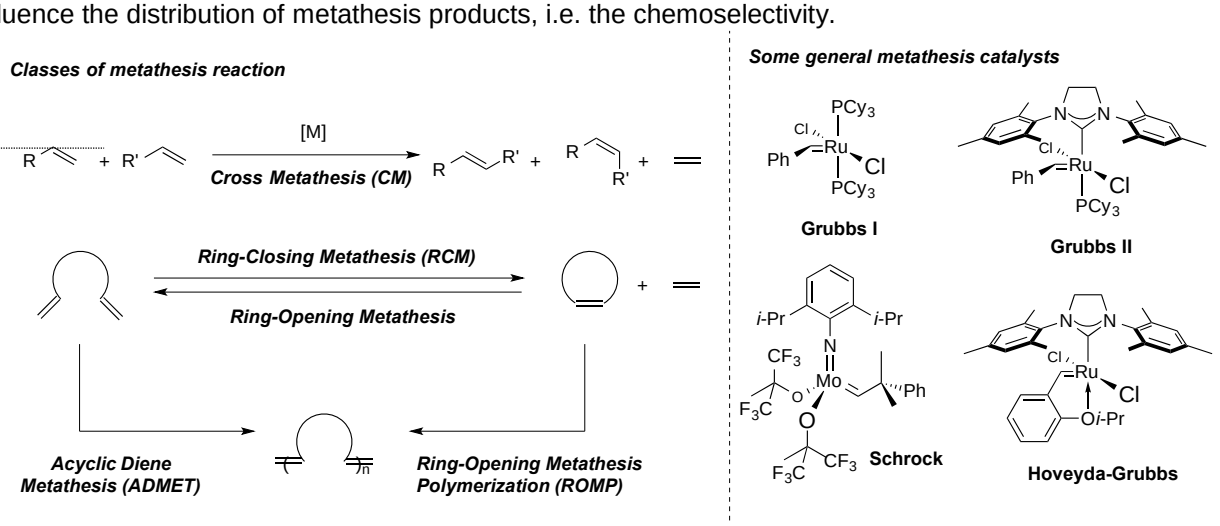
11. Chemoselective olefin metathesis

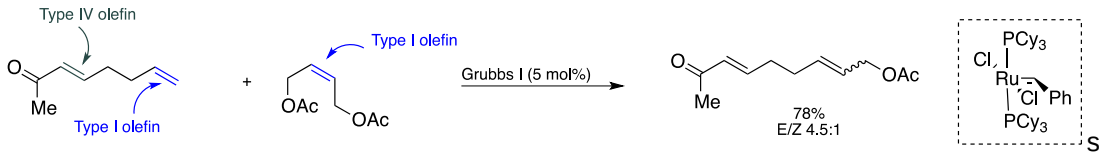
- Olefin metathesis has emerged as a highly powerful synthetic tool. Many classes of reactions (CM, RCM, ROMP) have been investigated; several reports have demonstrated that catalyst structure or type can influence the distribution of metathesis products, i.e. the chemoselectivity.



Hoveyda *Nature* **2007**, *450*, 243 & Nolan *Chem. Soc. Rev.* **2010**, *39*, 3305

11.1. Innate reactivity of olefins in metathesis reactions

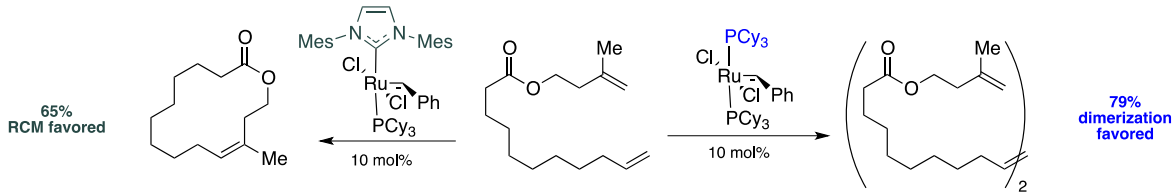
- Grubbs and coworkers developed an empirical system for categorizing olefins in metathesis. For example, highly reactive terminal olefins and allylic alcohols are considered ***type I***. ***Type IV*** olefins are "spectators" (no catalyst deactivation), and are slow participants in cross-metathesis.



Grubbs *JACS* **2003**, *125*, 11360

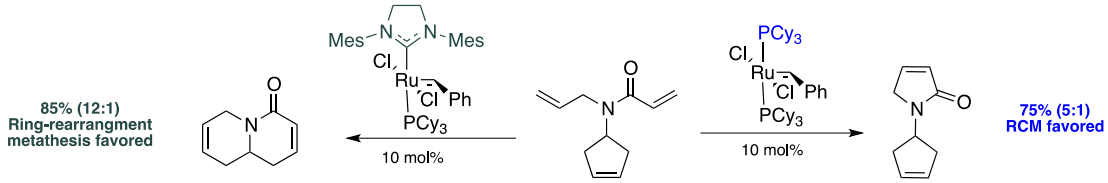
11.2. Catalyst controlled chemoselective metathesis reaction

- The bulky phosphine ligand in Grubbs I catalyst is sterically too hindered to engender RCM.



Furstner *CEJ* **2001**, *7*, 3236

- NHC ligands preferentially form the thermodynamic product, while phosphine ligands form the kinetic (RCM) product.



Ma *CEJ* **2004**, *10*, 3286

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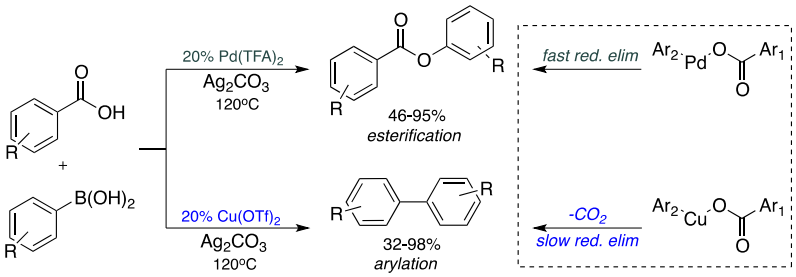
12. Product-selective catalysis

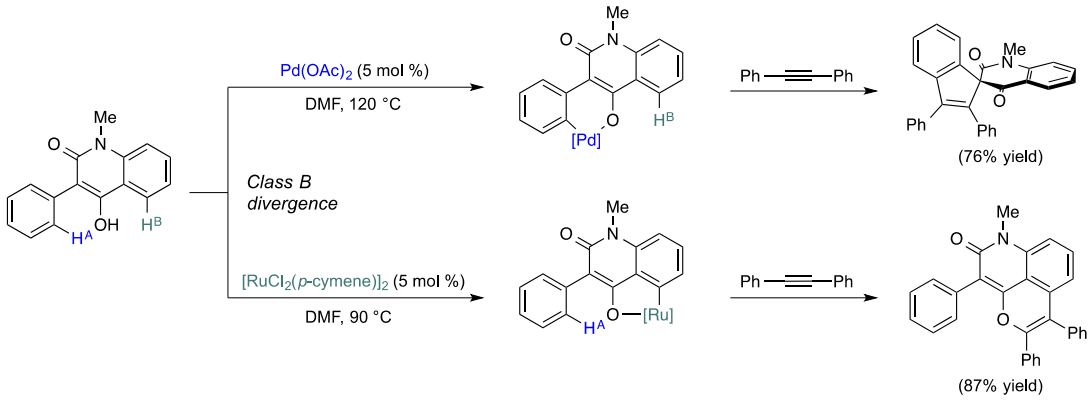
This is an emerging area of research concerning catalyst-controlled formation of two (or more) non stereo- or regioisomeric products from a common starting material. Many of these reactions were discovered serendipitously, and rational design of this kind of selectivity is not easy. However, advances in understanding of this type of selectivity and development of this mode of catalysis are increasingly relevant in modern synthesis, in which increased synthetic efficiency and selective functionalization of complex targets are highly desirable. Some notable examples are highlighted below.

- Changing the metal catalyst from Pd to Cu allows for accelerated decarboxylation over reductive elimination, with improved selectivity.



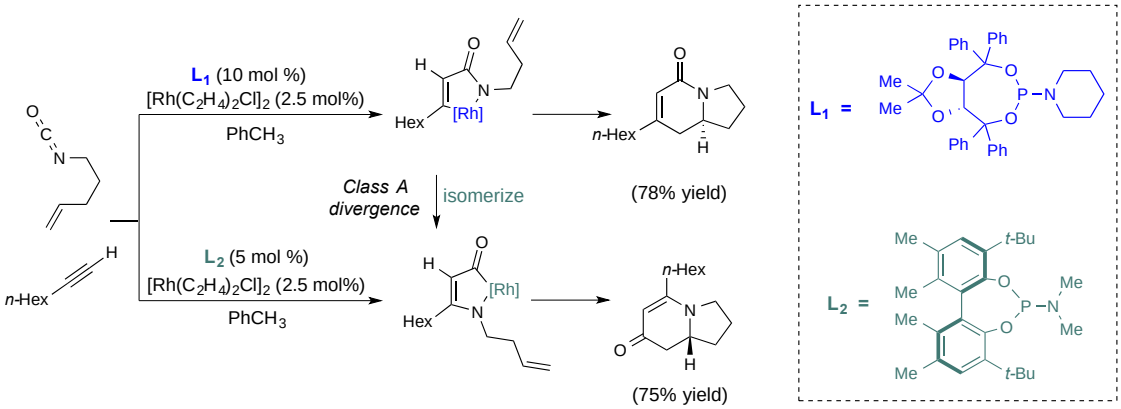
Liu *Chem. Commun.* **2011**, *47*, 677

- Depending on the metal used, site-selectivity of the C–H bond cleavage event can be altered.



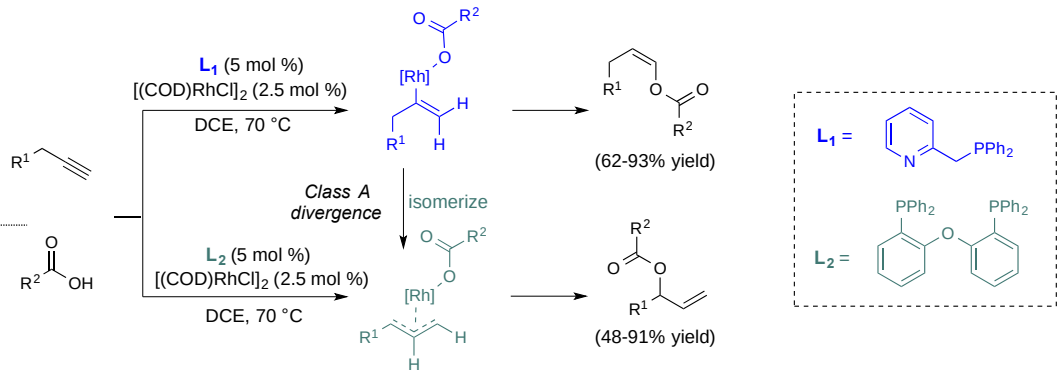
Lam *JACS* **2013**, *135*, 10829

- Rovis reported an elegant Rh(I) catalyzed formal [2+2+2] cycloaddition reaction between isocyanates and terminal alkynes. Using a TADDOL-derived phosphoramidite ligand, a lactam (top) is obtained in good yield and enantioselectivity. It was later found that BINOL-derived phosphoramidite ligand was effective for overriding the substrate bias, effecting the formation of a vinylogous amide (bottom).



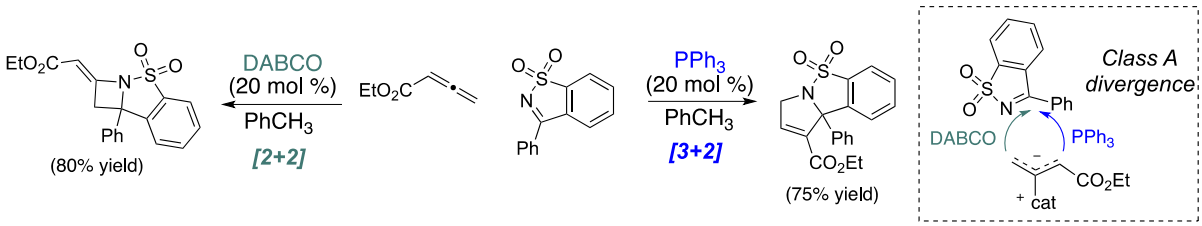
Rovis *JACS* **2006**, *128*, 12370 & *ACIE* **2009**, *48*, 2379

- Breit has disclosed an equally impressive insertion-isomerization relay in Rh catalysis.



Breit *OL*, **2010**, *12*, 5498 & *JACS*, **2011**, *133*, 2386

- Product selectivity is not unique for transition-metal catalysts. Organocatalysts can also induce product selectivity, as seen in this allene cycloaddition from Ye.



Ye *Chem. Commun.* **2012**, *48*, 1317

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