DOI: 10.1002/anie.201201787

Selective Catalysis

Catalytic Selective Synthesis

*Jessada Mahatthananchai, Aaron M. Dumas, and Jeffrey W. Bode**

Keywords:
catalysis · chemoselectivity · enantioselectivity · reaction mechanisms · regioselectivity

Dedicated to Professor Michael P. Doyle on the occasion of his 70th birthday

Complete control of the product of a catalytic reaction can be achieved on the basis of catalyst structure, even when the reaction conditions are nearly identical. Catalyst-controlled selectivity is well established for enantioselective catalysis but less formulated for catalytic regio-, chemo-, or product-selective reactions. This Review describes selective transformations of the same starting materials into two or more different products simply by the choice of catalyst. By collecting and highlighting examples of selective catalysis, we hope that the field will be encouraged by the progress that has been made while bringing attention to unmet needs in the design and mechanistic understanding of selective catalysts.

From the Contents

1. Introduction and Overview

Synthetic organic chemists are now widely versed in the concept and practice of catalytic enantioselective synthesis. Although designing ligands and catalysts to affect reactions in an enantioselective fashion is still considered to be difficult, the field has made incredible strides over the last 30 years.[1] The idea of using a chiral ligand or catalyst in a substoichiometric manner is now second nature, and even new reactions are often quickly rendered enantioselective by choosing one of the privileged ligands or catalysts that have proven so successful in other asymmetric reactions.[2] Furthermore, the availability of chiral ligands and catalysts has increased dramatically. The early successes with chiral ligands for transition metals and Lewis acids have now been expanded to include phase-transfer catalyst, chiral Lewis bases, and chiral protic acids as general platforms for designing and developing enantioselective reactions.

The underlying principle of catalytic enantioselective reactions is widely understood and easily represented in an energy diagram. In the simplest case, a prochiral or racemic starting material can be converted to either enantiomer of a chiral product. When an enantiopure catalyst is used, the pro-*R* and pro-*S* transition states are diastereomeric and may have different energies (Figure 1 a); if there is a difference in activation energy, one of the product enantiomers will be formed selectively. Many catalytic reactions are also subject to an uncatalyzed background reaction that gives an equal mixture of the enantiomeric products. Overcoming the background reaction as well as avoiding epimerization of the products is essential to achieving high enantioselectivity. A reaction that delivers the enantiomeric products in a ratio of 40:1 ratio or better (>95% enantiomeric excess or $>2.50\,\text{kcal mol}^{-1}$ energy difference at 23 °C) is generally considered to be "highly selective."

The overt application of the same analysis to other classes of catalyst-controlled selectivity is less common. In addition to enantioselectivity, three other types of selectivity are commonly recognized and described by a seminal review by Trost:[3] diastereoselectivity, regioselectivity, and chemoselectivity. In many cases, simple reaction diagrams cannot be drawn as easily to explain the selectivity. Incongruent transition states, thermodynamic stability of the products,

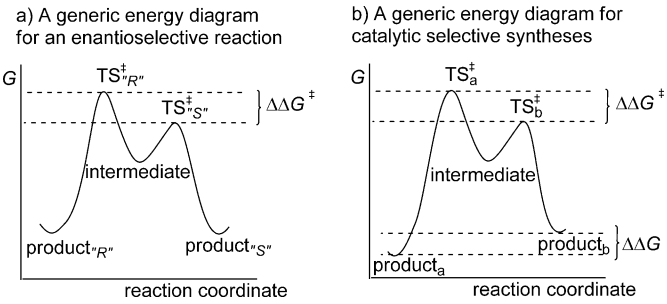
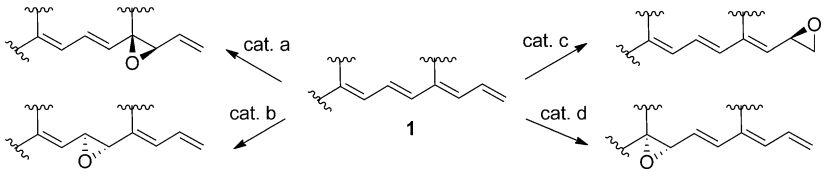


Figure 1. Energy diagrams of an enantioselective reaction and a catalytic selective synthesis. TS = transition state.

and equilibrium processes may all be involved in determining the overall outcome of such reactions. Despite these potential complications, there is growing recognition that all classes of selectivity can be exquisitely controlled by the design and choice of the appropriate catalyst. Subtle modifications to the catalyst or ligand structure can lead to divergent products, often with surprisingly high selectivity. In many, but not all, of

[*] J. Mahatthananchai, Dr. A. M. Dumas, Prof. Dr. J. W. Bode
Laboratorium für Organische Chemie, Department of Chemistry and Applied Biosciences
Swiss Federal Institute of Technology (ETH) Zürich
Wolfgang Pauli Strasse 10, 8093 Zürich (Switzerland)
E-mail: bode@org.chem.ethz.ch
Homepage: http://www.bode.ethz.ch/

these scenarios, the energy difference between two transition states comprised of the same substrates and nearly identical catalysts determines the selectivity of the reaction. Such reactions can be also be represented by an energy diagram (Figure 1b) and interrogated using many of the same kinetic and mechanistic probes commonly employed in the study of catalytic, enantioselective reactions. This Review will cover recent developments in the field of catalytic selective synthesis and will consider reactions in which the same substrate, under otherwise nearly identical conditions, gives different products by a change in the structure or type of catalyst.

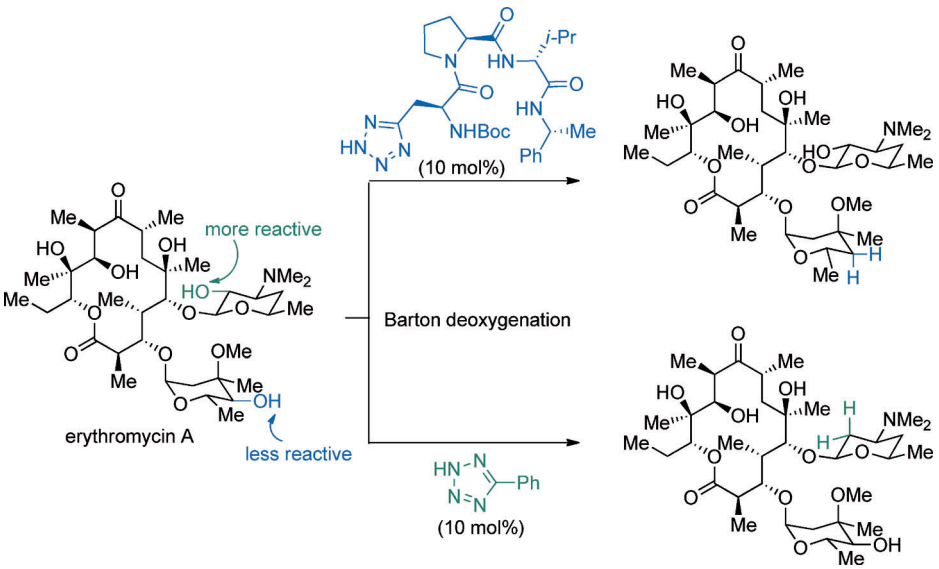


Scheme 1. Ideal catalytic site- and enantioselective monoepoxidations of tetraene.

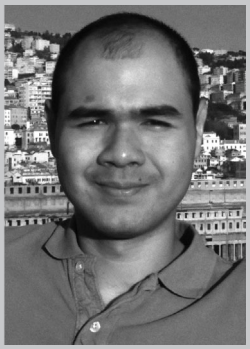
2. Motivation

The remarkable power of catalysis to affect exquisitely selective reactions, often at sites with little or no innate reactivity, is beautifully exploited by Nature's catalysts, enzymes, to produce small-molecule building blocks and to site-specifically modify complex organic structures including proteins and nucleic acids. The desire of organic chemists to gain a similar level of control over reaction outcomes by catalyst design and reaction development has been articulated by many of the leading researchers in this field. For example, Sharpless posited the problem of catalytic enantioselective and chemoselective monoepoxidation of alkenes in his Nobel-prize lecture.[4] The ideal would be four distinct catalysts to perform, in this case, site- and enantioselective epoxidations of a tetraene such as **1** (Scheme 1).

Miller et al. have formulated the inherent challenge in catalytic methods for specific functionalizations of complex molecules with multiple reactive sites.[5] Their work on selecting active catalysts from a large library of peptide-based scaffolds for late-stage Barton deoxygenation of poly-hydroxylated natural products at a specific site illustrates both a promising approach to this challenge, as well as the current limitation of small-molecule catalysis (Scheme 2).[6] Enzymes routinely accomplish such precise modifications of natural products but organic chemists are only now beginning to make progress in addressing these kinds of selectivity issues.

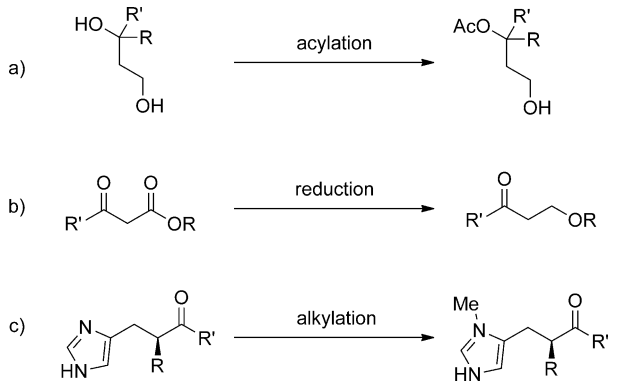


Scheme 2. Site-selective deoxygenation of a poly-hydroxylated natural product erythromycin A.



Jessada Mahatthananchai received his B.A. in 2009 from Skidmore College (New York), where he performed his research with Prof. Raymond J. Giguere. After receiving his M.S. from the University of Pennsylvania in 2010, he relocated with the group of Prof. Jeffrey W. Bode to ETH-Zürich to pursue his doctorate in organic chemistry. His research focuses on developing selective reactions catalyzed by N-heterocyclic carbenes.

Aaron M. Dumas received his B.Sc. from the University of Ottawa in 2004, where he conducted research with Prof. Alex Fallis. He performed his doctoral studies at the University of Waterloo with Prof. Eric Fillion on new reactions of alkylidene Meldrum's acids and earned his Ph.D. in 2009. Since 2010, he has been a postdoctoral researcher in the group of Prof. Jeffrey W. Bode at ETH-Zürich, where he has developed novel reagents and reactions for chemoselective amide-bond formations.



Scheme 3. Challenging selective transformations.

Scheme 3 depicts seemingly simple transformations for which no direct catalytic method is available. Current practice would rely on protection/functionalization/deprotection sequences to accomplish them. While this technology is highly reliable, it adds synthetic steps, decreases overall yields, and generates chemical waste.[7] The power of new catalytic methods lies in their ability to offer synthetic routes to previously inaccessible chemical pathways.

We have two motivations for writing this Review. First, we believe that the area of selective catalysis will continue to grow in importance and prominence over the coming years. Catalytic *enantioselective* synthesis has emerged as the pinnacle of achievement in small-molecule catalysis. The accomplishments are indeed incredible, but the emphasis on enantioselectivity often masks the challenges of regio-, chemo-, and diastereoselectivity. As Trost has asserted, engineering a catalyst that completely overrides inherent regio- or chemoselectivity to give exclusively the desired product requires creativity and insight.[8] These skills and accomplishments should be appreciated even when the products are not chiral or when a chiral catalyst is used to functionalize a molecule with preexisting chiral centers or even none at all.

Second, despite the rapid growth of publications documenting examples of selective catalysis, there has been no formal collection of recent advances. We hope to provide a reference work that captures the state of the art in selective catalysis up through early 2012. Further, we hope to remind our readers that the analysis of such reactions using the tools of physical organic chemistry can provide important insights into the origin of the unusual selectivities and provide a physical basis for often surprising outcomes. An improved mechanistic understanding of how such reactions and catalysis operate will aid the deliberate development of new catalysis designed to accomplish specific tasks in selective transformations of a given substrate.

Jeffrey W. Bode was introduced to the concept of catalytic selective synthesis while performing undergraduate research with Prof. Michael P. Doyle at Trinity University in San Antonio, Texas. Following doctoral studies at the California Institute of Technology and ETH-Zürich with Prof. Erick M. Carreira, and postdoctoral research at the Tokyo Institute of Technology with Prof. Keisuke Suzuki, he began his independent academic career at the University of California, Santa Barbara in 2003. In 2010, he moved to ETH-Zürich as a full professor. His research and teaching have been recognized by numerous awards, most recently the ACS E. J. Corey Award (2011).

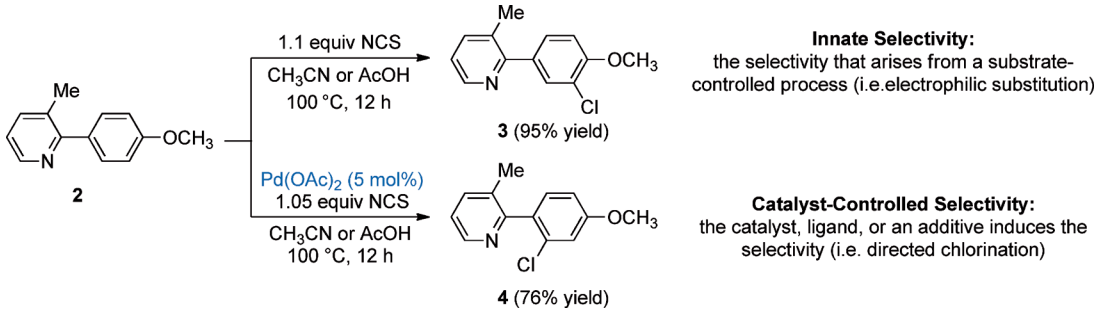
3. Innate Reactivity: the "Background Rate" of Catalytic Divergent Synthesis

All reactions that form chiral centers will necessarily give racemic products when conducted in the absence of a chiral, non-racemic catalyst. In many cases, such as in the catalytic enantioselective addition of a Grignard reagent to an aldehyde, the uncatalyzed reaction competes with the catalyzed process; this background reaction diminishes the influence of the chiral catalyst. In the same vein, any kind of selective catalytic process may compete with the innate reactivity of a substrate (Scheme 4). This innate reactivity can lead to a different undesired product or a mixture of products. The directed, palladium-catalyzed chlorination of arenes is an excellent example. In the absence of catalyst and under identical reaction conditions, **2** is selectively chlorinated by NCS *ortho* to the methoxy group. In the presence of $Pd(OAc)_2$, the catalytic pathway outcompetes the innate one and leads to the selective formation of regioisomeric product **4**.[9] *Ortho*-substituted product **3** arises from the innate pathway, whose transition state is lower in energy than the desired one in the absence of a catalyst. The requirement that selective catalysis outcompetes facile innate reactivity to provide unexpected selectivities or products is an enormous contemporary motivation for the design of more efficient and effective catalysts or ligands.[10]

4. Scope of this Review

The field of selective catalysis, even excluding enantioselectivity for the moment, is a vast and rapidly expanding area of research. In order to focus on those processes for which the selectivity is controlled by the catalyst type or ligand structure, we have adopted a few guidelines to define the scope of this Review.

Nearly all catalytic reactions discussed in this Review can be encompassed into two classes, labeled below as *Class A* and *Class B*. In *Class A* reactions, the catalyst undergoes reaction with the substrate to give a common intermediate, which undergoes a subsequent, divergent reaction based on the properties of the ligand or catalyst (Figure 2). An example of *Class A* selectivity is the work of Hayashi et al. in Rh-catalyzed regioselective conjugate additions to **5**, in which the phosphine ligand **7** gives predominantly attack on the more hindered site while diene ligand **6** adds the nucleophile to the less hindered carbon.[11] Both reactions proceed through common intermediate **8**, differing only on the ligand of the Rh complex.



Scheme 4. Selective functionalization of arene by directed, palladium-catalyzed chlorination. NCS = *N*-chlorosuccinimide.

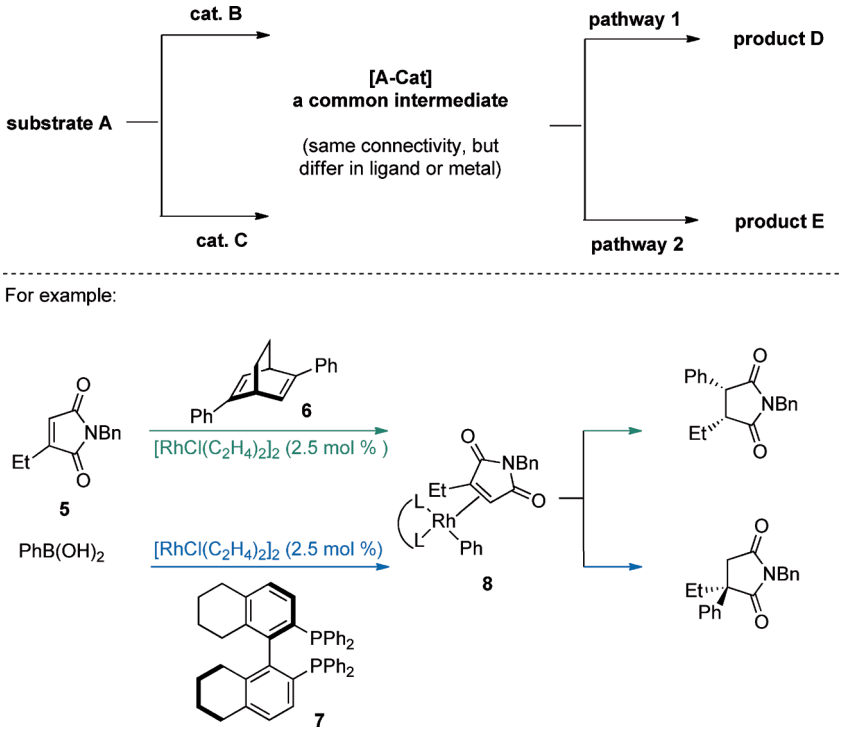


Figure 2. *Class A*: divergence from a common intermediate.

In *Class B* reactions, the initial interaction between the catalyst and the substrate leads to structurally distinct intermediates (Figure 3). Unlike *Class A* reactions, in which the initial substrate–catalyst adduct differs only in the ligand structure or catalyst type, the initially formed adducts in *Class B* reactions have divergent connectivity or structure. The formation of the product is determined by the nature of the initial adduct. An outstanding example is found in the work of Yoon et al.[12] The choice of catalyst determines how the oxaziridine collapses into a reactive 1,3-dipole; these divergent intermediates give different cycloaddition products.

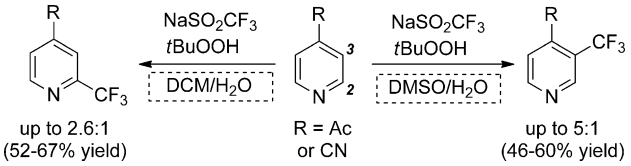
Many selective reactions mediated by factors other than the catalyst type have also been reported. While these will not be the focus of this Review, it is informative to consider the types of selective reactions that are omitted from this Review.

4.1. Solvent Effects

A common inducer of divergent selectivity is the reaction solvent. For example, Baran et al. have recently shown that trifluoromethylation of heterocycles with $NaSO_2CF_3$ is controlled largely by the choice of solvent (Scheme 5).[13] Substitution at the C2 position of 4-substituted pyridines was observed when the reaction was performed in a mixture of CH_2Cl_2/H_2O while C3 selectivity was observed in DMSO/water.

4.2. Over-Reaction

In a similar vein, subtle changes in the catalyst or ligand can lead to more or less active catalysts that determine whether or not a substrate undergoes a single or additional transformation at multiple reactive sites (Scheme 6).[14]



Scheme 5. A solvent effect on regioselectivity.

4.3. Differences in Protecting or Directing Groups

A very powerful and often-used strategy for controlling product selectivity in catalytic reactions is the installation of different protecting or directing groups onto the substrates.[15] A classic example is chelation versus Felkin–Anh diastereoselectivity in Lewis acid-catalyzed additions of nucleophiles to α-substituted aldehydes.[16] In the context of catalytic C–H activation, divergent regioselective arylation of indole was achieved by subtle changes in the structure of the N-

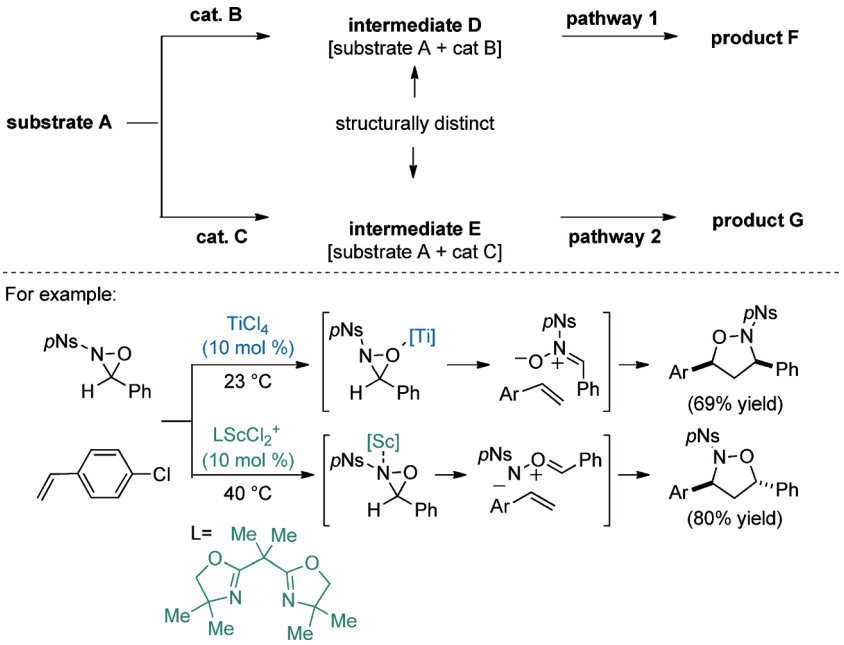
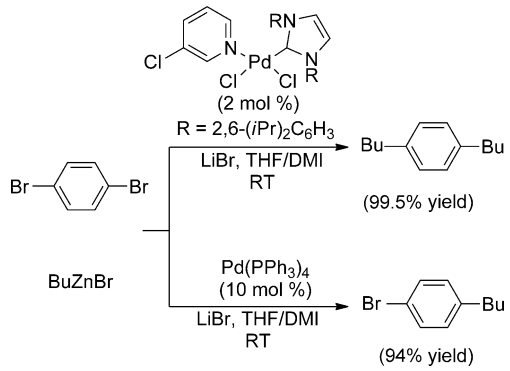
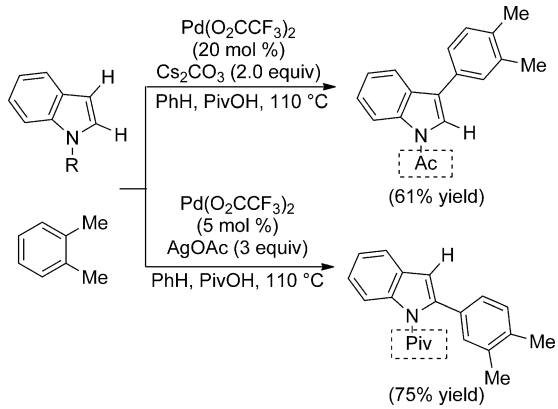


Figure 3. *Class B*: divergence from different catalyst–substrate complexes.



Scheme 6. An "overreaction". DMI = *N*,*N*′-dimethyl-2-imidazolidinone.



Scheme 7. Selectivity from a directing-group effect. Piv = pivaloyl, Ac = acyl.

protecting group (Scheme 7).[17] In this particular case, protecting group-controlled selectivity has recently been superseded by a very successful example of ligand design for catalytic regioselectivity (Scheme 14b).

The remainder of this Review collects recent examples of catalytic divergent selectivity. Most fall into *Class A* or *Class B*, but we have also included a few examples of catalytic reactions that are not easily categorized. For convenience, we have organized this Review first by the type of selectivity, followed by either the mode of catalysis or the functional groups undergoing the transformation.

5. Mechanistic Considerations

As commonly practiced in enantioselective catalysis, kinetic analysis serves as a tool for interrogating underlying mechanisms governing the enantiomeric ratio. Differential activation parameters ($\Delta\Delta G^{\ddagger}$, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) are the governing factors controlling the ratio of the two enantiomers [Eq. (1)]. These parameters can be measured directly from an Eyring plot of the natural logarithm of the enantiomeric ratio (which is a manifestation of k_{fast}/k_{slow} or $\Delta\Delta G^{\ddagger}$[18]) against the inverse temperature ($1/T$).[19] A catalytic, enantioselective transformation can be enthalpically-controlled (i.e. selectivity as a function of non-covalent binding interaction),[20] entropically-controlled (i.e. selectivity as a function of conformational flexibility),[21] or both depending on the reaction conditions (i.e. selectivity as a function of solvent effect).[22] Just like enantioselective catalysis, regio-, chemo-, and product-selective catalysis follow the same set of governing parameters for the determination of selectivity [Eq. (2)].[23,24] In these cases, the measured ratio between two outcomes is a direct measurement of the $\Delta\Delta G^{\ddagger}$ value between the two pathways, provided that the reaction is kinetically-controlled.[25] Otherwise, the free energy difference ($\Delta\Delta G$ in Figure 1b) is the deciding factor for the product distribution in a thermodynamically-controlled process.

Enantioselective catalysis :

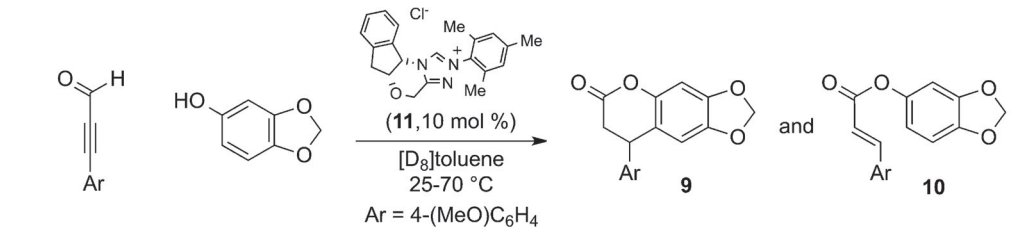
$$\ln[\text{e.r.}] = \ln\left[\frac{\text{Enantiomer1}}{\text{Enantiomer2}}\right] = \frac{-\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R} \quad (1)$$

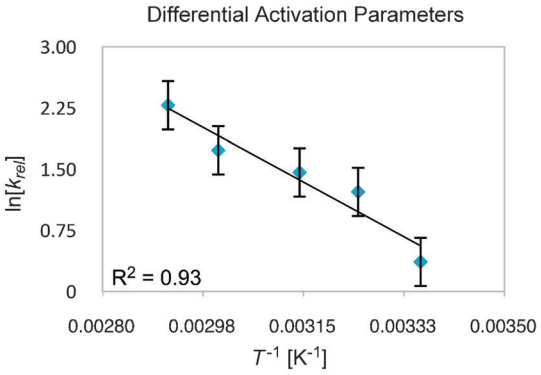
Other selective catalysis :

$$\ln[k_{rel}] = \ln\left[\frac{\text{Product1}}{\text{Product2}}\right] = \frac{-\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R} \quad (2)$$

We have shown previously that this kind of "partition experiment" can be useful in terms of deciphering the reaction mechanism and is particularly illuminating for the improvement of a selective catalytic process. In our study of the reaction of catalytically generated α,β-unsaturated acyl

a) A partition experiment:



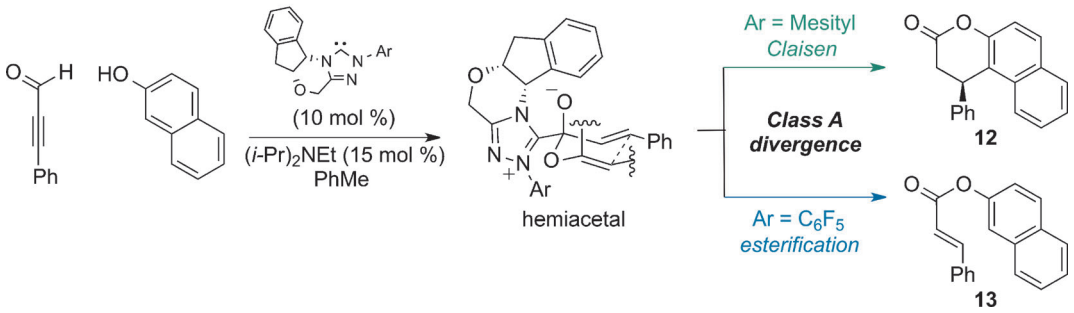


T(°C)	% 9	% 10	k_{rel}(9/10)	$\Delta\Delta G^{\ddagger}$
25	14	20	1.43	-0.33
35	16	54	3.38	-0.59
45	14	60	4.29	-0.86
60	13	73	5.62	-1.26
70	8	78	9.75	-1.53

($\Delta\Delta G^{\ddagger}$ in kcal/mol)

$\Delta\Delta H^{\ddagger}$ = 7.61 kcal mol^{-1}
$\Delta\Delta S^{\ddagger}$ = 26.62 cal K^{-1} mol^{-1}

b) An improved catalyst-controlled selective process:

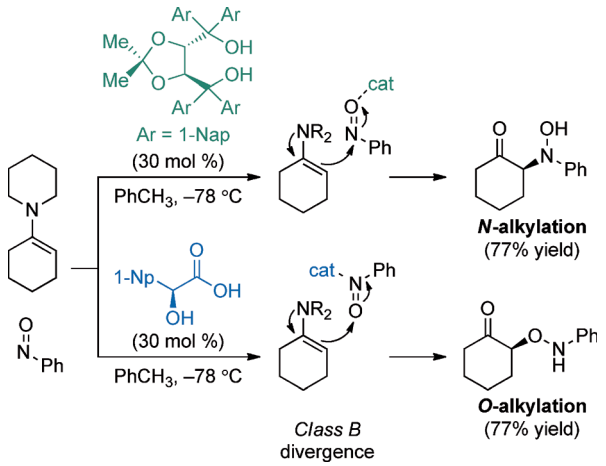


Scheme 8. Differential activation parameter measurement for product-selective catalysis.

azolium ions, we found that this species undergoes a facile acylation with nucleophile such as sesamol.[26] Two products **9** and **10** are derived from two distinct pathways, diverging from a common intermediate (Scheme 8a). The mode of reactivity of this particular N-heterocyclic carbene(NHC)-catalyzed reaction of an ynal and a nucleophile is governed by the pathways available to this hemiacetal—that is by the difference in the free energies of activation of the product-determining step.[27] We measured $\Delta\Delta H^{\ddagger}$ of 7.61 kcal mol^{-1} and $\Delta\Delta S^{\ddagger}$ of 26.62 cal K^{-1} mol^{-1} from an Eyring analysis of the product ratio (k_{rel} = %**9**/%**10**) over five temperatures (see plot in Scheme 8). These values paralleled the data obtained from the absolute rate analysis and substantiated our mechanistic proposal, in which the hemiacetal is the product-determining intermediate (*Class A* divergence). Following the mechanistic rationale deduced from this experiment, we developed a catalyst-controlled approach to selectively favor either esterification (**13**) or the Claisen rearrangement (**12**) pathway (Scheme 8b).[28] The mesityl moiety of the NHC catalyst is hypothesized to prolong the lifetime of the hemiacetal, allowing the right conformation for the rearrangement to be found (high $\Delta\Delta S^{\ddagger}$ value). In contrast, the N-C_6F_5 group renders its corresponding carbene a better leaving group, accelerating C–C bond cleavage during catalyst turnover.

6. Catalytic Regioselective Functionalization

Regioselectivity arises from a directional preference during bond formation or cleavage. In contrast to chemoselective reactions, where discrimination occurs between functional groups with their own distinct reactivity, regioselectivity is the differentiation of a single site among two (or more) positions *within the same functional group*. Regioselective catalysts, therefore, must exploit or overcome inherent steric and electronic asymmetries within the functional group in order to give regioenriched products. As will be shown below, catalysis can provide a useful means of enhancing a given regioisomeric preference, and in some



Scheme 9. Regioselective alkylation of nitrosobenzene.

cases of even reversing it. This concept can be illustrated by the example in Scheme 9, where the two electrophilic sites of nitrosobenzene are discriminated by the choice of catalyst, leading to completely *N*- versus *O*-alkylation of enamines.[29]

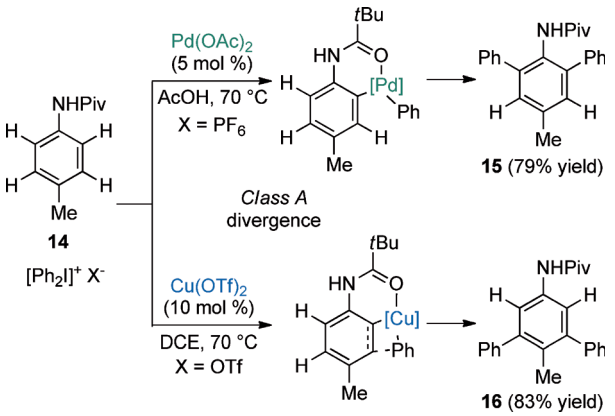
The advantage of regioselective catalysis lies in its ability to provide products in which the starting material has been transformed preferentially into a single regioisomer. This allows selective targeting of the location of a functional group in the product, and therefore control of the overall position of the atoms within the molecule. In this regard, regiocontrol can be considered complementary to enantioselectivity, since the location of the functional groups within a molecule can be just as important to its properties and function as the configuration of the stereocenter.

6.1. Regioselective Functionalization of Arenes

The positional preference in the functionalization of benzenoid arenes by electrophilic aromatic substitution is a prototypical example of regioselectivity. The electronic bias induced by the substituents on the arene and either the steric repulsion or covalent interaction between the activated electrophile and the π-nucleophile dictate *ortho*, *meta*, or *para* selectivity during the substitution. Although the standard concept that electron-donating groups are *ortho*/*para*-directing while electron-withdrawing groups are *meta*-directing still provides a useful predictor in electrophilic aromatic substitutions, the proliferation of new methods of aromatic C–H functionalization, particularly those based on transition-metal catalysis, cannot always be rationalized on a strictly Friedel–Crafts-type basis. For example, the "concerted metalation-deprotonation" (CMD) mechanism has been advanced as a general framework for rationalizing and predicting C–H functionalization for a wide range of (hetero)aromatics.[30]

In the following discussion, few examples are provided where an obvious directing effect of a substituent is the primary determinant of the regioselectivity—in particular those reactions in which a metallacycle is a putative intermediate and the substituent serves as a ligand for the catalyst. This has been an incredibly active area of research over the past decade, and numerous reviews dedicated to the topic have appeared.[31] The emphasis here is placed on examples where the same arene can be functionalized at different positions based on the choice of catalyst, or where substitution occurs at a site not predicted by conventional analysis.

Regioselective arylation of electron-rich pivanilides with diaryliodonium salts has been achieved with both Pd and Cu catalysis (Scheme 10). In the former case, Daugulis et al. demonstrated that $Pd(OAc)_2$-catalyzed arylation of **14** occurs

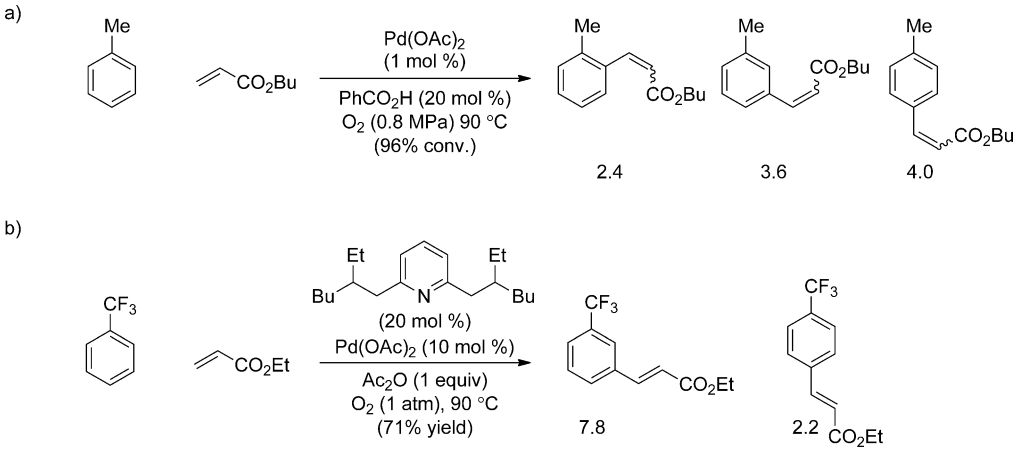


Scheme 10. Regioselective arylation of pivanilides. DCE = 1,2-dichloroethane.

in acidic solvent to give exclusively **15**; this reaction likely proceeds through a palladacyclic Pd^{II}/Pd^{IV} pathway to afford only di-*ortho* substitution (relative to the anilide).[32] *Meta* selective disubstitution of **14** can be achieved by $Cu(OTf)_2$ catalysis, as recently disclosed by Gaunt et al.[33] Computational studies suggest that anilide–Cu complexation plays a key role in the selectivity, but in this case carbocupration delivers *meta*-substituted arene **16**, rather than the *ortho* counterparts through reductive elimination as with Pd.[34]

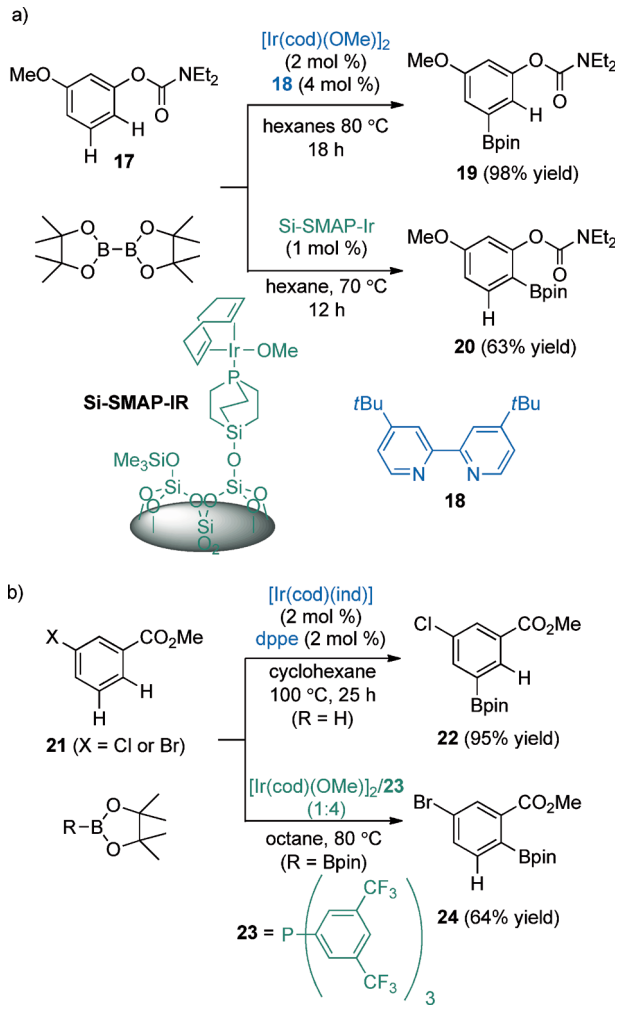
Direct oxidative olefination of arenes is a potentially useful means of preparing styrene derivatives from simple alkenes; however, current methods are poorly regioselective in the absence of a coordinating directing group (Scheme 11 a).[35] One factor that may prevent good selectivity in these reactions is the lack of a ligand to influence the environment around the catalytic metal center. Yu et al. have designed a bulky pyridine-based ligand that allowed the *meta*-selective functionalization of electron-poor arenes such as trifluorotoluene (Scheme 11 b).[36] Unfavorable steric repulsion between the substituent and the complex was invoked to explain the lack of *ortho* substitution. The preference for *meta* over *para* substitution could be explained either by electrophilic palladation or the greater acidity of the *meta* C–H bond.

C–H borylation of arenes by Ir^{I} catalysis is a useful method of selectively introducing a C–B functionality into (hetero)arenes.[37] With bidendate pyridine and phosphine ligands, the regioselectivity is controlled by steric factors in simple arenes, leading to *meta*-enriched arylboronates, and by electronic factors in heteroarenes such as pyridines and



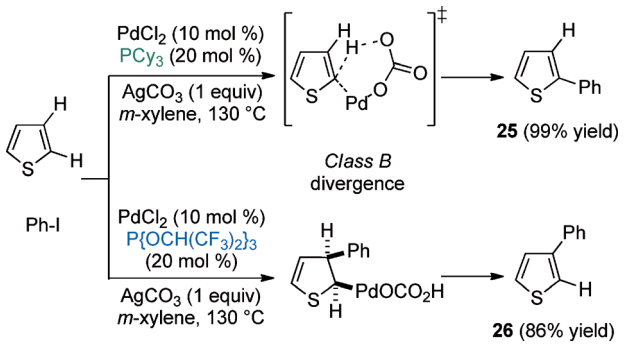
Scheme 11. Regioselectivity in direct olefination of toluene versus ligand-directed, *meta*-selective olefination of electron-poor arenes.

furans.[38] Nevertheless, ligand variation can lead to a reversal of regioselectivity (Scheme 12). In the case of phenol derivative **17**, "standard" conditions using an Ir/dtbpy complex leads to exclusive formation of *meta*-substituted **19**,[39] while the strong directing effect of the carbamate can be exploited to give *ortho*-substituted **20** when a solid-supported, monodentate phosphine is used (Scheme 12a).[40] Presumably the switch is due to the presence or absence of an open coordination site on the Ir^{III} intermediate formed from reaction of the catalyst with B_2pin_2 (*Class B* divergence mechanism). Similarly, regioselective borylation of halogenated benzoate esters **21** can be achieved based on the choice of phosphine ligand, with bidentate dppe giving *meta* product **22**[37b] and loosely coordinating, monodentate **23** giving *ortho* product **24** (Scheme 12b).[41]



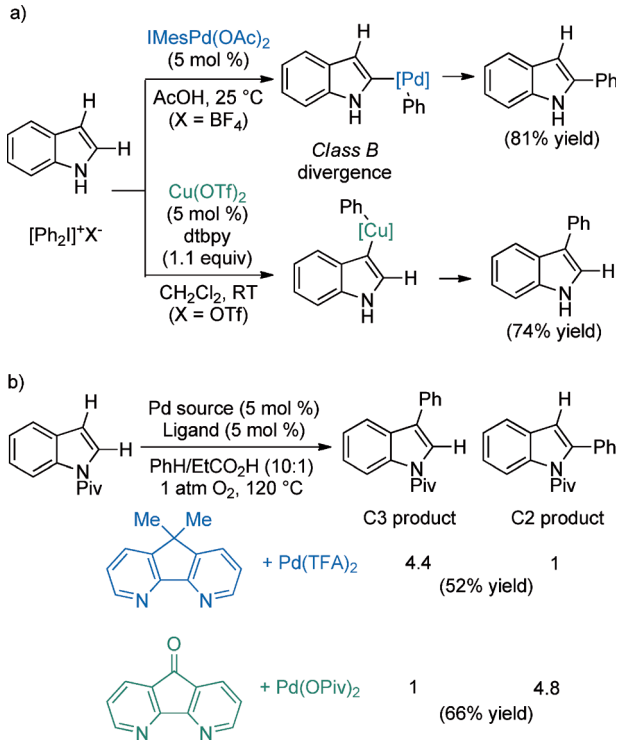
Scheme 12. Regioselective borylation of arenes. cod = cyclooctadiene, ind = indenyl, dppe = 1,2-bis(diphenylphosphino)ethane, Bpin = pinacolboryl.

Selective functionalization of heteroarenes is equally important but is often more difficult as the presence of heteroatoms within the ring induces large electronic asymmetries while coordination to the catalyst can lead to strong directing effects. In the case of thiophene, Itami et al. have shown that Pd-catalyzed arylation occurs at the more common α-position when the electron-rich phospine PCy_3 is used as ligand (Scheme 13). However, the selectivity can be nearly completely reversed by the use of electron-poor phosphite ligand $P[OCH(CF_3)_2]_3$.[42] Computations suggest that α-selectivity arises through concerted metalation-deprotonation, while a Heck-type carbopalladation gives the β product.[43] This structural isomers **25** and **26** are formed through *Class B* divergence.

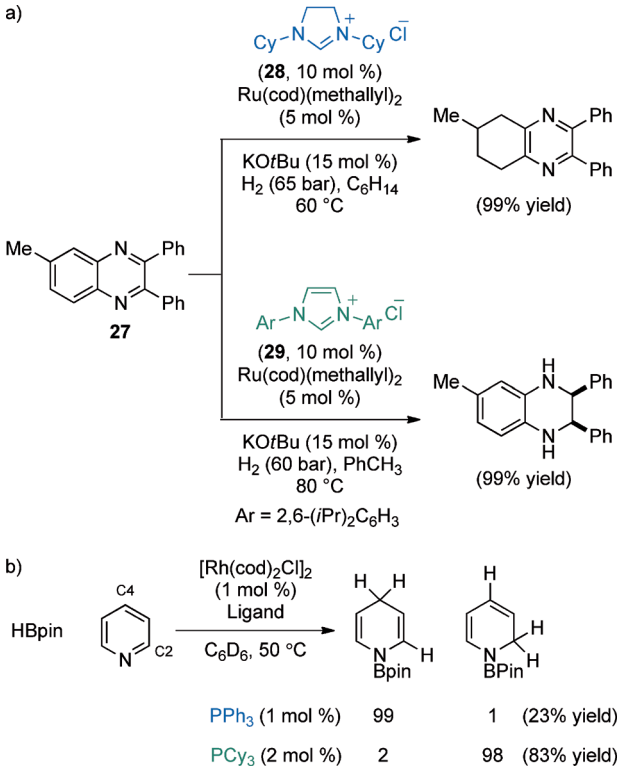


Scheme 13. Regioselective arylation of thiophene.

Indole has been intensely studied as a substrate for direct arylation; significant progress has been made in identifying conditions and catalysts for the regioselective functionalization of either the C2 or C3 positions. As in direct arylation of pivanilides (Scheme 14), regiodivergent arylation of unprotected indoles can be achieved by use of either Pd or Cu



Scheme 14. Regioselective arylation of indole controlled by a) choice of catalyst and b) choice of ligand. dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, TFA = trifluoroacetate.



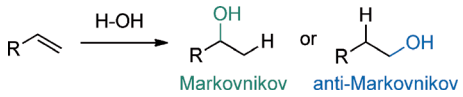
Scheme 15. Regioselective reductions.

catalysis (Scheme 14a). In this case, a Pd^{II}/Pd^{IV} cycle provides exclusive C2 arylation,[44] while the proposed Cu^{I}/Cu^{III} cycle leads to highly selective C3 arylation (C3:C2 12:1–14:1).[45] Interestingly, while both catalysts were thought to metallate indole at C3, rapid C3 to C2 migration for Pd was proposed to account for the formation of 2-phenylindole in that case. Reversal of regioselectivity in Pd-catalyzed arylations of indoles has also been observed through modification of added bases[46] or oxidants,[47] and very recently simply by tuning the properties of the ligand. Stahl et al. reported that C2 versus C3 selectivity could be altered based on the nature of the bridging functionality in the bipyridine ligands used (Scheme 14b); the origins of this effect are currently unknown.[48]

Catalyst-controlled, regioselective reductions of arenes are also possible. Glorius et al. described the reduction of quinoxalines **27** by NHC–Ru complexes, where either the all-carbon benzenoid ring or the heterocycle can be selectively reduced (Scheme 15a).[49] In this case, dihydroimidazolydene NHC ligand **28** gives completely selective reduction of the benzenoid portion of the molecule, while the unsaturated and aryl-substituted NHC **29** gives a complex that exclusively reduced the pyrazine portion. An explanation for this exquisite selectivity has not yet been proposed. Suginome et al. demonstrated regioselective hydroboration of pyridine under Rh^{I} catalysis (Scheme 15b). Highly selective, albeit low yielding, addition to C2 occurs with PPh_3 as ligand, while nearly complete C4 selectivity is observed using PCy_3.[50] Selective C2 hydroboration of pyridine has also been achieved with a Mg-based catalyst.[51]

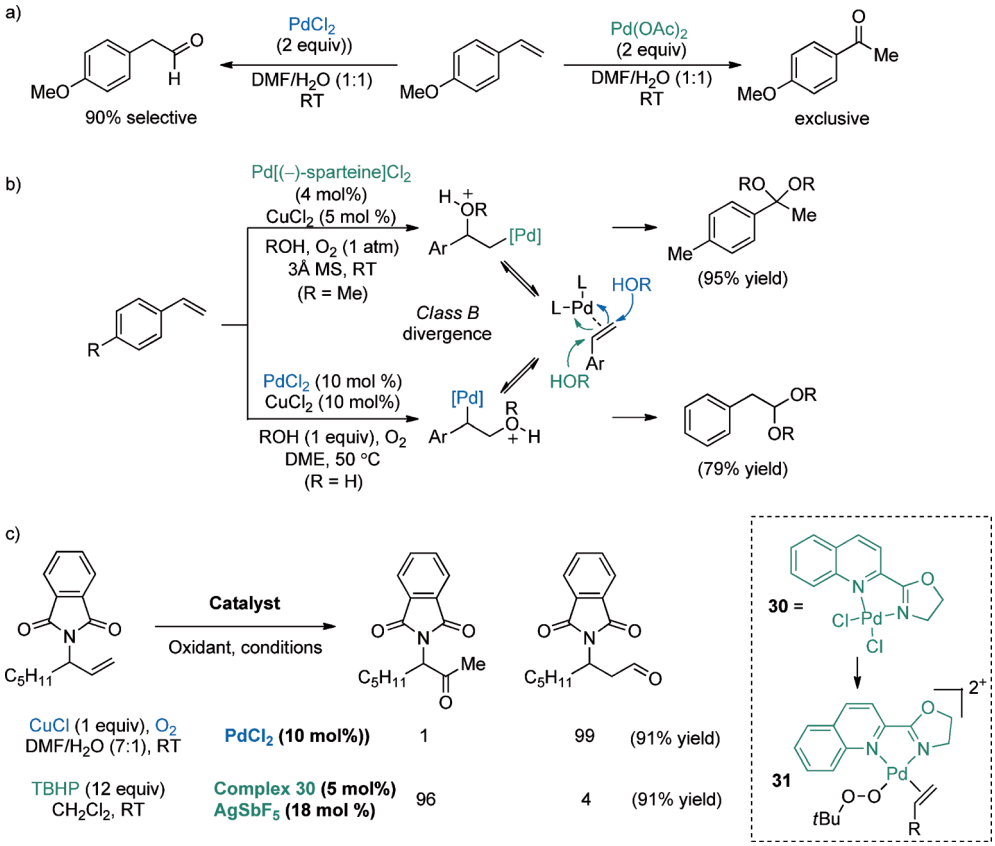
6.2. Regioselective Functionalization of Alkenes

Alkenes are among the most common feedstock chemicals, and their transformation into more elaborate derivatives by functionalization of the C=C bond is a mainstay of new reaction development. As with arenes, one of the key issues is controlling the site of substitution or addition to lead to one regioisomer or the other.[52] A generic example illustrating this using the prototypical reaction of alkene hydration is shown in Scheme 16.



Scheme 16. Regioisomers of alkene hydration.

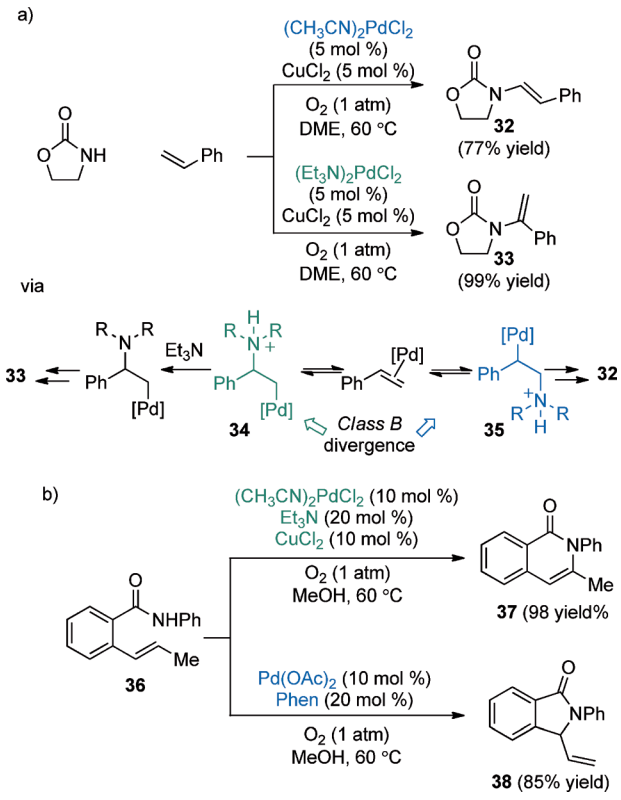
As recently emphasized by Hintermann et al., regioselective alkene hydration remains a challenging transformation, and essentially all direct catalytic methods remain largely under Markovnikov control.[53] On the other hand, recent work on *oxidative* hydration of alkenes by the Pd-catalyzed Wacker oxidation has led to the development of highly regioselective protocols that either enhance or reverse the innate selectivity of such reactions (Scheme 17). In fundamental stoichiometric reactions without an external oxidant, Spencer et al. have demonstrated that regioselectivity in the oxidation of 4-methoxystyrene can be controlled simply by the choice of Pd^{II} counterion, with acetate giving the Markovnikov ketone product and chloride the anti-Markov-



Scheme 17. Regioselective Wacker oxidations. TBHP = *tert*-butyl hydroperoxide.

nikov aldehyde (Scheme 17a).[54] This was proposed to arise from different modes of coordination of the catalyst to the double bonds in the starting material. In catalytic reactions of the related Wacker acetalization (Scheme 17b), conditions developed by Hosokawa et al. using $PdCl_2$ in DME solvent lead to the anti-Markovnikov oxidation of styrene.[55] The regioselectivity can be reversed by the use of $PdCl_2$·sparteine complex, as reported by Sigman et al.[56] The divergence has been explained by a reversible nucleopalladation step, wherein unligated Pd catalysts follow the thermodynamic anti-Markovnikov pathway while the sparteine complex gives the kinetic Markovnikov intermediate. Wacker oxidations of α-heteroatom terminal olefins have typically either poor or unpredictable selectivity, making the innate "preference" of a particular alkene difficult to judge a priori. In an interesting improvement of innate selectivity in such reactions, Feringa et al. demonstrated that phthalimide is a general controlling element that gives essentially perfect anti-Markovnikov selectivity (Scheme 17c).[57] Even more impressively, Sigman et al. have shown that specially designed Pd complex **30**, combined with the use of *t*BuOOH as oxidant, gave nearly complete selectivity for the Markovnikov ketone product, featuring an exquisite ligand-controlled process.[58] Detailed kinetic studies and synthesis of electronically distinct ligand frameworks suggest that a well-organized cationic Pd–alkene complex such as **31** leads to the observed high selectivity.[59]

The aza-Wacker reaction using O_2 as the terminal oxidant developed by Stahl et al. is a highly Markovnikov-selective method of preparing enamines from simple alkenes and amines (Scheme 18a).[60] Regioselectivity in the addition of oxazolidinone to styrene was found to be remarkably dependent on seemingly simple changes in the catalytic system, with nitrile ligands giving anti-Markovnikov **32** and tertiary amine ligands favoring Markovnikov **33**.[61] Mechanistic investigations reveal that the likely cause of the change in selectivity upon addition of a small amount of NEt_3 to the catalyst was irreversible deprotonation of the kinetic intermediate **34**, which prevents equilibration to the thermodynamic intermediate **35**.[62] This example constitutes another case of *Class B* divergence since intermediates **34** and **35** differ in their connectivity. Selectivity in the intramolecular aza-

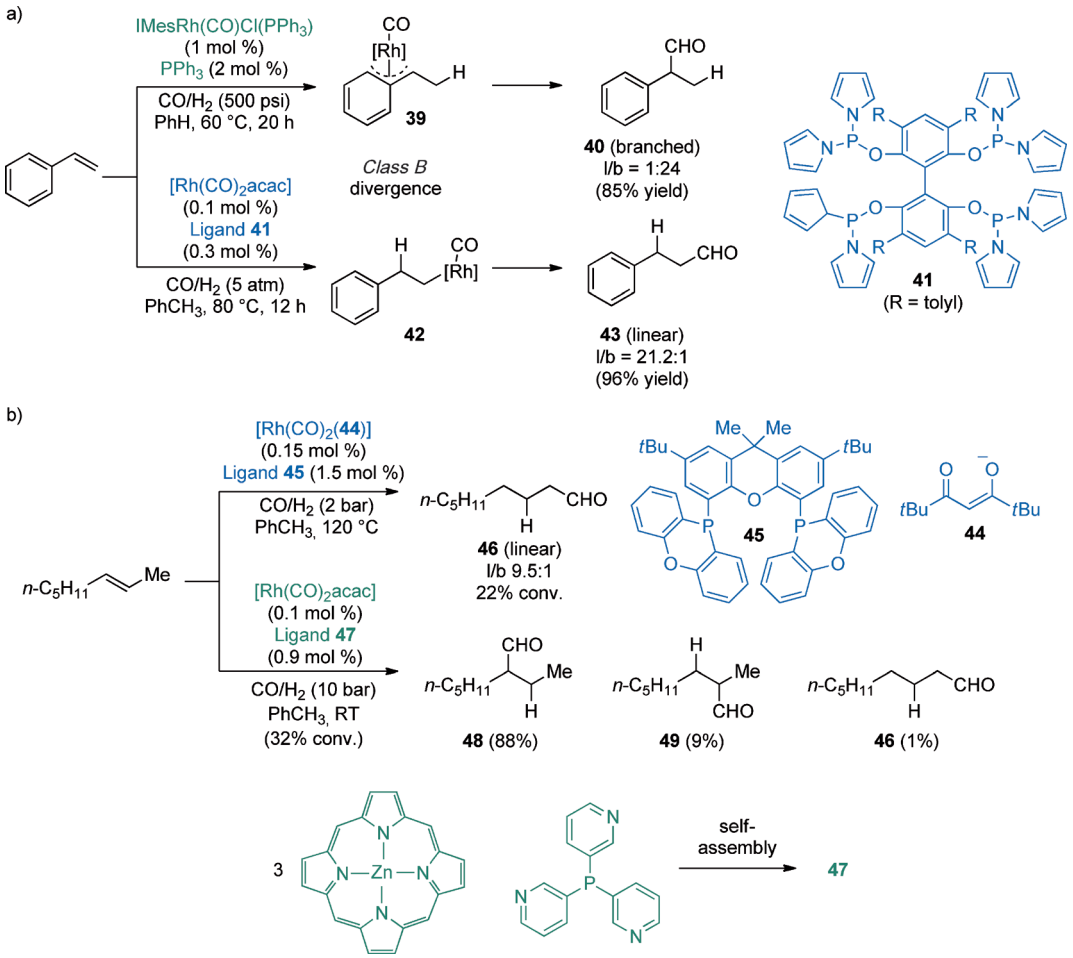


Scheme 18. Regioselective aza-Wacker oxidations. phen = phenanthroline.

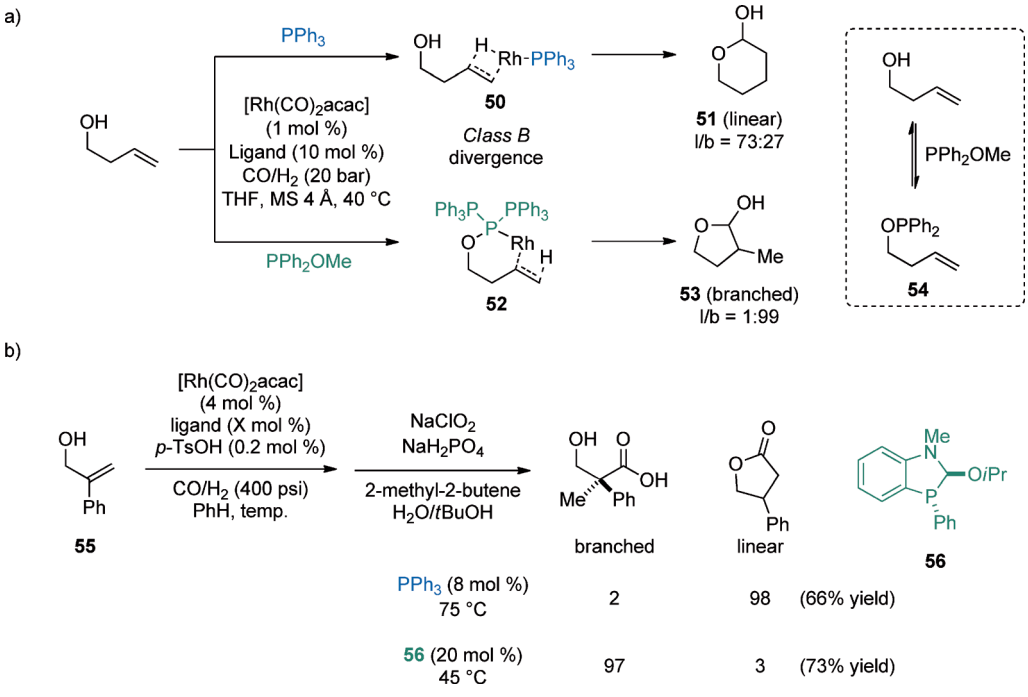
Wacker reaction of vinylbenzamides **36** to give 6-*endo* **37** or 5-*exo* **38** was recently reported; in this case, the reversal is attributed to changes in the steric bulk of the ligand (Scheme 18b).[63]

Rh-catalyzed alkene hydroformylation is one of the most important industrial processes employing homogeneous catalysts and has been studied extensively. With regard to regioselectivity, control of the linear-to-branched ratio of the aldehyde products must overcome a substantial substrate bias; styrene derivatives are branch-selective, while linear products are formed from alkyl-substituted terminal alkenes.[64] Improvements in branched/linear ratios by altering the reaction conditions or the introduction of new ligands often enhance the innate selectivity, but recently new ligands that can completely reverse the ratio of regioisomers have been described (Scheme 19). For example, hydroformylation of styrene with an NHC–Rh complex gives branched **40** through an innate pathway,[65] while bulky tetra-phosphine-based ligand **41** gives the regioisomeric linear product **43** (Scheme 19a).[66] In this case, favorable coordination of the Rh complex at the benzylic position (**39**) leads to **40**, while the steric bulk of ligand **41** places the metal on the less hindered terminal position (**42**) to yield **43**. Another important application, especially for transformation of refined crude oil fractions, is selective hydroformylation of octene isomers. van Leeuwen et al. described very bulky diphosphane **45**, which catalyzes selective formation of linear products from internal octenes such as *trans*-2-octene; this occurs through rapid double bond isomerization to 1-octene preceding the hydroformylation step.[67] On the other hand, Reek et al. have developed a self-assembled encapsulated Rh catalyst derived from **47** that not only prevents alkene isomerization, but can also distinguish the two alkene positions in *trans*-2-octene. This leads to highly selective formation of aldehyde **48** over regioisomeric branched product **49** or linear product **46** (Scheme 19b).[68]

Another highly useful means of controlling selectivity in hydroformylations is the use of scaffolding ligands that bind covalently and reversibly to the substrate, leading to a temporarily intramolecular transformation (Scheme 20). As first outlined in 2008 by both Tan et al.[69] and Breit et al.,[70] this can lead to dramatically improved and reversed selectivities in, for example, the hydroformylation of homoallylic alcohols (Scheme 20a). In this case, PPh_2OMe serves not only as a catalytic directing group for Rh but also as an electrophile for the alcohol, so that **54** becomes the active species. Whereas a ligand that cannot bind to the substrate, such as PPh_3, leads to the linear product **51** through innate pathway



Scheme 19. Regioselective non-directed hydroformylation. IMes = 1,3-dimesitylimidazol-2-ylidene.



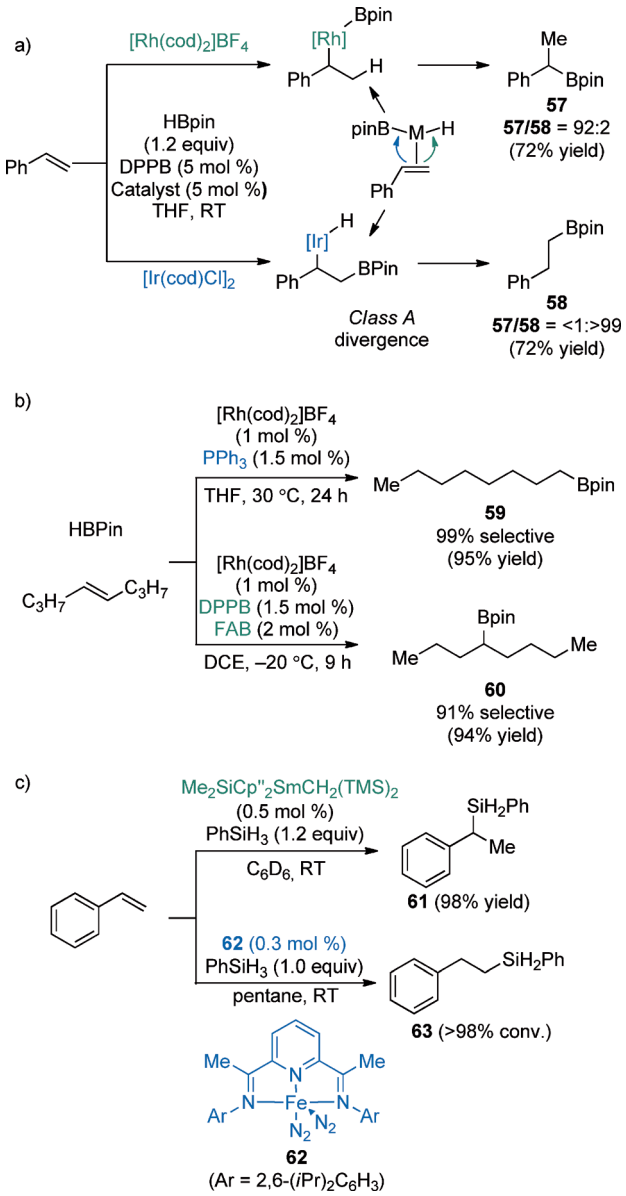
Scheme 20. Regioselective hydroformylation through reversible covalent attachment of scaffolding ligands.

50, directed hydroformylation gives branched **53** through selective 5-*endo* addition as in **52**. This powerful strategy can even be used to form quaternary centers from 1,1-disubstituted alkenes—a reaction so innately unfavorable that it has been formalized as Keulemans' rule.[71] Tan et al. described another scaffolding ligand **56** leading to highly selective formation of branched products, in which conventional PPh_3 gives essentially only the linear product (Scheme 20b).[72] As these reactions involve completely different connectivity in selectivity-determining steps, they fall under the *Class B* mechanism rubric.

Because the direct anti-Markovnikov hydration of alkenes is difficult to achieve, synthetic processes equivalent to it are highly valuable transformations.[73] The most common two-step procedure for formal hydration of alkenes to primary alcohols is the hydroboration–oxidation sequence. Catalytic hydroboration using less reactive catechol or pinacol boranes are particularly valuable. This also introduces a factor of catalyst control to the reaction, leading to the opportunity to form regioisomeric alkylboranes from common starting materials. For example, Crudden et al.[74] and Miyaura et al.[75] independently discovered the highly regiodivergent hydroboration of styrene based on the use of either Rh^I or Ir^I catalysis (Scheme 21a). In this case, the divergence can be attributed to selective alkene insertion into the Rh–H bond giving Markovnikov product **57** while insertion into the Ir–B bond gives the opposite product **58**.[74] In another interesting twist on regioselective hydroboration with HBpin, reaction of internal alkenes under Ir^I[75] or Rh^I catalysis alone gives nearly exclusive formation of the terminal boronate **59** through a series of rapid alkene isomerizations. Crudden et al. discovered that this selectivity can be reversed in favor of internal borane **60** by the simple addition of co-catalytic tris(pentafluorophenyl)-borane (FAB, Scheme 21b).[76] On the basis of NMR observation of possible catalytic intermediates, the Lewis acid was proposed to catalyze oxidative addition of the Rh^I catalyst into the H–B bond. Another important hydrometallation reaction, especially for industrial applications, is hydrosilation of alkenes. Regiodivergent hydrosilation of styrene with $PhSiH_3$, for example, can be achieved based on the choice of catalyst (Scheme 21c). Sm sandwich complexes are extremely selective for Markovnikov addition, giving **61** as the sole product under mild conditions.[77] On the other hand, well-defined low-valent iron catalyst **62** yields exclusively anti-Markovnikov product **63**.[78] Complexes related to **62** have been shown to catalyze highly anti-Markovnikov hydrosilation using tertiary silanes, including industrially relevant siloxanes.[79] A reversal of regioselectivity in hydrosilations of styrenes catalyzed by the same $[Cp_2Zr]$ ($Cp = C_5H_5$) complex has also been reported, where the regioselectivity is determined by the stoichiometry of the reductant.[80]

Buchwald et al. described a rare example of ligand-controlled regioselectivity[81] in the intramolecular Heck reaction of vinylanilines such as **64** (Scheme 22a).[82] In this case, $P(tBu)_3$ gave the six-membered Markovnikov acridine products **67**, while ligand **65** gave the seven-membered dibenzazepines **69**. A change in mechanism from a standard Heck pathway (**66**→**67**) to an electrophilic palladation (**68**→**69**) was proposed. It should be pointed out that catalyst control of the *intermolecular* Heck reaction remains a relatively undeveloped area despite considerable effort.[83] An example of regioselective hydroarylation of styrenes was reported by Yoshikai et al., in which this ligand-controlled process leads to selective formation of either Markovnikov product **70** or anti-Markovnikov product **71** (Scheme 22b). Yoshikai et al. speculate that the large IMes orients the metal center at the terminal position leading to **70**, while the favorable formation of a benzylcobalt species leads to **71**.[84]

Regiocontrol in hydrovinylation of dienes is possible using a low-valent cobalt catalyst (Scheme 23). Simple bisphosphine dppe is highly selective for the formation of the branched (Markovnikov) product **72**,[85] while phosphite-containing SchmalzPhos gives the linear product **73** with nearly perfect selectivity (3:97 branched/linear).[86] A highly linear-selective (>99:1) iron-based catalyst system for the



Scheme 21. Regioselective hydroboration and hydrosilation of alkenes. dppb = 1,4-bis(diphenylphospino)butane, FAB = tris(pentafluorophenyl)boron, Cp″ = a large cyclopentadienyl derivative, TMS = trimethylsilyl.

same reaction has also been reported, where the regioselectivity can be reversed by the choice of ligand (up to 16:84 linear/branched).[87]

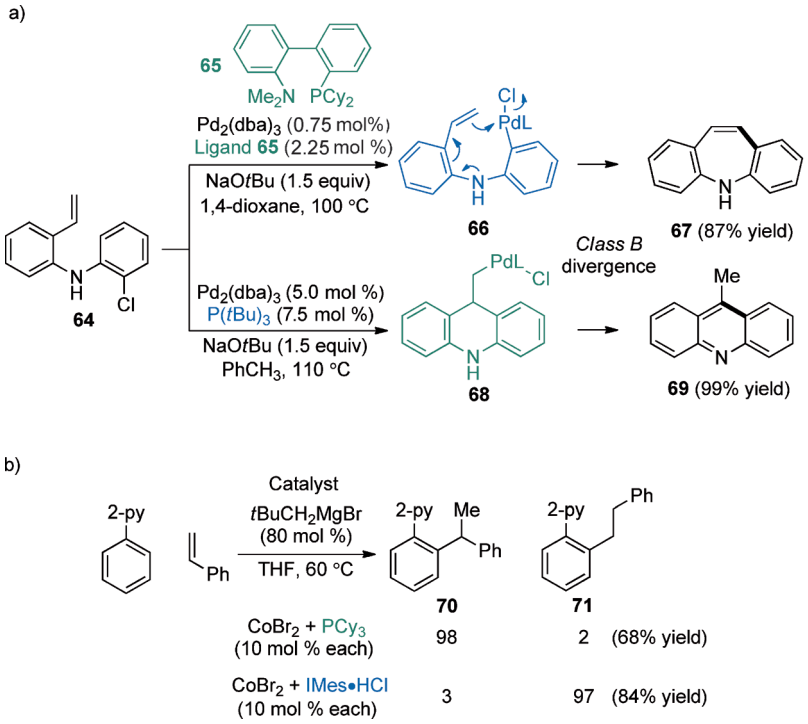
Electron-deficient alkenes conjugated with carbonyls typically react with nucleophiles with high β-selectivity due to the strongly polarized nature of the C=C bond and the favorable formation of a stabilized enolate products. The typical issue in these reactions is selective 1,4- versus 1,2-additions, examples of which are provided in Section 6.5. Nevertheless, regioselectivity must be considered when an alkene is activated at both ends by a carbonyl. Rh-catalyzed addition of phenylboronic acid to maleimide **5** (Scheme 24) could proceed by attack at either the more or less sterically hindered position. Shintani and Hayashi demonstrated that ligand control allowed selective addition to one or the other of these positions, with biphosphine ligands favoring the Markovnikov product **74** and chiral dienes giving anti-Markovnikov **75**.[11] The regioselectivity was rationalized by the different chiral environment provided by the ligand; both **74** and **75** were formed in high enantioselectivity as well.

Another interesting regiochemical switch involving electron-poor alkenes is demonstrated in [3+2] cyloadditions of nitrones with methacrolein (Scheme 25). Kündig et al. reported that cationic Fe^{II} complex **78** was highly selective for adduct **76**, where the oxygen is connected α to the aldehyde.[88] Switching to Rh^{II} catalyst **79**, β-oxygenated adduct **77** was formed as the major product (*Class A* divergence).[89] Observation of methacrolein-bound Lewis acid complexes suggested that this was the major mode of activation in both cases, although a rationale for the reversal in regioselectivity was not provided.

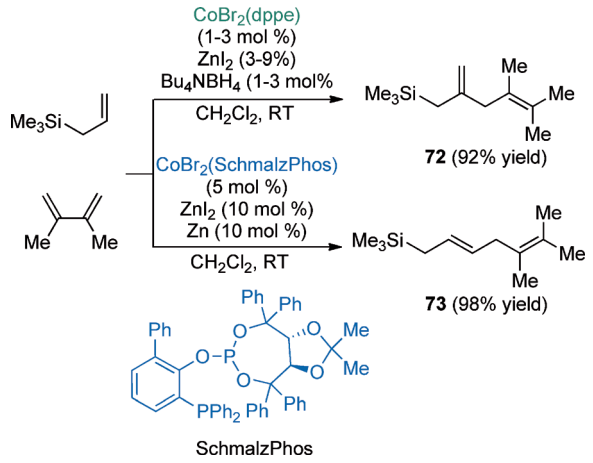
6.3. Regioselective Functionalization of Alkynes

Like alkenes, additions to alkynes can take place in two directions, and for terminal alkynes these can also be referred to as Markovnikov and anti-Markovnikov products. In Section 6.2, alkene hydration was used as an example for which a reliable regiodivergent method was lacking. In the case of terminal alkynes however, good solutions to this challenging transformation have emerged (Scheme 26). By taking advantage of the strong aurophilicity of alkynes, Nolan et al. have developed an Au–NHC complex that catalyzes the highly Markovnikov hydration of terminal alkynes, likely involving direct attack of water on a Au-activated alkyne such as **80**.[90] Hintermann et al. have described the highly anti-Markovnikov selective hydration of alkynes to give aldehydes catalyzed by a Ru-complex formed from a newly developed P,N ligand.[91] In this case, the likely intermediate is the Ru-vinylidene **81**, in which the former terminal position of the alkyne becomes the most electrophilic center, as suggested in the original report by Wakatsuki et al.[92] The difference in the mode of reactivity between Au and Ru in **80** versus **81** comprises another case of *Class B* divergence in the mechanism.

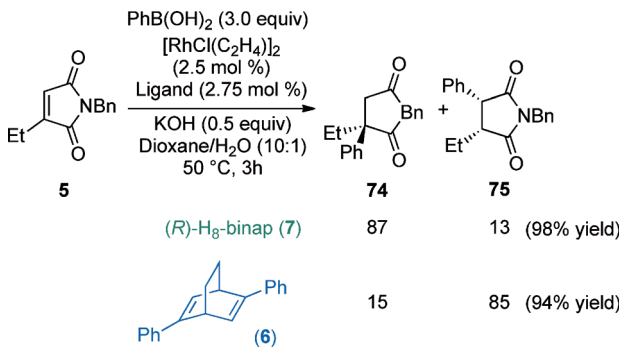
Significant progress in regioselective addition of other HX species have also been made. For example, Goossen et al. described a simple Ru-based system for nearly complete regiocontrol in the addition of carboxylic acids to alkynes to form vinyl esters (Scheme 27 a). In this case, adding a DMAP ligand to the metal center gave selective formation of the anti-Markovnikov product **82**, while the Markovnikov product **83** was formed without DMAP (*Class B* divergence).[93] Similar regiocontrol based on ligand coordination has been observed previously, however those reactions required more sensitive and less user-friendly Ru sources.[94] Catalyst controlled, regioselective intermolecular hydramination[95] and hydrothiolations[96] have also been reported. Regiocontrolled *intramolecular* additions to alkynes are possible, and the ability of a catalyst to overcome inherent kinetic ring-closure preferences in such systems is particularly emblematic of the power of new catalytic systems. For example, regioselective cycliza-



Scheme 22. Regioselective aryl additions to alkenes. dba = dibenzylideneacetone.



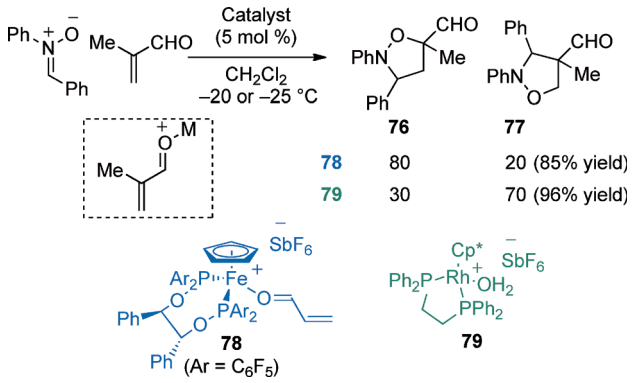
Scheme 23. Regioselective hydrovinylation of dienes.



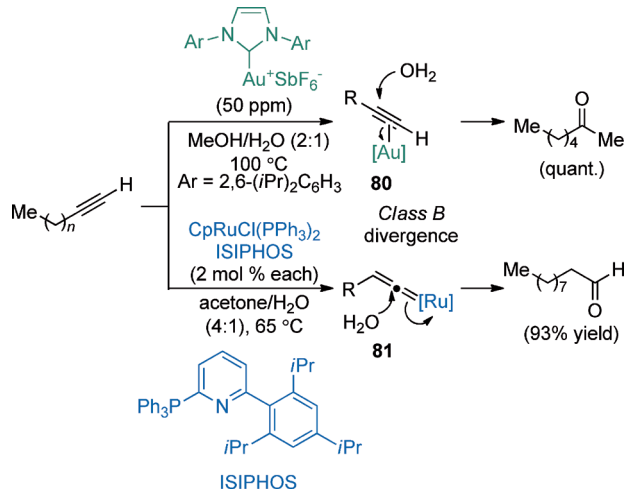
Scheme 24. Regioselective catalytic conjugate additions. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

tion of propargylguanidine **85** gives the 5-*exo* product **86** under Ag^{I} catalysis, while yielding 6-*endo* **84** with a Rh^{II} carboxylate (Scheme 27b).[97] Mechanistic studies suggest that reversible formation of a Rh^{II}-vinyl species leads to the formation of the thermodynamic 6-*endo* product since more reactive cationic Rh^{I} catalysts were 5-*exo* selective. In the homologous series, alkyne hydroamidation of amide **88** is completely selective for 7-*endo* cyclization (**87**) with $Bi(OTf)_3$, while $PtCl_2$ yields the opposite regioisomer **89** (Scheme 27c).

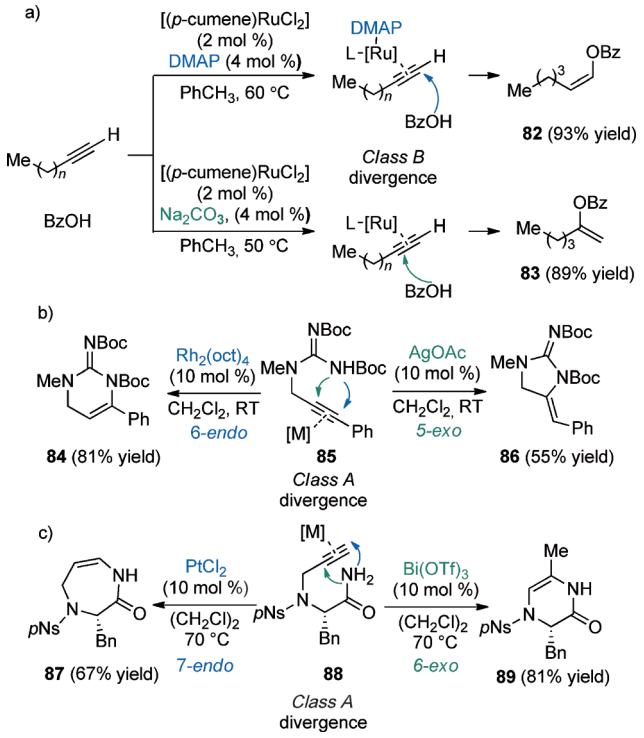
Regioselective formation of vinyl-metal species by hydrometallation of alkynes is particularly important since the products are valued as cross-coupling partners and nucleophiles. Terminal hydroboration of alkynes can be achieved with a number of catalysts, but internal (Markovnikov) hydroboration is difficult and until recently no one-step catalytic process was available. Hoveyda et al. have shown that Cu-NHC complex catalyzed hydroborations of a variety of terminal alkynes proceed with either internal (**90**) or



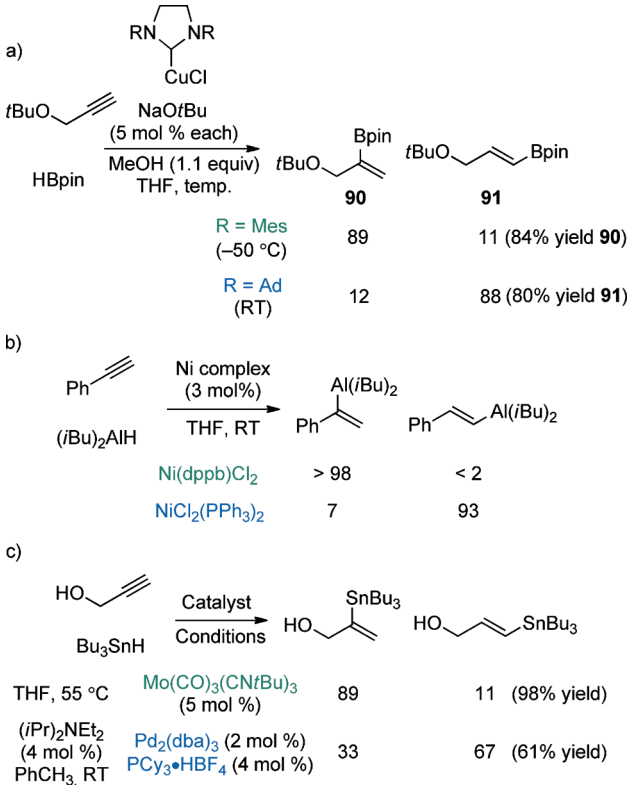
Scheme 25. Regioselective [3+2] cycloadditions.



Scheme 26. Regioselective hydration of terminal alkynes.



Scheme 27. Regioselective alkyne hydroelementalation. DMAP = 4-dimethylaminopyridine, Bz = benzoyl, Boc = *tert*-butoxycarbonyl.



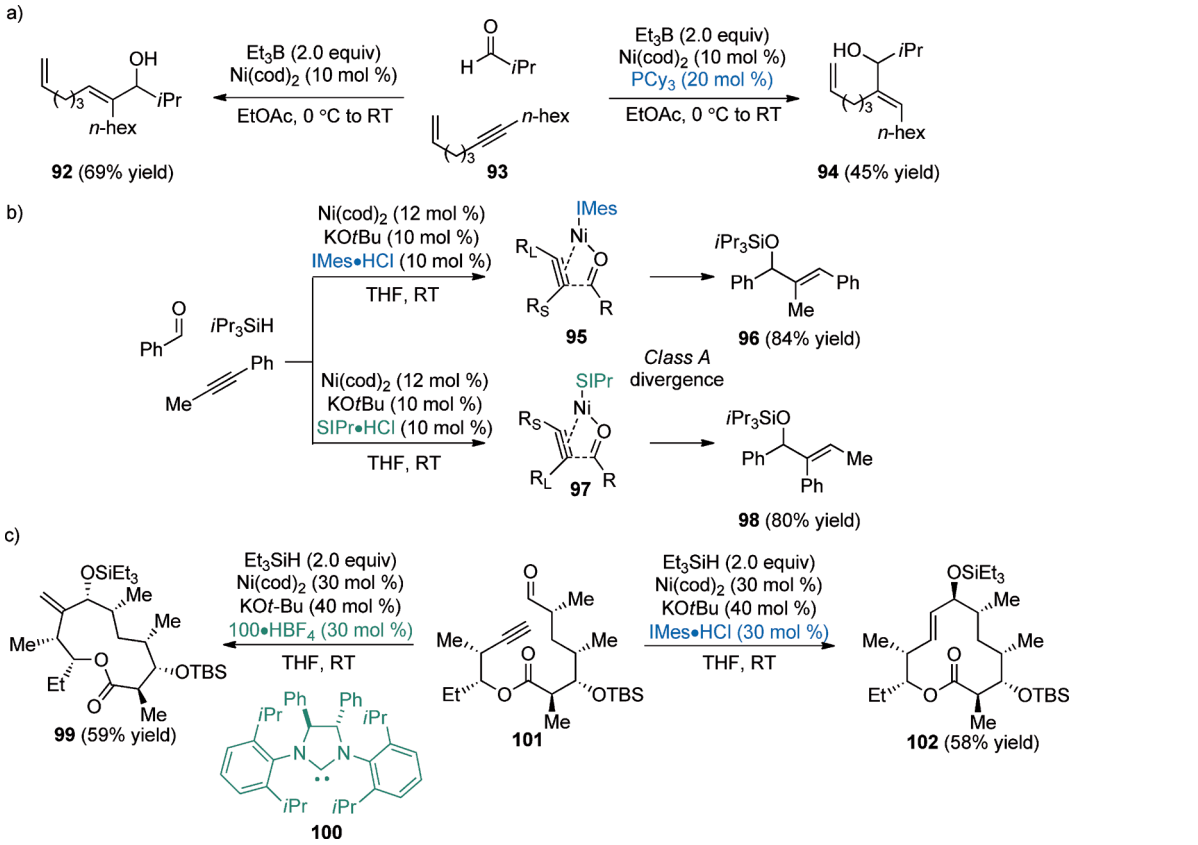
Scheme 28. Regioselective hydrometalations of alkynes.

terminal (**91**) selectivity depending on the ligand (Scheme 28a).[98] Mechanistic studies suggested that the regioselectivity arises at the stage of alkyne binding to the NHC-Cu-BPin complex, and is determined by a combination of steric and electronic factors on both the ligand and the alkyne. Pd-catalyzed regiodivergent silaboration of alkynes has also been reported.[99] Catalysis of styrene hydroalumination by Ni^{II} complexes was described by Hoveyda et al. (Scheme 28b).[100] Here, the catalyst plays an important role in determining internal versus terminal regioselectivity, as well as chemoselectivity since it modulates the basicity of Dibal-H and prevents abstraction of the relatively acidic terminal proton. Regioselective hydrostannations based on the choice of metal catalyst is also possible (Scheme 28c). Kazmaier et al. described the use of a Mo^0 catalyst containing bulky isonitrile ligands for the internal selective hydrostannation of propargyl alcohol,[101] while Chong et al. reported that trialkylphosphine ligands on a Pd center gives terminal selectivity.[102] It should be pointed out that the Chong system also dramatically improves the regioselectivity compared to more conventional $[(PPh_3)_2PdCl_2]$, which favors the internal product.

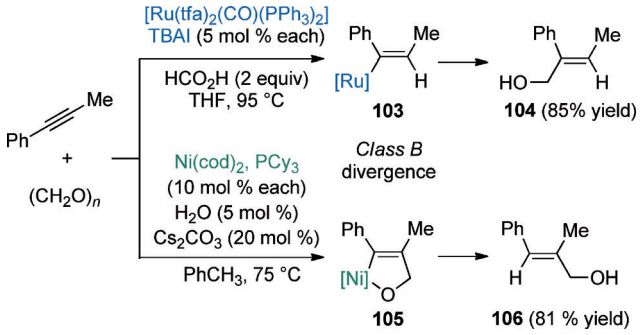
Somewhat surprisingly, catalyst-controlled regioselective C–C bond formations involving alkynes are less well developed than their heteroatom or metallic counterparts.[103] Some impressive examples have been reported for alkyne–aldehyde reductive couplings.[104] Jamison et al. first described a regiodivergent coupling of non-conjugated enyne **93** in which addition of a phosphine ligand could completely reverse the innate selectivity of the process (Scheme 29a).[105] Likewise, Montgomery et al. demonstrated that appropriate choice of ligand could reverse the regioselectivity of reductive coupling for even those alkynes with a strong preexisting bias, such as 1-phenyl-2-propyne (Scheme 29b).[106] Computational studies support a model in which the steric contour of the ligand determines the orientation of the alkyne substituents in the transitions states, with **95** leading to **96** and **97** leading to **98**, respectively.[107] This effect could even be applied in the intramolecular macrocyclizations of complex ester **101**, giving **99** and **102** as single regioisomers simply by changing the ligand—a typical example of *Class A* divergence (Scheme 29c).[108]

An interesting variation on this reductive coupling of alkynes was disclosed by Breit and Krische et al., who reported regiodivergent hydromethoxylation of internal alkynes based on the choice of metal catalyst (Scheme 30).[109] Here, Ru-catalyzed coupling of formaldehyde with 1-phenyl-1-propyne proceeds to give product **104** where the hydrogen has been added adjacent to the methyl group. Under Ni catalysis, the opposite regioisomer **105** is formed; in each case, the observed products are the only regioisomers formed. This was attributed to a change in mechanism, where hydroruthenation leads to intermediate **103** in route to **104** whereas carbonickelation gives **105** as an intermediate to **106**. This is therefore a case of *Class B* selectivity.

Some catalyst-controlled highly regioselective cycloadditions involving alkynes have been reported. Perhaps the best known example is the divergence between Cu^I- and Ru^{II}-catalyzed azide–alkyne cycloadditions. As introduced by Meldal et al.[110] and Sharpless et al.,[111] Cu catalysis is almost completely selective for the formation of 1,4-substiti-

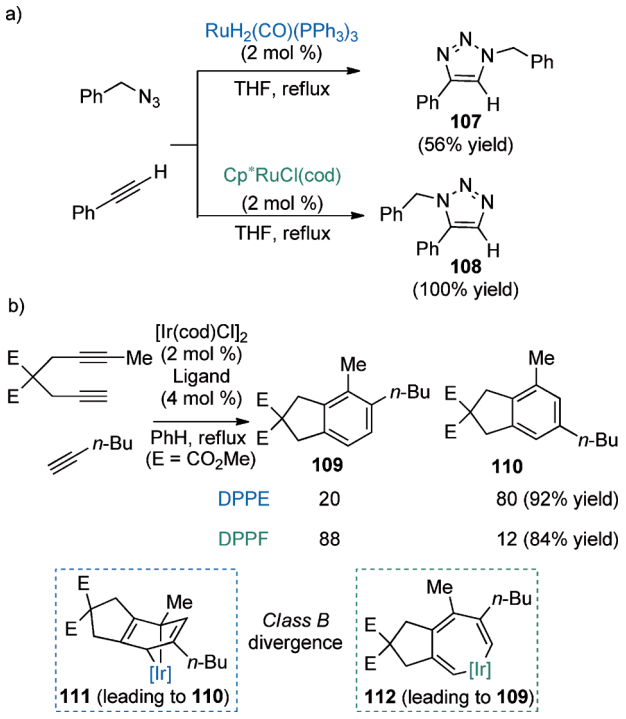


Scheme 29. Regioselective inter- and intramolecular reductive alkyne–aldehyde couplings.



Scheme 30. Regiodivergent reductive coupling.

tuted 1,2,3-triazoles such as **107**, while the Ru^{II} variant gives selectively the 1,5-regioisomer **108**.[112] Interestingly, the choice of Ru catalyst is also important, as certain complexes lead to completely selective, albeit lower yielding, formation of the 1,4-product **108** (Scheme 31 a).[113] Transition metal-catalyzed [2+2+2] cycloadditions of alkynes have been studied extensively, however only a single example of catalyst-controlled regioselectivity has been reported (Scheme 31 b).[114] In this case, smaller bidendate ligand dppe gives selective formation of the *meta*-product **110**, while larger dppf affords *ortho*-product **109**. This was attributed to a change in mechanism based on dicoordination of dppe yielding an iridacycle that reacted through Diels–Alder adduct **111**, while monocoordination of dppf allows a migratory insertion pathway to give intermediate **112**.



Scheme 31. Regioselective cycloadditions involving alkynes. Cp* = pentamethylcyclopentadienyl.

6.4. Regioselective Functionalization of Conjugated Dienes and Enynes

Compared to the reactions of alkenes and alkynes, where only two regioisomeric products can be formed, additions to conjugated dienes or enynes are more complicated. As illustrated in Figure 4, H–X addition across a terminal diene can form up to six different products, depending on the Markovnikov or anti-Markovnikov directionality of the new bonds being formed as well as the selectivity for reaction with either internal or terminal 1,2-addition or conjugate 1,4-addition. In the following section, examples of regiocontrolled reactions are presented wherein selectivity between at least two of these pathways has been demonstrated through catalyst control.

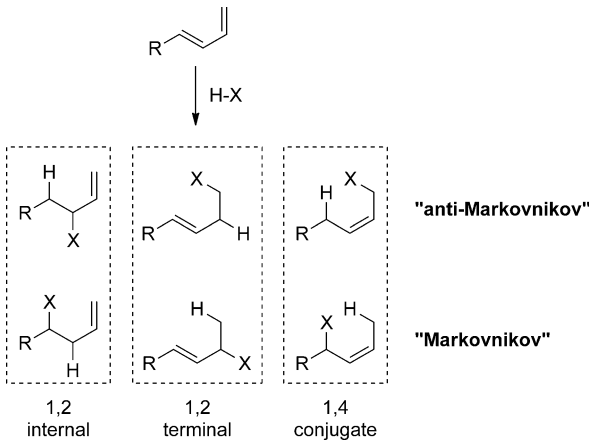
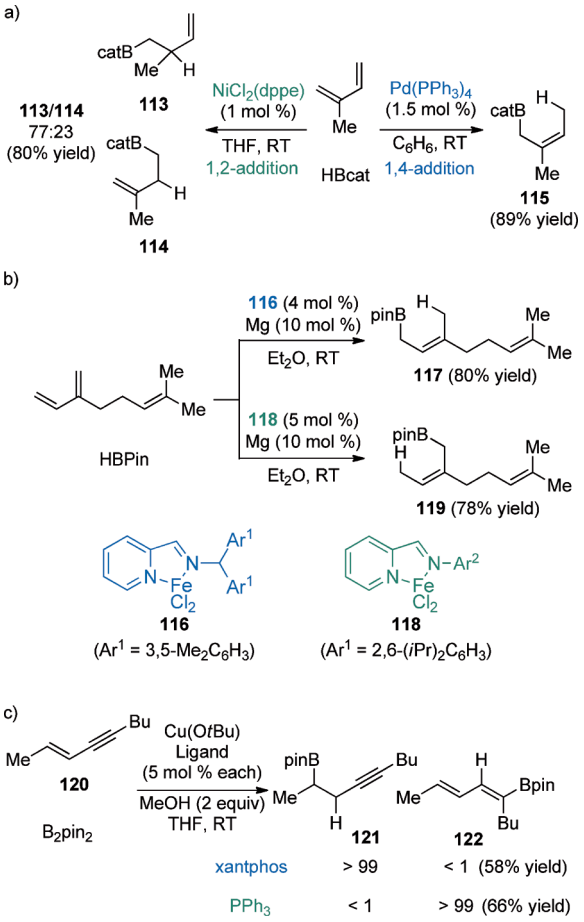


Figure 4. Products possible from additions to conjugated dienes.

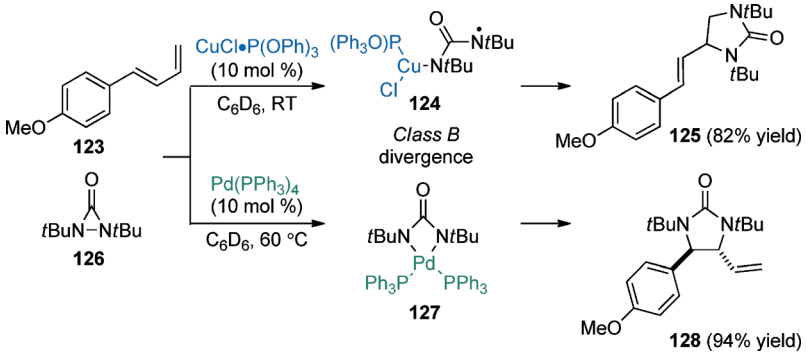
As with alkenes, regioselective hydroboration of dienes is a useful transformation not only as a means of performing formal hydration but also because the products are often reactive allyl boronates that can be used for nucleophilic additions. Selective 1,4- versus 1,2-hydroboration of dienes with catecholborane has been achieved based on the use of Pd- or Ni-based catalysts, respectively (Scheme 32a). In the Pd-catalyzed reaction, hydroboration of isoprene proceeded with complete 1,4- and Markovnikov selectivity to give **115** as the sole product.[115] On the other hand, Ni catalysis is completely selective for 1,2-addition (though a mixture of internal and terminal products **113** and **114** is obtained).[116] Regioselective 1,4-hydroboration of dienes based solely on variation of the ligand has recently been reported using a low-valent iron catalyst (Scheme 32b).[117] Here, hydroboration of the diene portion of myrcene with HBpin yields either **117** using benzhydryl-substituted ligand **116**, or **119** from aryl-containing **118**. In a formal 1,2-hydroboration of enyne **120** under copper catalysis (Scheme 32c), bidentate xantphos gave complete selectivity for addition across the alkene portion to furnish



Scheme 32. Regioselective hydroboration of dienes and enynes.

121, while monodentate PPh_3 gave **122** by reaction with the alkyne.[118]

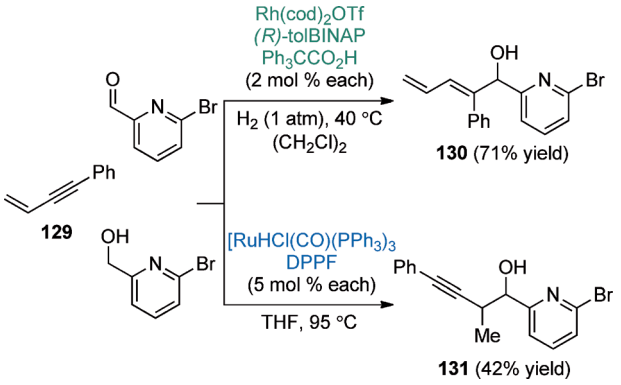
Shi and co-workers have described incredibly selective diamination reactions of dienes proceeding under divergent Pd or Cu catalysis (Scheme 33). In the Cu-catalyzed reaction of diaziridinone **126** with styrene derivative **123**, only the product of terminal diamination (**125**) was formed,[119] while the Pd-catalyzed reaction gave the product of internal substitution (**128**) as the only detectable regioisomer.[120] Mechanistic investigations suggest that a Cu^{II} species, detected by EPR spectroscopy and possibly urea radical



Scheme 33. Regiodivergent 1,2-diamination of dienes.

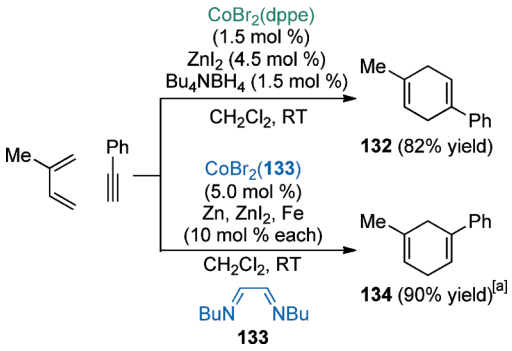
124, is a likely intermediate in the Cu-catalyzed reaction.[121] NMR studies of the reaction between **126** and $[Pd(PPh_3)_4]$ demonstrated that four-membered Pd^{II} complex **127** was formed under the reaction conditions.[122] In neither reaction were products of 1,4-diamination formed; this can be attributed to the kinetic preference for five-membered ring formation in the stepwise formation of the urea products. Although these studies demonstrate that a divergence in mechanism occurs when changing the catalytic metal, this information does not provide a strong rationalization for the observed selectivities. Subsequent investigations have also shown that an internal/terminal switch in regioselectivity can be achieved simply by changing the counterion on the Cu catalyst.[123]

Krische et al. have developed exquisitely atom-economical and highly selective divergent C–C bond forming reactions by employing conjugated enynes as pronucleophiles (Scheme 34). Using a Rh^I catalyst, enyne **129** undergoes reductive coupling to give **130** as the sole regioisomer—this is formally the product of regioselective 1,2-carbohydration of the alkyne portion.[124] Under Ru^{II} catalysis, the aldehyde is formed in situ, the selectivity is reversed, and **131** is formed as the sole regioisomer; **131** is the result of net Markovnikov carbohydration of the alkene.[125]



Scheme 34. Regioselective coupling of aldehydes and enynes. dppf = 1,1′-bis(diphenylphosphino)ferrocene.

Diels–Alder cycloadditions are perhaps the quintessential reactions of dienes. However, very few catalyst systems have been reported that can reverse the regioselectivity of these reactions, despite the synthetic potential of such a process. This is in part due to the inherent electronic biases that are key to the success of the reaction in the first place—an electron-rich diene reacting with an electron-poor dienophile. While Lewis acid catalysis can *enhance* the regioisomeric ratio in favor of the innate reactivity, it is rare for the catalyst to cause a complete reversal.[126] However, such a reversal is possible for Diels–Alder reactions involving electronically neutral partners (Scheme 35). Hilt et al. have reported that the [Co(dppe)]-catalyzed Diels–Alder reaction between isoprene and phenylacetylene gave the "*para*" product **132** exclusively.[127] A nearly complete (97:3 *m*/*p*) reversal in selectivity was observed when a [Co(diimine)] complex was used, giving "*meta*" product **134** as the main cycloadduct.[128]



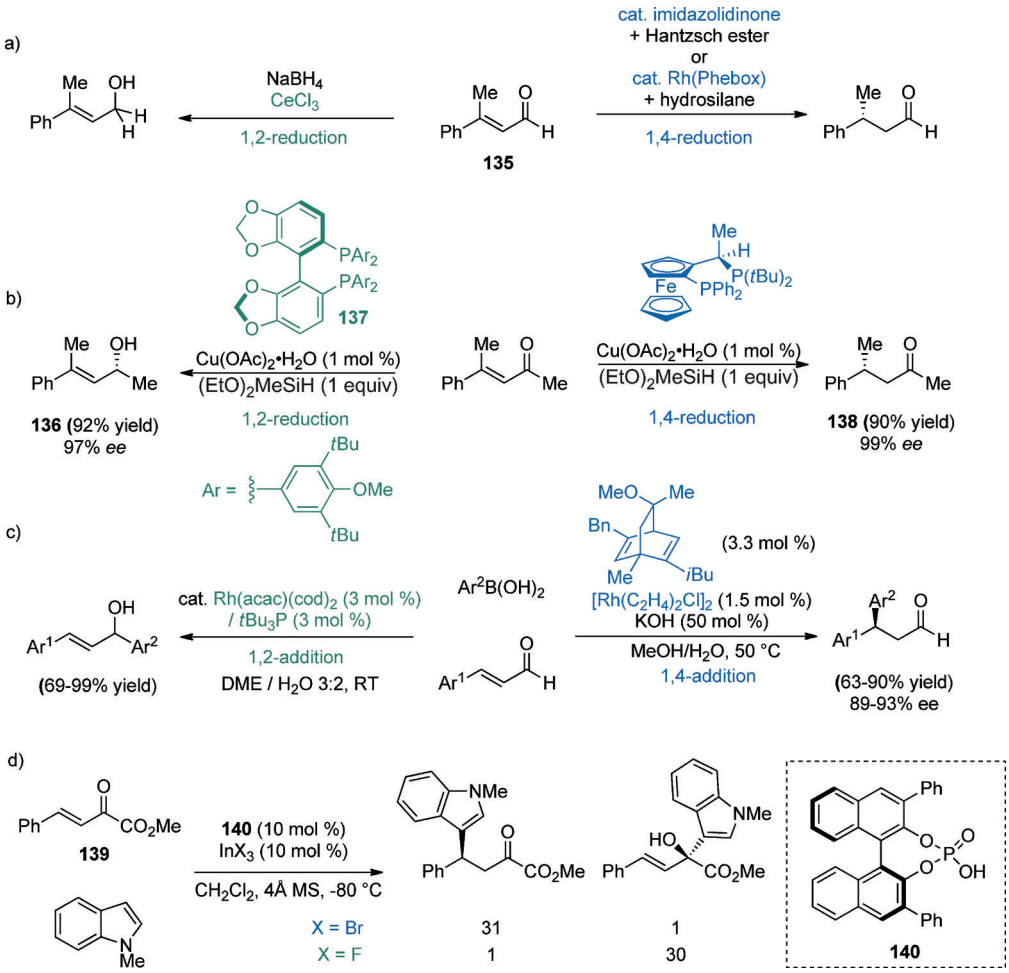
Scheme 35. Co-catalyzed regioselective Diel–Alder reactions. [a] Yield after DDQ oxidation. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Computational studies suggest that the regioselectivity is due to the different steric environment around the metal center, as well as a change in the order of bond formation during the stepwise formal cycloaddition.[129]

6.5. Catalytic Regioselective Reactions of α,β-Unsaturated Carbonyl Compounds

α,β-Unsaturated carbonyl compounds represent one of the most versatile functional groups in organic chemistry. They are excellent ambident electrophiles, which react with nucleophiles in 1,2-addition (at C=O bond) or 1,4-addition (at C=C bond). For α,β-unsaturated acid derivatives, a regioselective reaction[130] at each site usually depends on the substrate and/or the nucleophilic partner (the hard and soft acids and bases concept).

For enones and enals, achieving high regioselectivity becomes more challenging. Nonetheless, significant advances in selective 1,2-addition versus 1,4-addition have been made. For example, α,β-unsaturated aldehydes such as **135** (Scheme 36a) can be selectivity reduced to the corresponding α,β-unsaturated alcohol using Luche conditions.[131] Conjugate reduction of **135** can be achieved using either catalytic Rh^I catalyst and $(EtO)_2MeSiH$ as the reducing agent[132] or organocatalytic reduction with an imidazolidinone catalyst and Hantzsch ester as the hydride source.[133] Similarly, Aue and Lipshutz et al.[134] recently disclosed two catalytic systems to perform selective 1,2- and 1,4-reduction of β,β-disubstituted enones (Scheme 36b) based on their own earlier work,[135] and that of Carreira[136] and Buchwald.[137] Empirical observation demonstrates chiral biaryl ligand **137**'s preference for 1,2-reduction (**136**) while ferrocenyl-based ligands tend to catalyze 1,4-reduction (**138**); computational investigation reveals this ligand-controlled selectivity to be a result of subtle and complex interactions between the substrate, solvent, and steric factor of the ligands. While conjugate addition of arylboronic acids to enones using Rh catalysts and phosphine ligands has been extensively investigated,[138] the same transformation with α,β-unsaturated aldehydes proved elusive until Carreira's report using a chiral diene-Rh catalyst system, which provides exquisite enantio- and regiocontrol.[139] This stands in contrast to Rh-phosphine systems,



Scheme 36. Regioselective 1,2-addition versus 1,4-addition reactions.

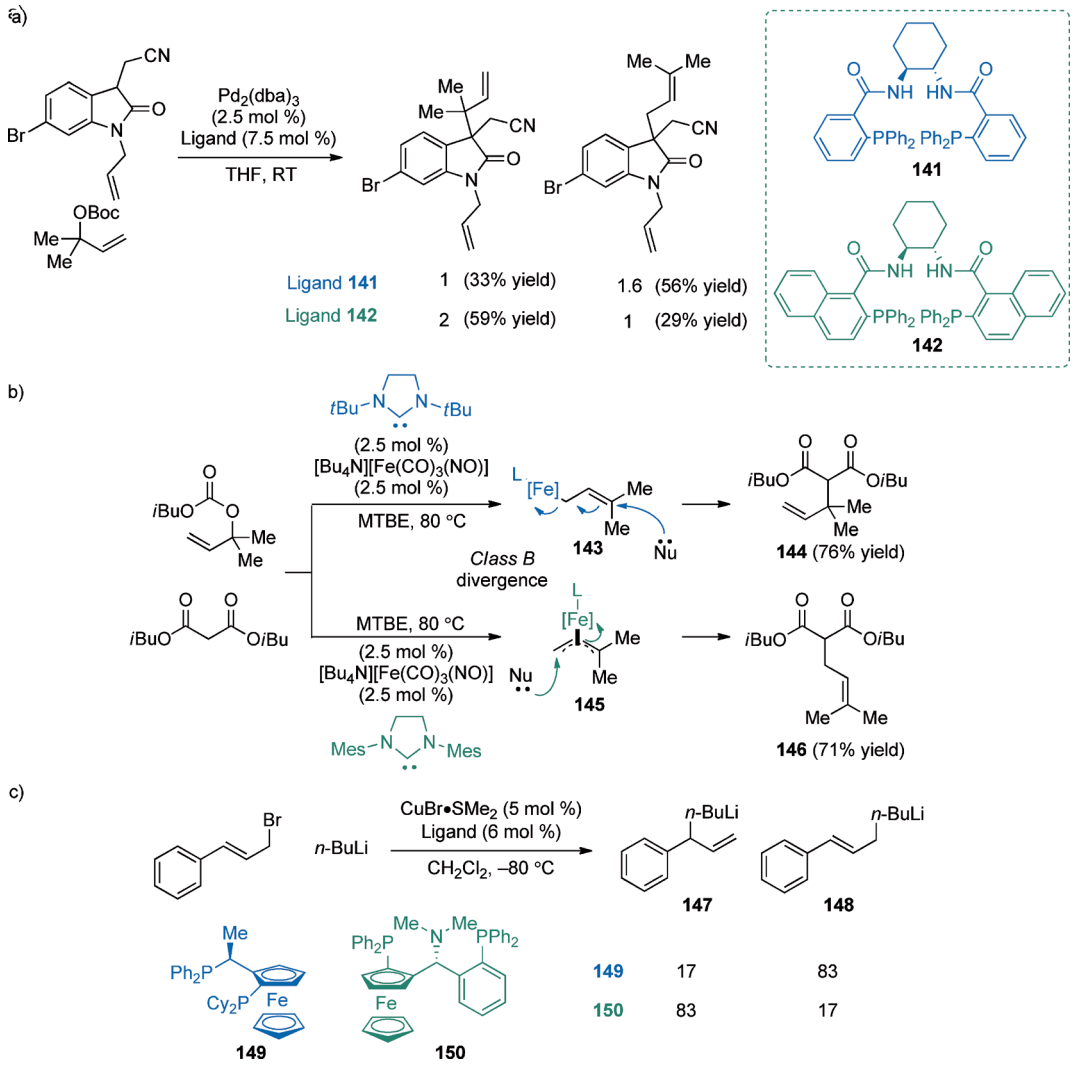
which tend to furnish 1,2-addition products predominantly (Scheme 36c).[140] Luo et al. recently reported regioselective 1,2-addition and 1,4-addition reactions of *N*-methyl indole to enone **139** based on the choice of the counterion (Scheme 36d).[141] It is worth noting that this reaction is highly regioselective with respect to the indole as well (only the C3 position is functionalized).

6.6. Regiodivergent Substitution of Allylic Reagents

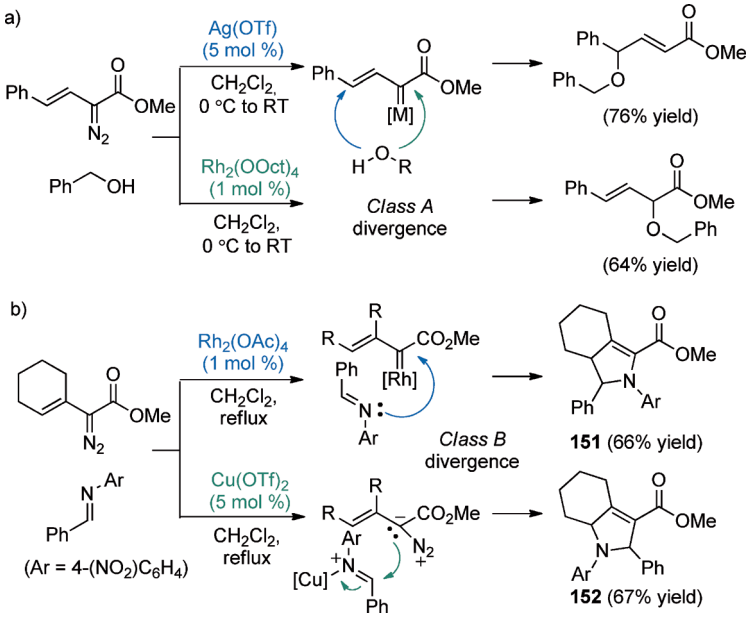
Allylic electrophiles are very useful reagents due to their enhanced reactivity relative to their saturated counterparts and the possibility of controlling the regioselectivity of the substitution to increase product diversity. The sheer number of investigations precludes a comprehensive discussion here.[142] Rather, some representative recent examples that highlight new developments in this field are exemplified. Transition metal-catalyzed allylic substitution is a powerful method for forming new products with excellent control of linear or branched regioselectivity.

The typical strategy for regiodivergent substitution is to change the metal catalyst; for example, Pd^0 catalysis favors linear products[143] while Ir^I catalysts are highly selective for branched products.[144] Regiocontrolled substitutions based on changing the ligand around the same metal are also possible (Scheme 37).[145] For example, Trost et al. demonstrated that prenylation and reverse prenylation of oxindoles could be achieved with a Pd^0 catalyst (Scheme 37a).[146] This is particularly impressive because Pd typically favors the linear product and adjacent all-carbon quaternary centers are formed. Another example was reported by Plietker et al., where the NHC ligand on an anionic Fe catalyst controlled branched versus linear selectivity in substitutions of prenyl carbonates (Scheme 37b).[147] In this case, a mechanistic divergence from σ-allyl Fe complex **143** leading to **144** with a bulky ligand (*t*Bu)-NHC to unprecedented Fe π-allyl complex **145** leading to **146** with smaller aryl-NHC is invoked to explain the selectivity. Later work demonstrates the feasibility and catalytic activity of Fe π-allyl intermediates.[148] A related substitution reaction is the S_N2/S_N2' reaction of allylic halides, where regiocontrol can be difficult to achieve. Nevertheless, a powerful example of the utility of catalytic control in such reactions was recently demonstrated by Feringa et al. (Scheme 37c).[149] In this case, even a highly reactive nucleophile such as *n*BuLi could be steered toward either S_N2 product **148** or S_N2' product **147** simply by changing the ligand on the copper catalyst.

Another useful class of functionalized allylic reagents are vinyldiazo compounds, where advantage can be taken of both the large number of metal salts known to form carbenoids by nitrogen extrusion and of the possible vinylogous reactivity.[150] Davies et al. described highly regioselective O–H insertion reactions of vinyldiazoacetates, where Ag^I favors vinylogous reactivity while Rh^{II} leads to insertion at the former diazo center (Scheme 38a).[151] As reported by Doyle et al., an interesting mechanistic dichotomy in formal cycloadditions of imines with vinyldiazoacetates leads to selective formation of either dihydropyrrole **151** or **152** from Rh^{II} or Cu^{II} catalysis, respectively (Scheme 38b).[152] In this case, formation of a Rh-carbenoid is followed by attack of the imine nitrogen leading to **151**, while Lewis-acid activation of



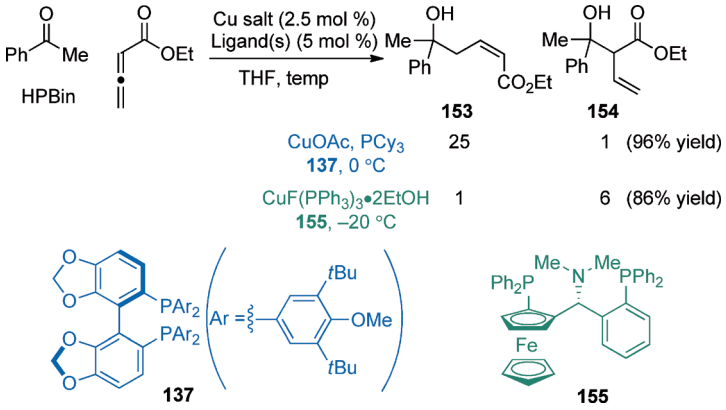
Scheme 37. Regioselective allylic substitutions.



Scheme 38. Regioselective reactions of vinyldiazoacetates.

the imine favors nucleophilic addition of the diazo center, ultimately yielding to a regioisomeric product **152**.

Regiodivergence of allyl nucleophiles under catalyst control is rare, especially in comparison to the progress that has been made in the electrophilic series. In an excellent example of such control, Kanai and Shibasaki et al. described the Cu-catalyzed regioselective reductive aldol reaction of allenoates with ketones (Scheme 39).[153] Here, use of a CuOAc/DTBM-Segphos complex resulted in a highly γ-selective addition to give **153** as the major product. In contrast, use of CuF/Taniaphos (**155**) reversed the selectivity to the more hindered α-center, favoring product **154**.



Scheme 39. Regioselective reductive aldol reactions.

7. Catalytic Chemoselective Functionalization

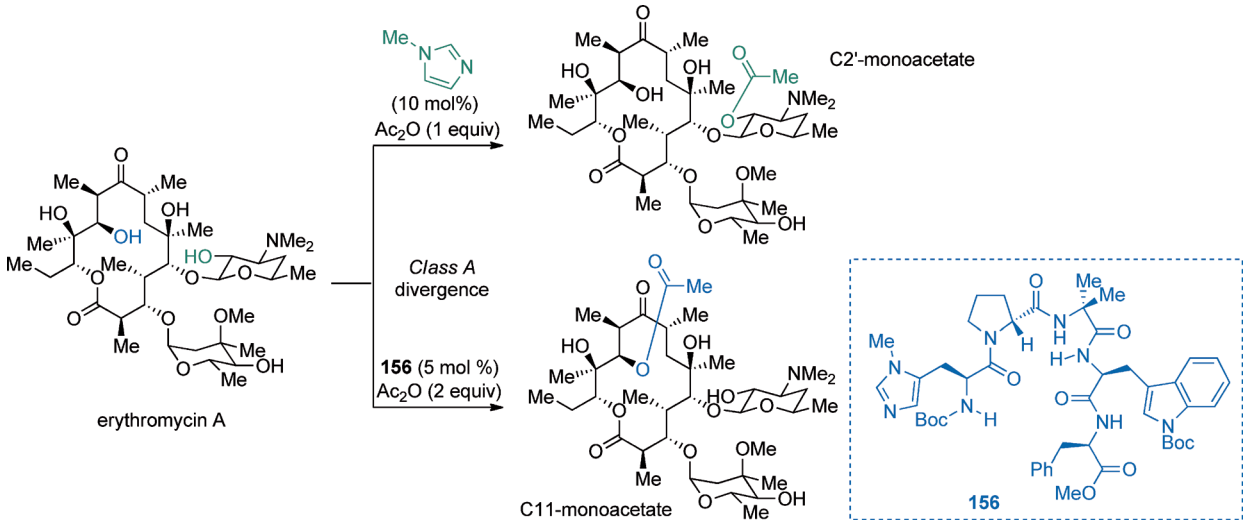
A chemoselective reaction is the preferential transformation of one functional group in a molecule with two or more similarly reactive sites. Similar to regioselectivity, chemoselectivity improves synthetic efficiency and reduces chemical waste and undesired byproducts. Achieving high level of chemoselectivity is desirable and has long captured the interest of chemists. To illustrate this idea, this section will be organized based on the type of transformation rather than the functional group involved and will focus on the development of catalytic chemoselective reactions.[154]

7.1. Catalytic Chemoselective Functionalization of Heteroatoms

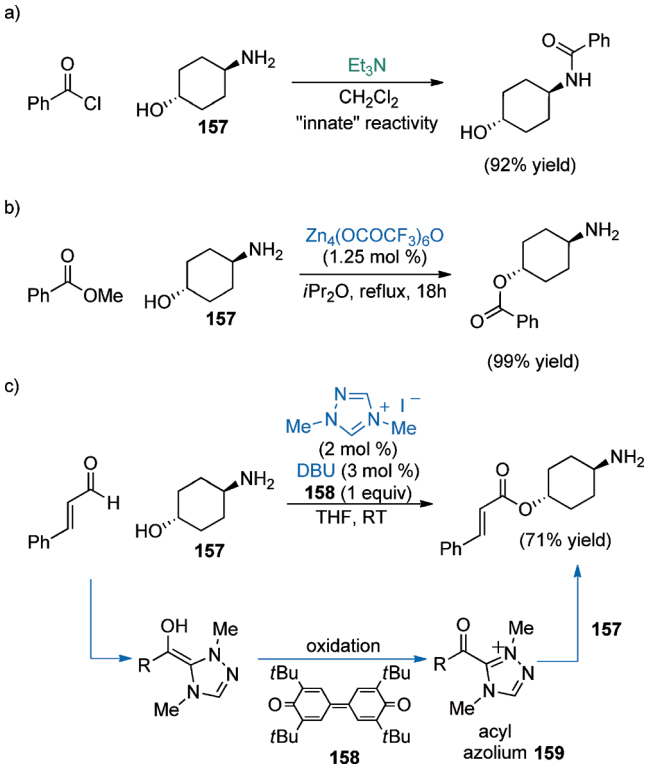
Selective functionalization of a molecule containing more than one nucleophilic sites remains a fundamental challenge. For example, selective acylations of a primary alcohol over a secondary or tertiary site may be feasible. Many known, successful examples[155] harvest the innate steric, relative acidity (i.e. phenolic versus aliphatic hydroxy) or nucleophilicity (i.e. amine versus alcohol acylation). Reversing these preferences has proven intractable. Nonetheless, examples from a growing body of literature document new strategies to engineer these desired transformation.[156] As seen earlier in Section 2, Miller et al.[5] have developed a peptide-based library of catalysts and identified **156** as an active catalyst to achieve monoacylation at the least reactive C11 position in comparison to the 2-OH position ("the background rate"), which is most reactive and is acylated first with catalytic *N*-methylimidazole and acetic anhydride (Scheme 40).

Equally challenging is selective functionalization of alcohols in the presence of amines. Designing a catalyst for this reaction requires either suppressing the innate superior nucleophilicity of the amino group (the "innate" reactivity in Scheme 41 a)[157] and/or enhancing the rate of the reaction with the alkoxy group. Two examples here elucidate these approaches. Mashima et al. have disclosed the use of a polymeric oxophilic Zn catalyst, which activates the alcohol over the amine for selective *O*-acylation of amino alcohol **157** (Scheme 41 b).[158] This unusual chemoselectivity (not unlike that of the enzyme lipase) can also be achieved through Studer's approach with N-heterocyclic carbene catalysts (Scheme 41 a).[159] In this particular case, the chemoselectivity arises from the catalytically generated acylating agent, acyl azolium **159**, which is known to prefer acylation of alcohols and water due to rapid equilibrium with its hemiacetal.[160]

Chemoselective *O*- and *N*-arylation reactions have been reported by Buchwald et al. In Scheme 42 a, aminoalcohol **161** undergoes a selective *N*-arylation under 5 mol % CuI and ligand **160**.[161] The anionic nature of the enolate ligand derived from **160** attenuates the electrophilicity of the metal center to favor preferential coordination of the amine over the alcohol. In contrast, ligand **162** makes the corresponding Cu^{I} complex more oxophilic and favors binding of the alcohol, likely a *Class A* divergence category. Similarly, the oxygen or nitrogen atom of 1,2 amino alcohol **163** (Scheme 42 b) can be



Scheme 40. Chemoselective acylation of poly-hydroxylated natural product erythromycin A.



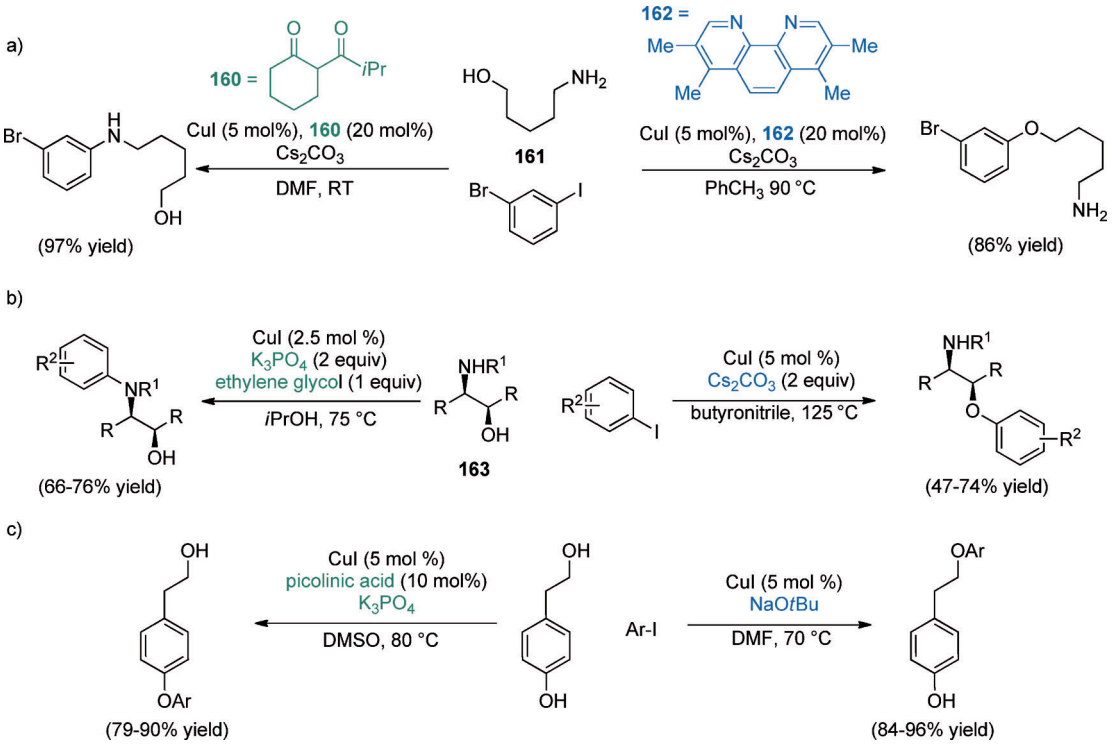
Scheme 41. Chemoselective reactions of amino alcohols. DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene.

selectively arylated with Cu^{I} catalysis depending on the reaction conditions and additive, which dictates the relative tightness of chelation.[162] With its curious selectivity, CuI has also been employed in selective arylation of primary and phenolic alcohols in the presence of the other (Scheme 42c). Maiti et al. have demonstrated this principle with two CuI catalytic systems: one with picolinic acid as a ligand and another with a relatively stronger base (which surprisingly affords aliphatic arylation).[163] Although the chemoselectivity of these reactions is still ligand-controlled, the choice of appropriate solvent and temperature contribute to the exquisite control of the desired pathway.

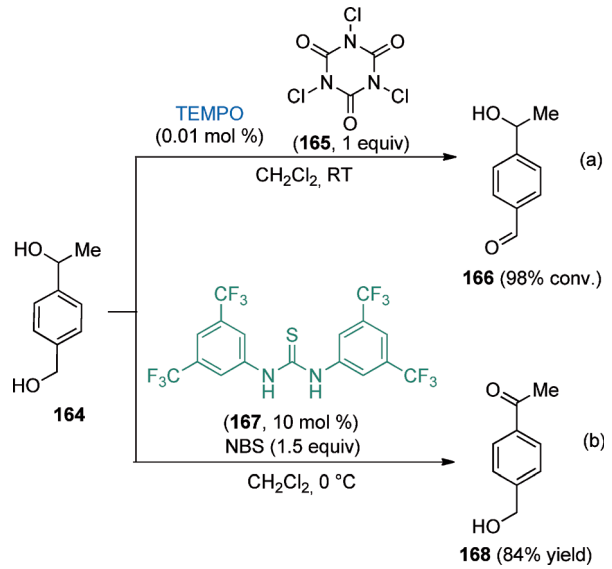
Innate steric preferences can also be exploited for selective reactions with a high level of chemocontrol. Selective oxidations of primary alcohols in the presence of a secondary site have been reported such as in the case of TEMPO oxidation of **164** (Scheme 43a).[164] Overcoming innate steric bias necessitates that the kinetics of the catalytic reaction at the more sterically hindered site be more favorable than the background reaction at the innate site. The innate steric preference in substrates such as **164** can be suppressed using a combination of thiourea catalyst **167** and NBS, where oxidation on the secondary site is the result of a hydride abstraction mechanism to generate a carbocation intermediate (Scheme 43b).[165]

7.2. Catalytic Chemoselective Olefin Metathesis Reactions

Olefin metathesis has proven to be one of the most useful and widely applicable methods in organic synthesis.[166] It therefore comes as no surprise that the ability to selectively perform metathesis on a specific pair of olefins is desirable and has gained attention of practitioners in this field. In 2003 Grubbs et al. categorized different classes of olefins based on



Scheme 42. Cu^{I}-catalyzed chemoselective *O*- and *N*-arylation reactions.

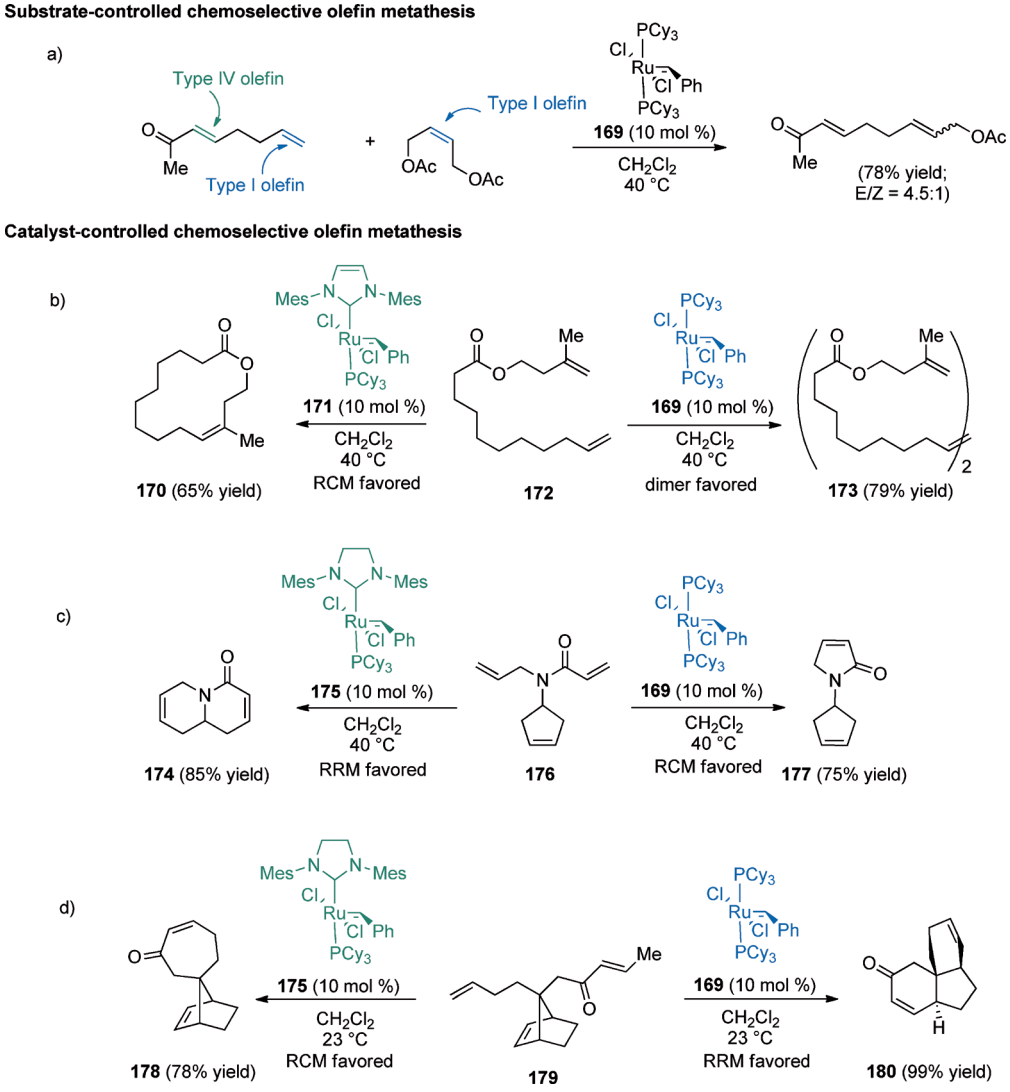


Scheme 43. Chemoselective oxidation reactions. TEMPO = 2,2,6,6-tetramethylpiperidine N-oxyl, NBS = *N*-bromosuccinimide.

well-documented observation of the innate reactivity of olefins in metathesis reactions and paired this innate preference with a different class of catalysts.[167] Olefins that participate in metathesis are typically categorized into ***types I*** to ***IV***, in which ***type I*** is most reactive and ***type IV*** the opposite. Terminal olefins and allylic alcohols fall under ***type I*** for catalyst **169** while enones are considered ***type IV*** olefins because they are spectators and slow in cross-metathesis (Scheme 44a). Many reports on catalyst-controlled chemoselective olefin metathesis have emerged and readers are directed to a recent, comprehensive review by Nolan et al. for a full account.[168] Here a few cases will be showcased to highlight the importance of this type of selective reaction. Fürstner et al. (Scheme 44b)[169] and Grubbs et al.[170] independently reported two catalytic systems for chemoselective ring-closing metathesis (RCM) and dimerization reactions. First-generation Grubbs' catalyst **169** was found to favor dimerization (**173**), in which the selectivity was largely controlled by the steric bulk of the substrate. RCM was possible with second-generation Grubbs' catalyst and affords macrocycles such as **170** in good yield. In his study of "ring-rearrangement metathesis" (RRM), Ma et al. reported that first-generation Grubbs' catalyst prefers RCM product **177** while the desired rearranged product **174** was preferred with catalyst **175** (Scheme 44c).[171] In this case, the Ru catalyst with an NHC ligand prefers the thermodynamic product **174** while the phosphine ligand prefers kinetic product **177**. This type of divergence is also observed with **179**; however, in this case second-generation Grubbs' catalyst prefers RCM over RRM (Scheme 44d).[172]

7.3. Catalytic Chemoselective Arene Functionalizations

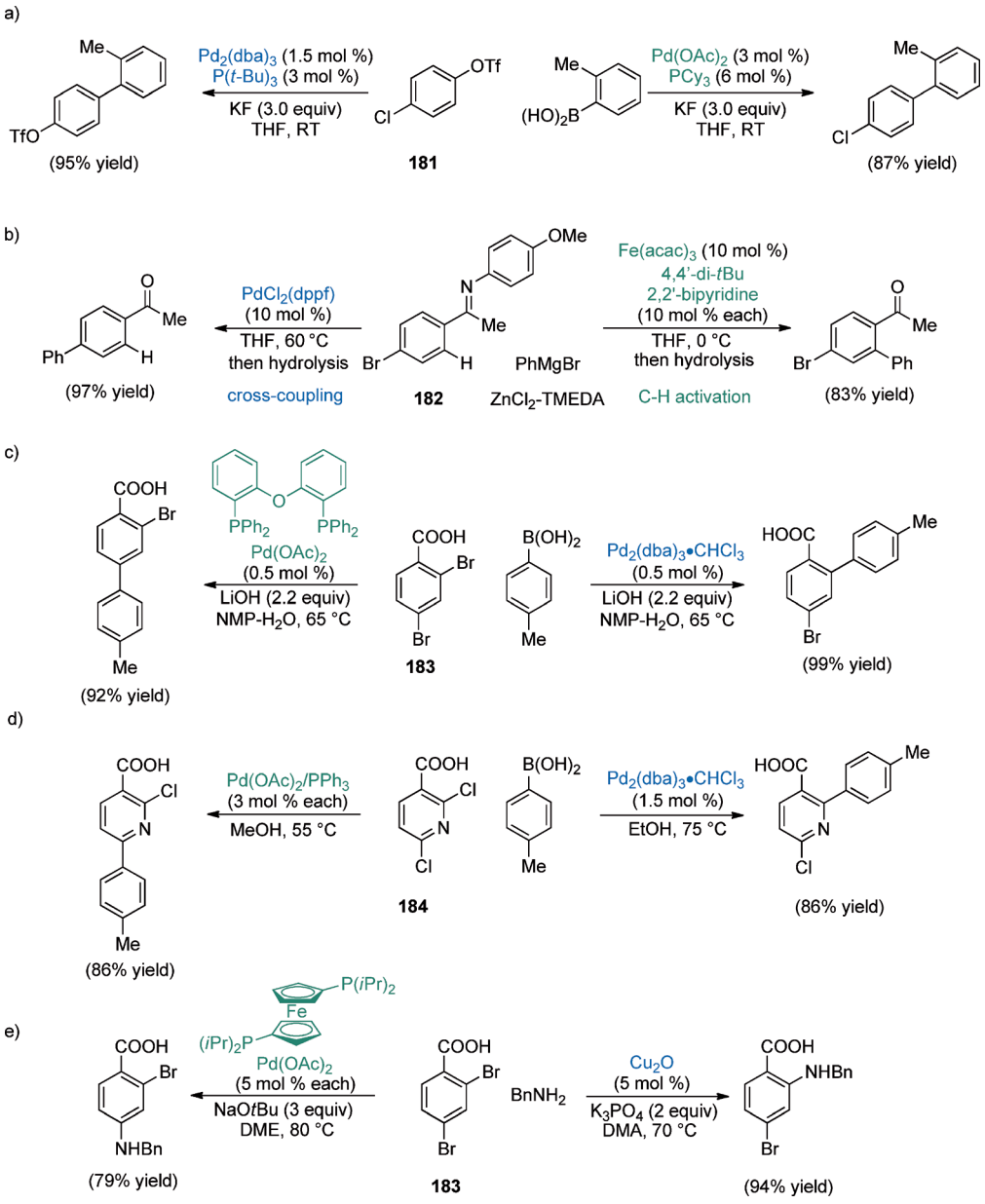
As seen earlier in Section 6.1, the ability to control the product outcome in functionalization of arenes is desirable



Scheme 44. Examples of chemoselective olefin metathesis reactions.

because it allows for late-stage modification and diversification from a common scaffold. In this respect, it would be useful if different catalytic systems are available, for example, for selective cross-coupling from a common di- or trisubstituted arene.

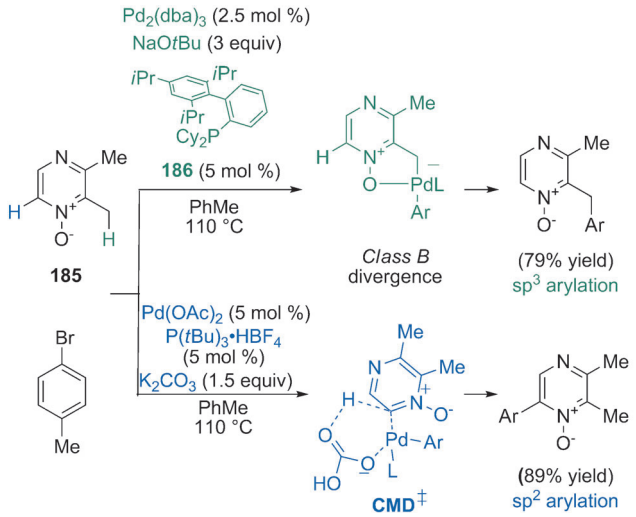
In 2000, Fu et al. reported an impressive chemoselective Suzuki–Miyaura cross-coupling reaction from arene **181** (Scheme 45a).[173] Mechanistic work by Fu and later computational investigation by Schoenebeck and Houk[174] revealed that a monoligated Pd species (favored with $P(tBu)_3$) prefers C–Cl insertion, and bisligated Pd (the active species with PCy_3) favors C–OTf insertion (*Class B* divergence). Schoenebeck has reported extensive solvent and additive effects on the selectivity of this particular reaction.[175] Similar reactivity in Kumada coupling was reported earlier by Hayashi et al.[176] Likewise, Nakamura et al. reported a selective Negishi coupling of **182** with a Pd catalyst versus a C–H activation/*ortho*-arylation mediated by an iron catalyst (Scheme 45b).[177] Houpis et al. have developed an elegant protocol for selective carboxylate-directed Suzuki–Miyura cross coupling for aryl dibromide **183** (Scheme 45c).[178] Changing the ligand and Pd sources affect the switch in chemoselectivity: the more bulky ligand directs an oxidative addition at the less hindered *para* position while oxidative addition is irreversible at the *ortho* position for a system without a similar ligand (also *Class B* divergence). This concept has also been successfully applied to site-selective cross-coupling of boronic acids and dichloro heterocycles such as **184** (Scheme 45d)[179] and site-selective monoamination of dibromobenzoic acid **183** with Pd versus Cu catalysts (Scheme 45e).[180]



Scheme 45. Example of catalytic chemoselective arene functionalization reactions.

7.4. Other Catalytic Chemoselective Functionalizations

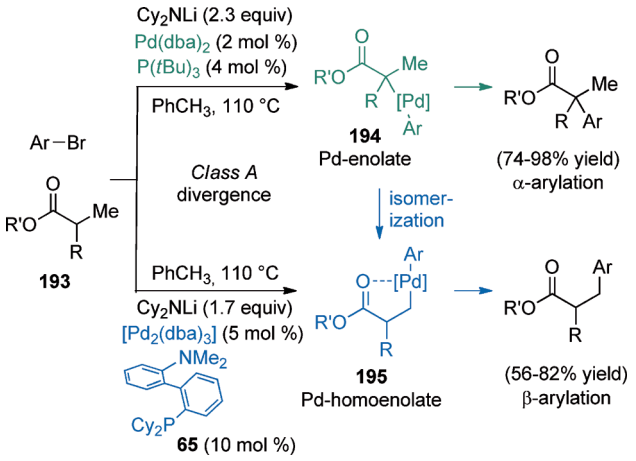
Similar to chemoselective arene functionalization, functionalization of other types of C–H bond offers an opportunity for late-stage modification. Selective modification of, for example, sp^3 versus sp^2 C–H bonds is feasible due the relative acidity of each type of C–H bond (pK_a), bond strength, or rate of C–H bond oxidation and may assist in rational design of catalyst or ligand to achieve the desired selectivity. In this section, some notable examples that use this approach are presented. Fagnou et al. disclosed a method of chemoselective sp^2 and sp^3 arylations of *N*-oxides such as **185**, in which the choice of the base, along with Pd source, allows for selective C–H bond functionalization by deprotonation at different sites (Scheme 46).[181] Mechanistically, these reactions follow *Class B* divergence from the product-determining palladation of **185**. The more acidic sp^3 C–H bond is cleaved with strong base (i.e. NaO*t*Bu); weaker carbonate cannot



Scheme 46. Fagnou's selective sp^2 and sp^3 arylations.

directly deprotonate but allows for chelation to form a six-membered transition state of a concerted metalation–deprotonation (CMD) pathway[182] to activate the sp^2 C–H bond.[183]

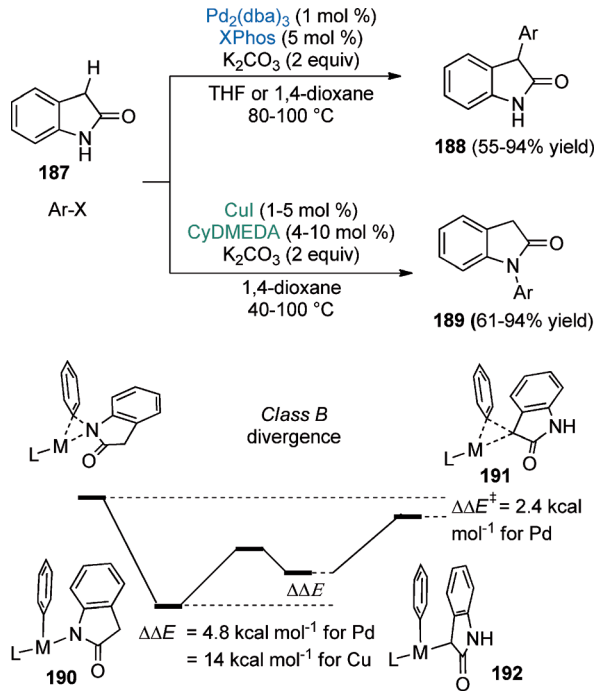
The relative acidity of the proton at the α-position of carbonyl compounds makes functionalization of this class of compound by metal or small organic molecule catalyst an area of research that has received much attention.[184] For example, Buchwald demonstrated that selective α-arylation (**188**) versus *N*-arylation (**189**) of lactams such as **187** is possible (Scheme 47).[185] Computational investigation establishes that *N*-arylation is favored for the Cu catalyst due to thermodynamics: the Cu–N complex **190** is 14 kcal mol^{-1} lower in energy than the Cu–C complex. However, C-arylation is favored for the Pd system due to the Curtin–Hammett equilibrium between the Pd–C and Pd–N complexes; the transition state of reductive elimination from Pd-complex **191** is lower in energy by 2.4 kcal mol^{-1}. In a similar manifold, Hartwig et al. described the catalytic generation of palladium enolate **194** from ester **193**, which undergoes reductive elimination to give the α-arylated product (Scheme 48, top).[186] A conceptually related transformation through catalytic generation of palladium homoenolate **195**



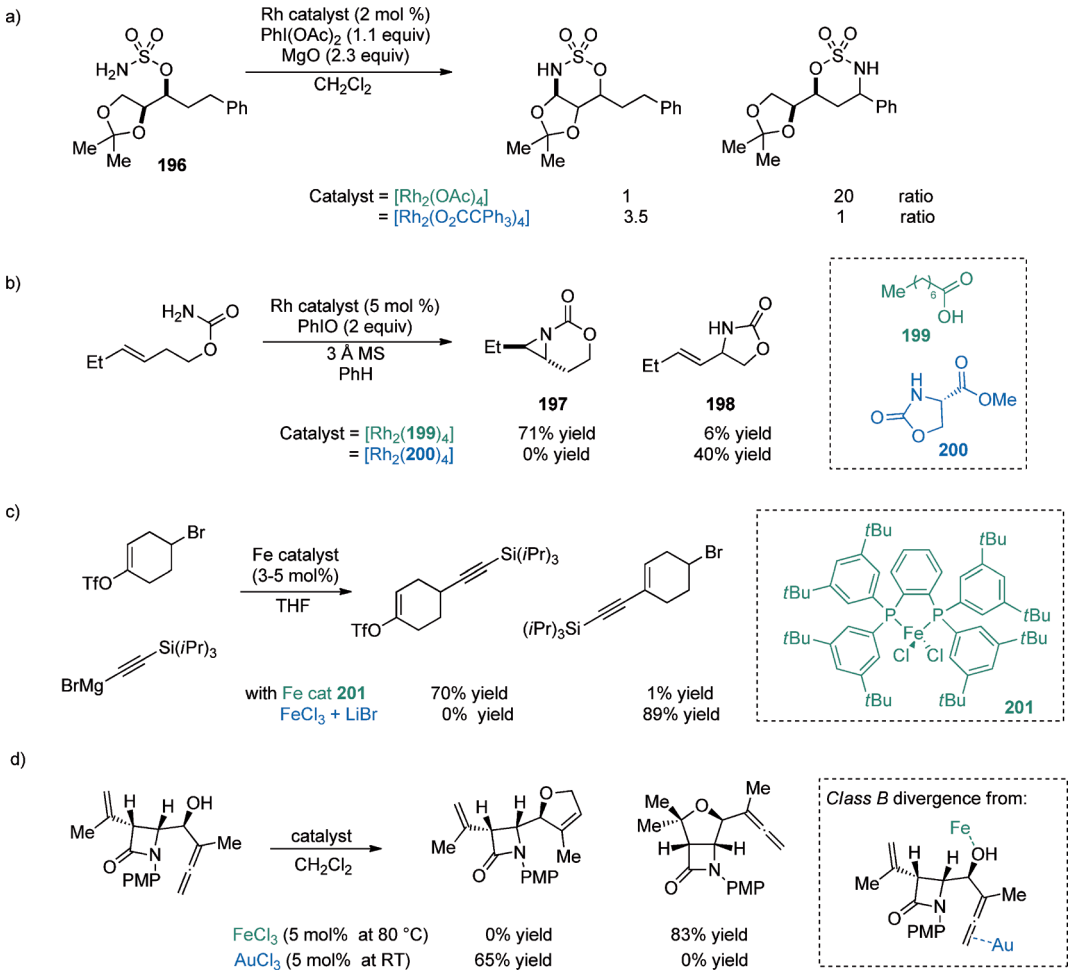
Scheme 48. Pd-catalyzed chemoselective α- versus β-arylation.

has proven elusive. However, Clot and Baudoin reported ligand-controlled Pd-catalyzed β-arylation for electron-withdrawing aryl halides (Scheme 48, bottom).[187] Detailed kinetic and DFT studies revealed that the rate-determining step of this reaction with DavePhos (**65**) is the Pd enolate–homoenolate isomerization sequence; β-arylation was kinetically favored for DavePhos, but not for P(tBu)$_3$, due to the stabilization the metal center from the ligand's biaryl backbone.[188] Unlike the case above from Buchwald, in which the selectivity arises from two intermediates with distinct connectivity (*Class B*), these examples of chemoselective arylations follow our *Class A* definition, in which the divergence arises from a ligand-controlled Pd-enolate reductive elimination or isomerization.

Du Bois et al. observed that a benzylic C–H bond in **196** can be selectively cleaved and aminated by a smaller ligand (OAc) on a Rh catalyst while a more sterically demanding catalyst such as [Rh$_2$(O$_2$CCPh$_3$)$_4$] performs the same task for the secondary C–H bond, although with a lesser degree of chemocontrol (Scheme 49a).[189] Similarly, Hayes et al. reported selective allylic C–H oxidation and aziridination reactions again by using two dirhodium catalyst–ligand combinations: carboxylate ligand **199** tends to give aziridine **197** while carboximidate **200** prefers allylic C–H insertion, yielding **198** (Scheme 49b).[190] Nakamura et al. developed a Sonogashira-type alkynylation using Fe catalysts, where Fe-SciOPP catalyst **201** afforded exclusive sp–sp^3 coupling while simpler FeCl$_3$ with LiBr gave sp–sp^2 coupling. This selective cleavage of an sp versus an sp^3 C–X bond is proposed to have an origin in the radical character of the organoiron species



Scheme 47. Buchwald's selective N- versus C-arylations. CyDMEDA = *trans-N,N'*-dimethyl-1,2-cyclohexanediamine.



Scheme 49. Miscellaneous catalytic chemoselective reactions.

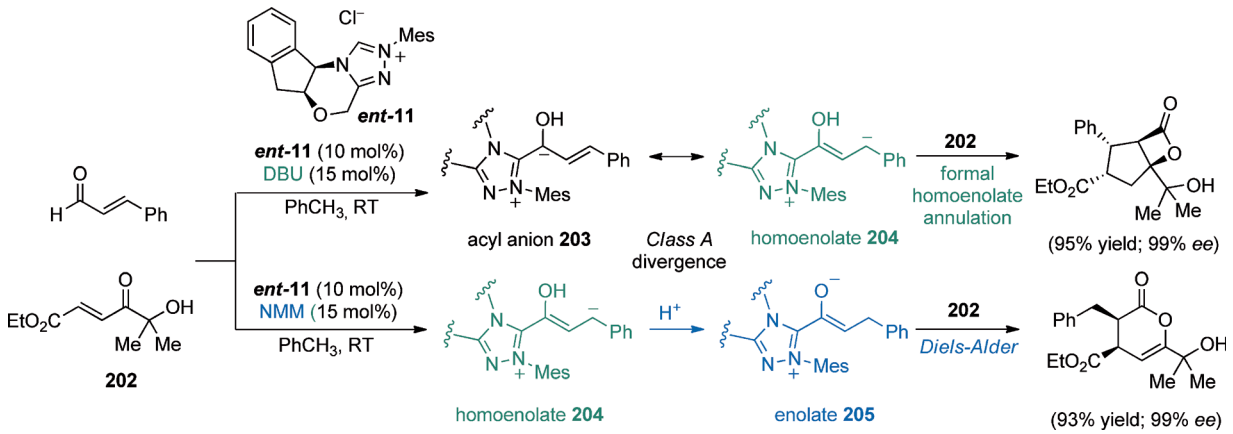
from **201** versus the simpler ferrate complexes for $FeCl_3$ (Scheme 49c).[191] Lastly Alcaide and Almendros reported completely chemoselective Au- and Fe-catalyzed cycloetherifications of alkenes or allenes in the presence of one another (Scheme 49d).[192] Divergent reactivity from ligand-controlled processes in Scheme 49a and b belong to *Class A*, while the selectivity in the last two examples originate from distinct intermediates (*Class B*).

8. Product-Selective Catalysis

Product-selective catalysis is a recent area of research that deals with catalyst-controlled reactions with the preferential formation of two (or more) unrelated constitutionally isomeric products that are not stereo- or regioisomers. Many of these reactions were discovered serendipitously, and rational design of this kind of selectivity is not obvious. However, advances in understanding this type of selectivity and development of this mode of catalysis are especially relevant in modern synthesis, in which increased efficiency and selective functionalization of complex targets is highly desirable. While we try in this Review to highlight as much detail as is presented in the original reports, many product-selective reactions require future mechanistic elucidation to explain the origin of the selectivity and guide rational design of such chemistry.

8.1. Organocatalytic Product-Selective Catalysis

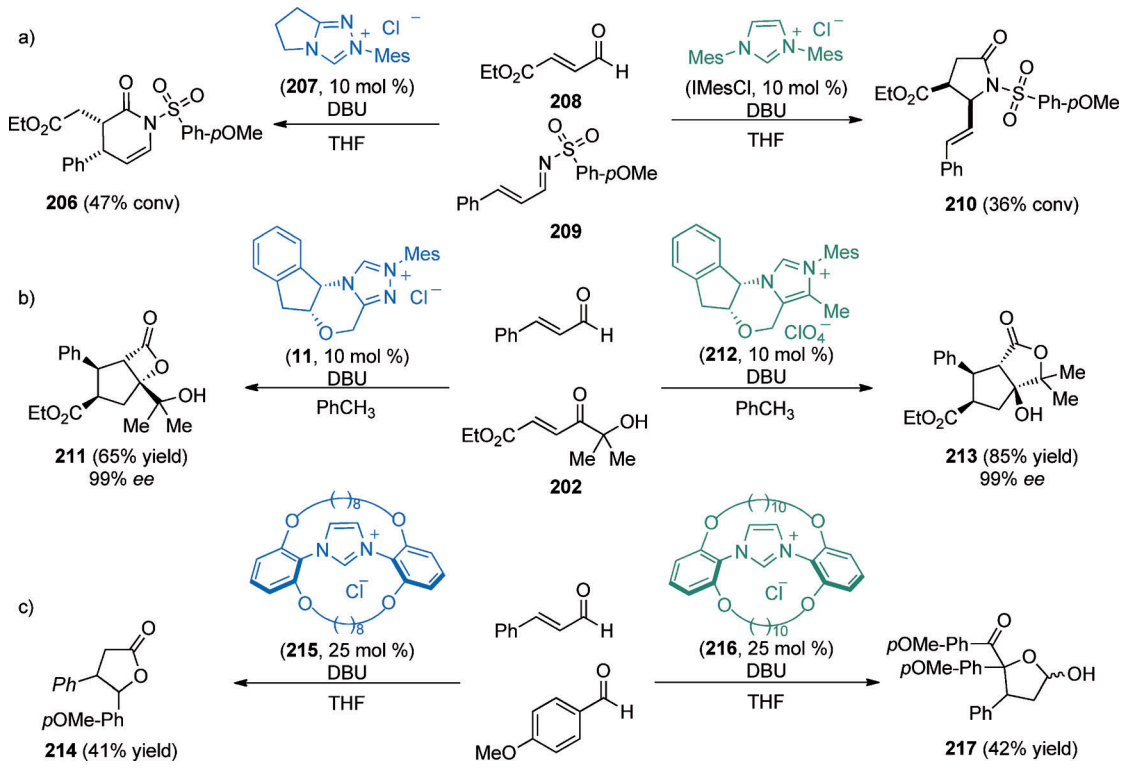
N-heterocyclic carbenes (NHC) offer a unique mode of catalysis due to their facile access to acyl anion, homoenolate, ester enolate, and activated carboxylate equivalents.[193] Selective generation of the desired intermediate can be subtle; co-catalytic base may also be product-determining. For example, a combination of *N*-mesityl triazolium salt *ent*-**11**, weak amine base such as *N*-methylmorpholine (NMM) and an α,β-unsaturated aldehyde leads to chiral ester enolate equivalent **205**, from protonation of homoenolate **204**,[194] which can be intercepted by oxo diene **202** to give a Diels–Alder cycloaddition (Scheme 50). A stronger base such as DBU deters protonation of **204** and gives rise to a formal homoenolate–annulation cascade.[195] Protonation of the homoenolate **204** is product-determining; this example represents *Class A* divergence, in which the selectivity is induced by the structure of the catalyst. With this idea as a guiding principle, our group has demonstrated that product selectivity



Scheme 50. Catalytic generation of various reactive intermediates in NHC catalysis. NMM = *N*-methylmorpholine.

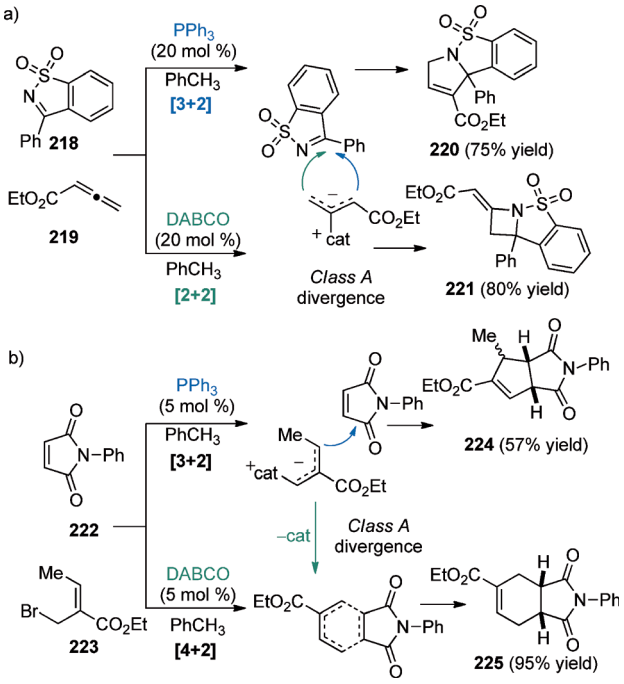
in NHC catalysis is an outcome of a judicious choice of the azolium salt in terms of both the type[196] of the NHC and the *N*-aryl substitution.[197] Divergence between homoenolate and enolate pathways was observed for aldehyde **208** and imine **209** (Scheme 51 a); the selectivity here is controlled solely by the choice of the catalyst.[198] Imidazolium catalysts gave product **210** arising from addition of homoenolates similar to **204** to imine **209** followed by catalyst turnover, whereas aza-Diels–Alder product **206** was obtained from triazolium **207**. The chiral triazolium salt **11** gave the aforementioned annulated product **211**; while otherwise identical chiral imidazolium salt **212** gave constitutional isomer **213** (Scheme 51 b).[199] Catalyst choice controls the stereochemical course of the reaction between cinnamaldehyde and **202**, which in turn gives rise to the formation of either product **211** or **213**. This example is notable because the product selectivity is ultimately determined by a diastereoselective process, even though the chiral elements of the catalysts are of same configuration. Lüning et al. reported another impressive control of product selectivity based on the chain length of the bimacrocyclic imidazolium salts such as **215** and **216** (Scheme 51 c).[200] Smaller-chain NHC **215** leads to expected homoenolate annulation product **214** while the slightly longer chain NHC mediates a self-dimerizing (benzoin) reaction followed by a conjugate addition to afford product **217**.

Besides NHC catalysis, Ye et al.[201] reported another organocatalytic example of *Class A* divergence, in which



Scheme 51. Examples of product selectivity from catalyst-controlled processes.

a formal [3+2] or [2+2] cycloaddition between **218** and **219** is a function of the choice of nucleophilic catalysts such as DABCO or PPh_3 (Scheme 52a). Similar product selectivity from the same set of catalysts was also reported by He et al. (Scheme 52b). In this case, DABCO catalyzes the formation of **225** through a [4+2] cycloaddition from allylic bromide **223** and **222** while PPh_3 mediates a formal [3+2] annulation to give **224**.[202]

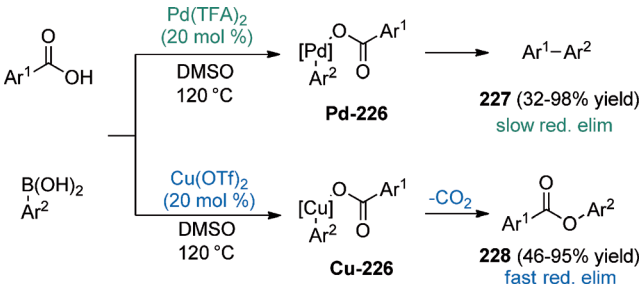


Scheme 52. Product selectivity from nucleophilic catalysis. DABCO = 1,4-diazabicyclo[2.2.2]octane.

8.2. Product-Selective Metal Catalysis

The ability to catalytically generate transient reactive intermediates is not unique to small organic catalysts. Transition metal-catalyzed reactions have also received much attention due to their versatility, broad applicability, and predictability. For these reasons, the combination of metal catalysts and a vast selection of ligands serves as an ideal platform for developing product-selective catalysis. As seen earlier in the examples for both regio- and chemoselective catalysis, the same underlying principles for controlling selective catalysis also apply to product selectivity. Liu et al. reported that changing the metal catalyst from Cu to Pd switches a selective cross-coupling reaction to a catalytic esterification (Scheme 53). The divergence arises from the relative stability of the metal–ester complexes **226**. Cu^{II} catalysis favors faster reductive elimination and furnishes ester **227**, while the Pd^{II} catalyst accelerates decarboxylation and yields cross-coupling (**228**).[203]

In recent years, Au complexes have emerged as powerful catalysts for a range of cyclizations and cycloisomerizations. Equally interesting is the use of gold catalysts in contrast to other metals for achieving high selectivity, sometimes with

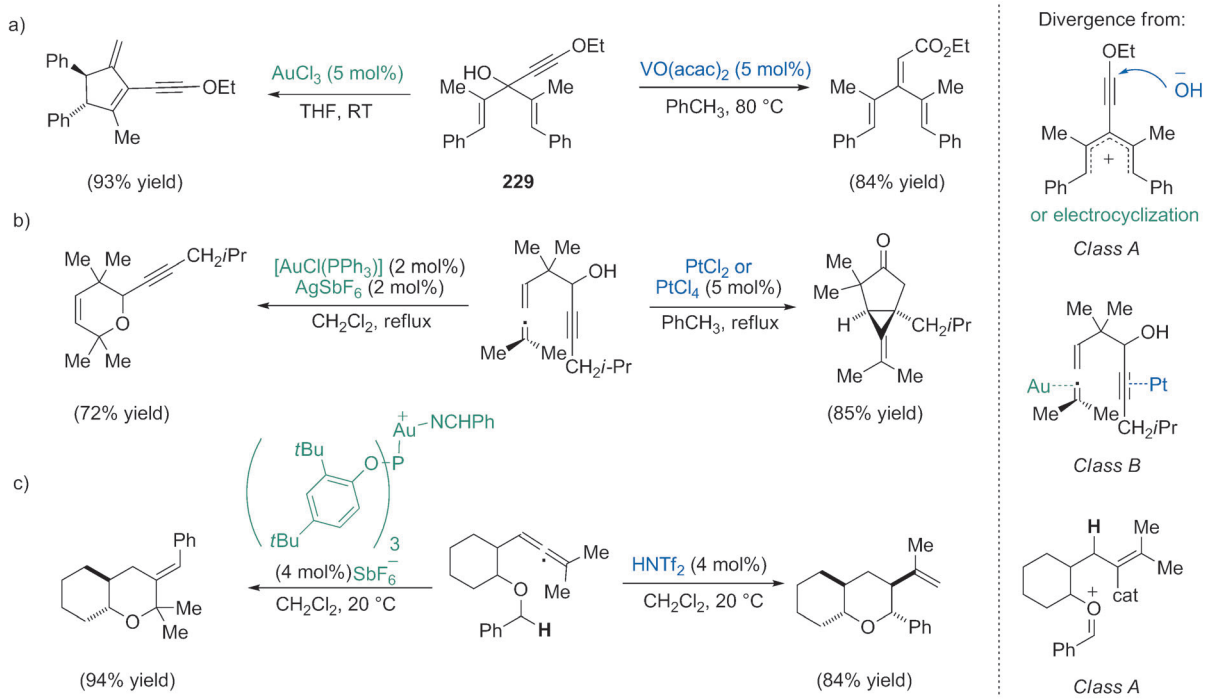


Scheme 53. Selective cross-coupling versus esterification reactions.

rather surprising mechanistic pathways. West et al. reported a prototypical example that demonstrates the uniqueness of gold catalysis in this context. Treating **229** with $[VO(acac)_2]$ leads to a Meyer–Schuster-type rearrangement (hydration followed by a tautomerization) while a Nazarov-type 4π electrocyclization is selectively promoted by $AuCl_3$ (Scheme 54a).[204] Complex multistep catalytic pathways can be achieved with Au catalysts, which exhibit high affinity for allene activation in the presence of other highly active functionality. We highlight two examples of catalytic divergence from Au versus Pt[205] and Au versus Bronsted acid[206] catalysis in the same manifold (Scheme 54b and c).

Besides changing the catalytic metal, product selectivity can also be achieved by ligand-controlled processes. In 2006, Rovis et al. reported an elegant Rh^{I}-catalyzed formal [2+2+2] cycloaddition reaction between isocyanate and terminal alkyne (Scheme 55a). Using TADDOL-derived phosphoramidite ligand **230**, lactam **232** is obtained in good yield and enantioselectivity.[207] The synthetic utility of this method is also demonstrated in the total synthesis of (+)-lasubine II. It was later found that BINOL-derived phosphoramidite ligand **233** was effective for overriding the substrate bias for the formation of intermediate **231** (top), which decarbonylates and reinserts to form the regioisomeric intermediate **234** (bottom) to afford vinylogous amide **235** as the major product in high enantiomeric excess. Vinylogous amide **235** also serves as a suitable platform for further elaboration into indolizidine alkaloid (−)-209D.[208] A similar, equally impressive ligand-controlled insertion–isomerization relay in Rh catalysis has been disclosed by Breit et al. (Scheme 55b).[209] Finally, Fox et al. reported product-selective cyclopronation reactions catalyzed by Rh complexes; the choice of the ligands dictates if direct cyclopronation occurs, which in turn controls the outcome of the final product (Scheme 55c).[210]

Impressively, gold catalysts offer unique ability for fine-tuning, with a certain degree of predictability, the nature of the ligand and its impact on the catalytic pathways.[211] As seen earlier in Section 8.1, N-heterocyclic carbenes can exert exquisite levels of product selectivity as organocatalysts. NHCs also function similarly when used as ligands in controlling selectivity in metal catalysis, especially in combination with Au catalysts. Recently, Merz and Hong (Scheme 56a)[212] reported that cyclic carbene ligands mediate an enyne cyclization reaction of **236** to catalytically generate **239**, which was trapped by indole to form product **240** with a good level of product selectivity. A more hindered acyclic diami-



Scheme 54. Divergent reactivities from gold catalysis.

nocarbene was found to divert the enyne cyclization pathway and catalyze a hydroamination reaction to form **238**, in which indole trapped the postulated carbocation **237**. In a similar manner, Duschek and Kirsch (Scheme 56b)[213] reported ligand-controlled products from pinacol (**243**) and sigmatropic rearrangements (**245**), whereby the selectivity is dependent upon the electronic nature of the ligand. The electron-rich catalyst is postulated to generate a cationic vinylgold species **242** poised for a desilylation followed by a pinacol rearrangement. The otherwise identical electron-deficient catalytic system forms **245** through a heterocyclization from the intermediate **244**. Both examples in Scheme 56 follow *Class B* divergence regardless of whether the product selectivity is electronically or sterically controlled.

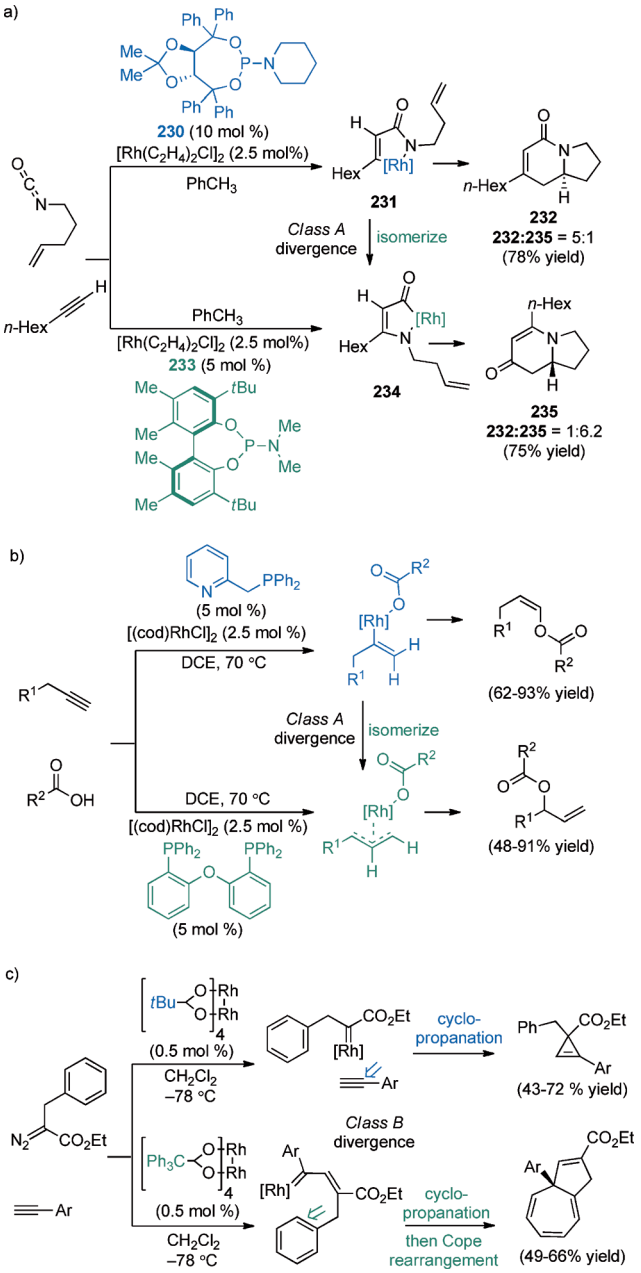
The examples so far can be classified into either *Class A* or *B* divergence, in which either the choice of ligand or metal determines the product selectivity. In many instances, however, the control of selectivity is less obvious; a judicious combination of metal, additive, and/or ligand type must be taken into account together. We show three more examples of cycloisomerization reactions, in which product selectivity arises from: 1) an additive effect (Scheme 57a for Pd-catalyzed cycloisomerization of alkylidene cyclopropyl ketones);[214] 2) the combination of metal and base choices (Scheme 57b for Cu-catalyzed rearrangements of *N*-allyl enamines);[215] 3) the combination of metal and ligand choices (Scheme 57c for Cu-catalyzed carbonyl ylide insertion reaction).[216]

Besides C–C or C–heteroatom bond formations, metal catalysts offer a unique mode of activity for product-selective bond cleavages. In their study of derivatization of phenolic lignin, Hanson and Silks[217] reported unusual C–O versus C–C cleavage through aerobic oxidation of **248** (Scheme 58). Vanadium catalyst **249** selectively breaks the C–C bond between the aryl group (bearing two OMe groups) and the adjacent hydroxy group to form **250** and **251** while another vanadium complex **252** cleaves only a C–O bond to afford **253** and **254**.

9. Other Approaches to Selective Catalysis

This Review has focused exclusively on homogeneous catalysis as a means of controlling product selectivity. This is by no means the only solution and researchers in other area of catalysis are actively pursuing other solutions to controlling product selectivity. We highlight three important or emerging areas. Enzymes are well known as highly selective catalysts that often give divergent products from the same substrate. Scientists have sought to exploit this exquisite selectivity in effecting organic transformation to develop enantio-, chemo-, and product-selective enzymes by discovery, design, and directed evolution.[218] Two examples showcase two remarkable sets of enzymes for regioselective functionalization. Faber et al.[219] reported alkene and arene carboxylation of hydroxystyrene by decarboxylase enzymes (Scheme 59a). Challis et al.[220] disclosed regio- and stereodivergent oxidative cyclizations catalyzed by Rieske-oxygenase-like enzymes, resulting in macrocycles of different ring size (Scheme 59b).

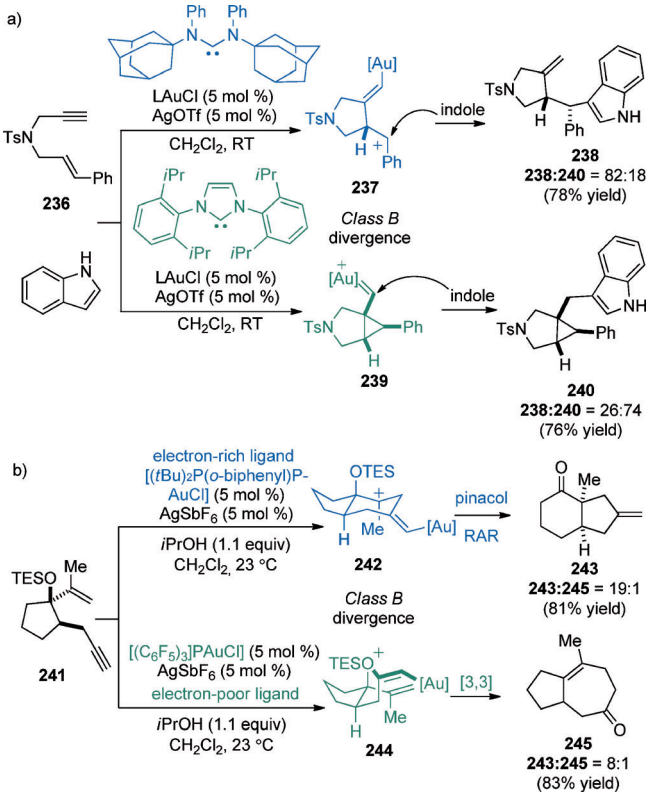
Heterogeneous catalysis can also offer solutions to product selectivity by the choice of catalyst, surface, and other factors that are currently under intense investigation. For example, Corma et al.[221] disclosed a Sn-zeolite beta catalyst for chemoselective Baeyer–Villiger oxidation (**256**) of dihydrocarvone **255** without an epoxidation of the alkene (**257**). The reverse selectivity—epoxidation with the absence



Scheme 55. Product selectivity from changing ligands in Rh catalysis.

of Baeyer–Villiger oxidation—was achieved by using heterogeneous Ti-zeolite beta catalyst (Scheme 60a). In a similar manner, Koper et al.[222] reported that glycerol can also be oxidized to glyceraldehyde or glyceric acid almost exclusively on Pt-electrode catalyst. However, in the presence of bismuth, chemoselective secondary alcohol oxidation[223] dominated and led to an elegant approach to the production of dihydroxyacetone—a compound of cosmetic-industry interest (Scheme 60b). HPLC and in situ FTIR studies show that the presence of Bi blocks the pathway for primary alcohol oxidation and provides a specific Pt–Bi surface site poised for secondary alcohol oxidation.

We close with a new concept for inducing selectivity under otherwise identical reaction conditions. Kanan et al. have



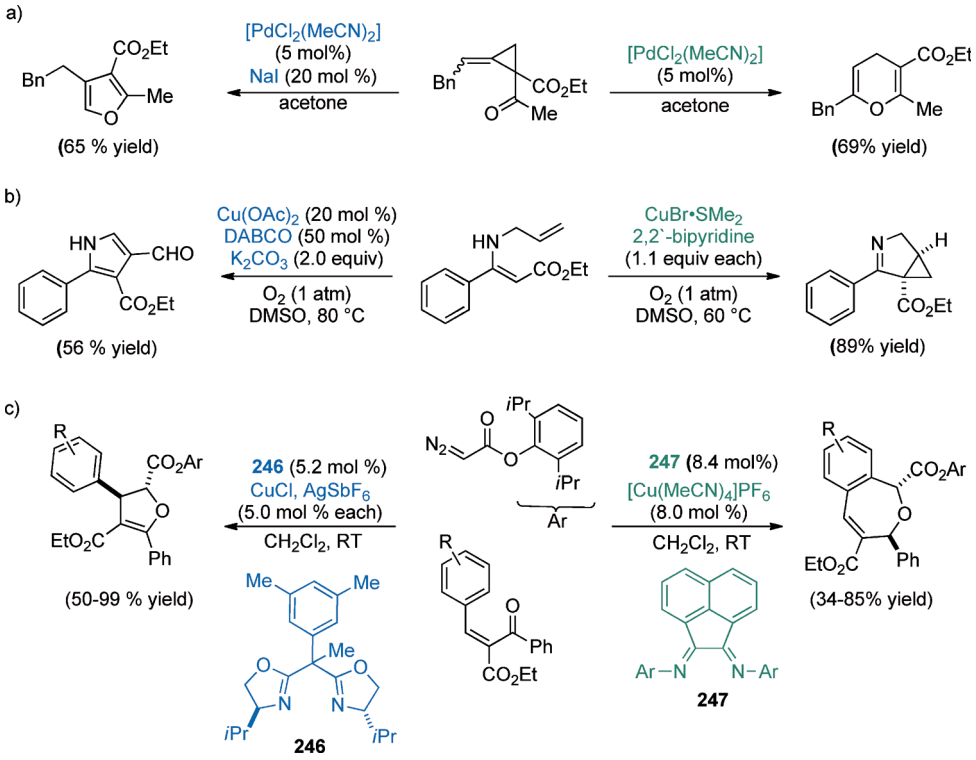
Scheme 56. Ligand-controlled product selectivity from gold catalysis.

recently reported a curious case of the rearrangement of *cis*-stilbene oxide catalyzed by Al_2O_3 deposited on Si electrodes to form either aldehyde **259** or ketone **260** (Scheme 61).[224] This strategy relies on a field–dipole effect, in which selectivity ($\Delta\Delta G^{\ddagger}$) is a function of electric field strength (E) and the difference in chemical potential ($\Delta\mu$).

10. Summary and Outlook

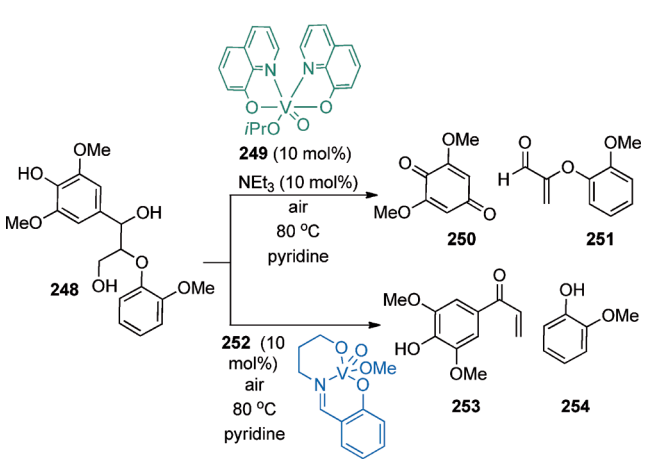
The long-stated goal of catalysis is to selectively transform a given starting material into the desired product, with complete control of product selectivity and stereochemistry. As we hope this treatise shows, organic chemists have made great progress in the design and study of catalysts for exquisitely selective transformations. Many of these advances have been fuelled by the enormous effort directed towards catalytic, enantioselective synthesis. This research has demonstrated convincingly that almost any catalytic reaction can be rendered enantioselective by a combination of hard work, ligand design, and a bit of luck. The successes in this realm have clearly encouraged researchers to extend these principles and tactics to the arguably even more difficult challenge of regio-, chemo-, and product selectivity.

As with the early days of catalytic enantioselective synthesis, many of the results included in this Review were serendipitous, particularly in the case of product selectivity. More work is needed to make the design and optimization of a selective catalysis a routine and predictable practice. This will be aided by improved mechanistic understanding, both of



Scheme 57. Other examples of cycloisomerizations with complex mechanistic pathways.

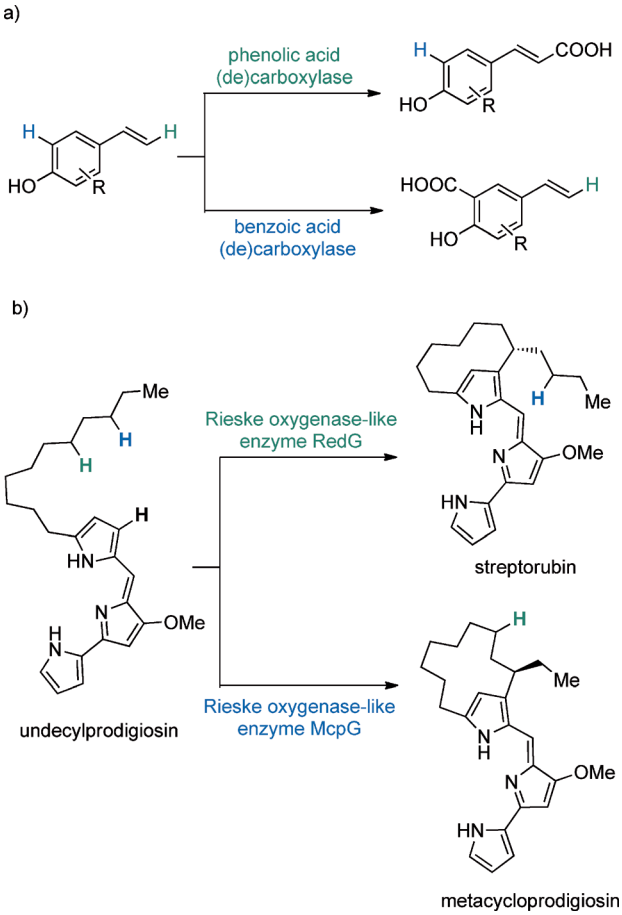
done to what *needs* to be done. While celebrating the success of selective catalysis, we should not forget that there are still many fundamental transformations that cannot be easily and directly accomplished by a single catalytic reaction. The anti-Markovnikov hydration of alkenes, the specific hydrogenation of a single alkene in a polyunsaturated substrate or the conversion of an amide into an amine in the presence of a ketone are representative transformation for which there are no straightforward catalytic solutions. These and hundreds of other high value but difficult transformations should keep organic chemists busy for years to come. As environmental concerns and diminishing natural resources reduce the choice of available



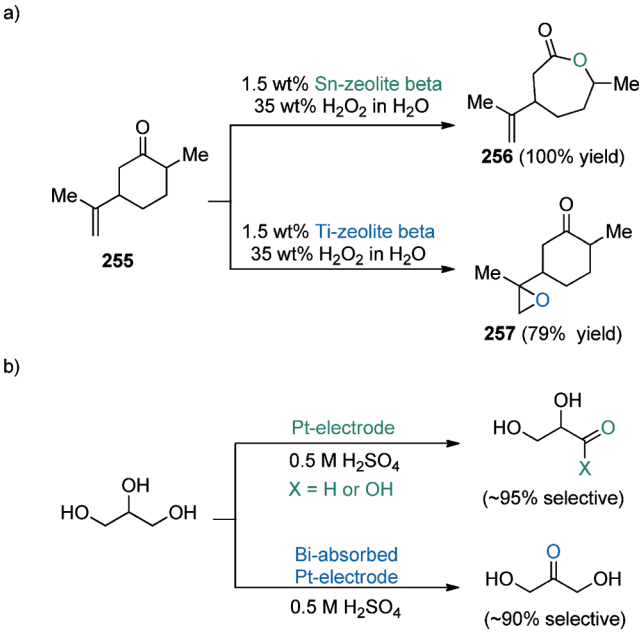
Scheme 58. Selective bond cleavage reactions.

the underlying principles governing the selective reactions as well as the remarkable, but often very subtle, effect of ligands on controlling the outcome of the transformation. Computational methods to visualize and rationalize the transition states governing the selective reactions offer an exciting dimension for improving the understanding and design of selective catalysts. For practical application, strictly catalyst-controlled selectivities can often be further enhanced by traditional approaches such as change of solvent, temperature, or additives.

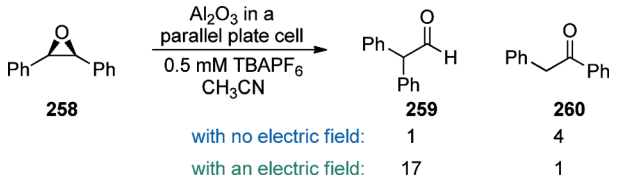
Now that the principles behind selective catalysis, including enantioselectivity, are well-established and widely practiced, the emphasis in the field must shift from what *can* be



Scheme 59. Enzyme-catalyzed regioselective functionalizations.



Scheme 60. Chemoselective oxidation reactions.



Scheme 61. Electric field-induced product-selective catalysis.

substrates, the design of the right catalyst for a given transformation will only become more important.

This work was supported by ETH-Zürich and a fellowship from Novartis (to J.M.).

Received: March 5, 2012
Published online: September 25, 2012

[1] a) W. A. Nugent, T. V. RajanBabu, M. J. Burk, *Science* **1993**, *259*, 479 – 483; b) B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5348 – 5355; c) M. S. Taylor, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5368 – 5373.
[2] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691 – 1693.
[3] B. M. Trost, *Science* **1983**, *219*, 245 – 250.
[4] K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2126 – 2135; *Angew. Chem. Int. Ed.* **2002**, *41*, 2024 – 2032.
[5] a) C. A. Lewis, S. J. Miller, *Angew. Chem.* **2006**, *118*, 5744 – 5747; *Angew. Chem. Int. Ed.* **2006**, *45*, 5616 – 5619; b) C. A. Lewis, K. E. Longcore, S. J. Miller, P. A. Wender, *J. Nat. Prod.* **2009**, *72*, 1864 – 1869; c) T. P. Pathak, S. J. Miller, *J. Am. Chem. Soc.* **2012**, *134*, 6120 – 6123.
[6] P. A. Jordan, S. J. Miller, *Angew. Chem.* **2012**, *124*, 2961 – 2965; *Angew. Chem. Int. Ed.* **2012**, *51*, 2907 – 2911.
[7] a) B. Trost, *Science* **1991**, *254*, 1471 – 1477; b) I. S. Young, P. S. Baran, *Nat. Chem.* **2009**, *1*, 193 – 205; c) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896 – 2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854 – 2867.
[8] B. Trost, *Angew. Chem.* **2012**, *124*, 7182 – 7184; *Angew. Chem. Int. Ed.* **2012**, *51*, 7074 – 7076.
[9] D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Org. Lett.* **2006**, *8*, 2523 – 2526.
[10] For a review of innate versus directed reactions in the context of C–H functionalization, see T. Brückl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **2012**, *45*, 826 – 839. For a review of site-selectivity in C–H functionalization, see S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936 – 946.
[11] R. Shintani, W.-L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5628 – 5629.
[12] K. M. Partridge, I. A. Guzei, T. P. Yoon, *Angew. Chem.* **2010**, *122*, 942 – 946; *Angew. Chem. Int. Ed.* **2010**, *49*, 930 – 934.
[13] Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411 – 14415.
[14] I. Larrosa, C. Somoza, A. Banquy, S. M. Goldup, *Org. Lett.* **2011**, *13*, 146 – 149.
[15] For example, a) G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498 – 2543; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450 – 2494; b) K. L. Tan, *ACS Catal.* **2011**, *1*, 877 – 886.
[16] A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191 – 1224.
[17] D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072 – 12073.
[18] R. E. Gawley, *J. Org. Chem.* **2006**, *71*, 2411 – 2416.
[19] For example, a) I. Toth, I. Guo, B. E. Hanson, *Organometallics* **1993**, *12*, 848 – 852; b) D. Enders, E. C. Ullrich, *Tetrahedron: Asymmetry* **2000**, *11*, 3861 – 3865.
[20] R. R. Knowles, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 5030 – 5032.
[21] a) Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 7457 – 7461; *Angew. Chem. Int. Ed.* **2010**, *49*, 7299 – 7303; b) Y. Sohtome, B. Shin, N. Horitsugi, K. Noguchi, K. Nagasawa, *Chem. Asian J.* **2011**, *6*, 2463 – 2470.
[22] Y. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 9440 – 9443; *Angew. Chem. Int. Ed.* **2010**, *49*, 9254 – 9257.
[23] This approach has been demonstrated in a non-catalytic reaction: M. Nigam, M. S. Platz, B. M. Showalter, J. P. Toscano, R. Johnson, S. C. Abbot, M. M. Kirchhoff, *J. Am. Chem. Soc.* **1998**, *120*, 8055 – 8059.
[24] Besides this Eyring approach shown here, linear-free-energy relationship (i.e. Hammett analysis) can also be applied to elucidate electronic factors governing selectivity. For example, a) E. W. Werner, K. B. Urkalan, M. S. Sigman, *Org. Lett.* **2010**, *12*, 2848 – 2851; b) E. W. Werner, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 13981 – 13983.
[25] The concept of kinetic versus thermodynamic control in organic reactions was introduced by Woodward and Baer: R. B. Woodward, H. Baer, *J. Am. Chem. Soc.* **1944**, *66*, 645 – 649.
[26] J. Mahatthananchai, P. Zheng, J. W. Bode, *Angew. Chem.* **2011**, *123*, 1711 – 1715; *Angew. Chem. Int. Ed.* **2011**, *50*, 1673 – 1677.
[27] The product-determining step is defined as "*the step of a stepwise reaction, in which the product distribution is determined. The product-determining step may be identical to, or occur later than, the rate-controlling step on the reaction coordinate.*" See P. Muller, *Pure Appl. Chem.* **1994**, *66*, 1077 – 1184. For a recent discussion in the context of complex catalytic reactions, see E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120 – 3126; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066 – 3072.

[28] a) J. Mahatthananchai, J. Kaeobamrung, J. W. Bode, *ACS Catal.* **2012**, *2*, 494 – 503; b) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810 – 8812.
[29] a) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080 – 1081. For other regiodivergent reactions of nitroso electrophiles, see: b) *N*-alkylation: T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 6046 – 6047; c) *O*-alkylation: C. Palomo, S. Vera, I. Velilla, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2007**, *119*, 8200 – 8202; *Angew. Chem. Int. Ed.* **2007**, *46*, 8054 – 8056.
[30] a) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2012**, *77*, 658 – 668; b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 – 1345.
[31] a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624 – 655; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169.
[32] O. Daugulis, V. G. Zaitsev, *Angew. Chem.* **2005**, *117*, 4114 – 4116; *Angew. Chem. Int. Ed.* **2005**, *44*, 4046 – 4048.
[33] R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593 – 1597.
[34] B. Chen, X.-L. Hou, Y.-X. Li, Y.-D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 7668 – 7671.
[35] a) M. Dams, D. E. De Vos, S. Celen, P. A. Jacobs, *Angew. Chem.* **2003**, *115*, 3636 – 3639; *Angew. Chem. Int. Ed.* **2003**, *42*, 3512 – 3515. For similar reports see: b) H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337 – 338; c) T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2003**, *125*, 1476 – 1477.
[36] Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072 – 5074.
[37] a) J.-Y. Cho, C. N. Iverson, M. R. Smith, *J. Am. Chem. Soc.* **2000**, *122*, 12868 – 12869; b) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, M. R. Smith, *Science* **2002**, *295*, 305 – 308; c) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390 – 391.
[38] For overviews and studies on the inherent reactivity in these reactions, see: a) J. F. Hartwig, *Chem. Soc. Rev.* **2011**, *40*, 1992 – 2002; b) I. I. B. A. Vanchura II, S. M. Preshlock, P. C. Roosen, V. A. Kallepalli, R. J. Staples, J. R. E. Maleczka, D. A. Singleton, I. I. I. M. R. Smith, *Chem. Commun.* **2010**, *46*, 7724 – 7726.
[39] T. E. Hurst, T. K. Macklin, M. Becker, E. Hartmann, W. Kügel, J.-C. Parisienne-La Salle, A. S. Batsanov, T. B. Marder, V. Snieckus, *Chem. Eur. J.* **2010**, *16*, 8155 – 8161.
[40] K. Yamazaki, S. Kawamorita, H. Ohmiya, M. Sawamura, *Org. Lett.* **2010**, *12*, 3978 – 3981.
[41] N. Miyaura, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535 – 1553; note, catalyst loading was not provided in the manuscript.
[42] K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chem.* **2010**, *122*, 9130 – 9133; *Angew. Chem. Int. Ed.* **2010**, *49*, 8946 – 8949.
[43] S.-Y. Tang, Q.-X. Guo, Y. Fu, *Chem. Eur. J.* **2011**, *17*, 13866 – 13876.
[44] N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972 – 4973.
[45] R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172 – 8174.
[46] a) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050 – 8057; b) L. Joucla, N. Batail, L. Djakovitch, *Adv. Synth. Catal.* **2010**, *352*, 2929 – 2936.
[47] D. Stuart, K. Fagnou, *Top. Organomet. Chem.* **2012**, DOI: 10.1007/3418_2012_52.
[48] A. N. Campbell, E. B. Meyer, S. S. Stahl, *Chem. Commun.* **2011**, *47*, 10257 – 10259.
[49] S. Urban, N. Ortega, F. Glorius, *Angew. Chem.* **2011**, *123*, 3887 – 3890; *Angew. Chem. Int. Ed.* **2011**, *50*, 3803 – 3806.
[50] K. Oshima, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2012**, *134*, 3699 – 3702.
[51] M. Arrowsmith, M. S. Hill, T. Hadlington, G. Kociok-Köhn, C. Weetman, *Organometallics* **2011**, *30*, 5556 – 5559.
[52] M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448 – 3479; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368 – 3398.
[53] L. Hintermann, *Top. Organomet. Chem.* **2010**, *31*, 123 – 155.
[54] J. A. Wright, M. J. Gaunt, J. B. Spencer, *Chem. Eur. J.* **2006**, *12*, 949 – 955.
[55] T. Hosokawa, T. Ohta, S. Kanayama, S. Murahashi, *J. Org. Chem.* **1987**, *52*, 1758 – 1764.
[56] A. M. Balija, K. J. Stowers, M. J. Schultz, M. S. Sigman, *Org. Lett.* **2006**, *8*, 1121 – 1124.
[57] B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc.* **2009**, *131*, 9473 – 9474.
[58] B. W. Michel, J. R. McCombs, A. Winkler, M. S. Sigman, *Angew. Chem.* **2010**, *122*, 7470 – 7473; *Angew. Chem. Int. Ed.* **2010**, *49*, 7312 – 7315.
[59] B. W. Michel, L. D. Steffens, M. S. Sigman, *J. Am. Chem. Soc.* **2011**, *133*, 8317 – 8325.
[60] J. L. Brice, J. E. Harang, V. I. Timokhin, N. R. Anastasi, S. S. Stahl, *J. Am. Chem. Soc.* **2005**, *127*, 2868 – 2869.
[61] V. I. Timokhin, N. R. Anastasi, S. S. Stahl, *J. Am. Chem. Soc.* **2003**, *125*, 12996 – 12997.
[62] V. I. Timokhin, S. S. Stahl, *J. Am. Chem. Soc.* **2005**, *127*, 17888 – 17893.
[63] G. Yang, W. Zhang, *Org. Lett.* **2012**, *14*, 268 – 271.
[64] B. Breit, *Top. Curr. Chem.* **2007**, *279*, 139 – 172.
[65] A. C. Chen, L. Ren, A. Decken, C. M. Crudden, *Organometallics* **2000**, *19*, 3459 – 3461.
[66] S. Yu, Y.-m. Chie, Z.-h. Guan, Y. Zou, W. Li, X. Zhang, *Org. Lett.* **2009**, *11*, 241 – 244.
[67] L. A. van der Veen, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Angew. Chem.* **1999**, *111*, 349 – 351; *Angew. Chem. Int. Ed.* **1999**, *38*, 336 – 338.
[68] M. Kuil, T. Soltner, P. W. N. M. van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2006**, *128*, 11344 – 11345.
[69] T. E. Lightburn, M. T. Dombrowski, K. L. Tan, *J. Am. Chem. Soc.* **2008**, *130*, 9210 – 9211.
[70] C. U. Grünanger, B. Breit, *Angew. Chem.* **2008**, *120*, 7456 – 7459; *Angew. Chem. Int. Ed.* **2008**, *47*, 7346 – 7349.
[71] A. I. M. Keulemans, A. Kwantes, T. van Bavel, *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 298 – 308.
[72] X. Sun, K. Frimpong, K. L. Tan, *J. Am. Chem. Soc.* **2010**, *132*, 11841 – 11843.
[73] A triple-relay catalysis system exploiting the high regioselectivity of the Wacker oxidation combined with a Ru-catalyzed transfer hydrogenation for the formal anti-Markovnikov hydration of alkenes is an impressive atom-economical solution to this problem. See: G. Dong, P. Teo, Z. K. Wickens, R. H. Grubbs, *Science* **2011**, *333*, 1609 – 1612.
[74] C. M. Crudden, Y. B. Hleba, A. C. Chen, *J. Am. Chem. Soc.* **2004**, *126*, 9200 – 9201.
[75] Y. Yamamoto, R. Fujikawa, T. Umemoto, N. Miyaura, *Tetrahedron* **2004**, *60*, 10695 – 10700.
[76] C. J. Lata, C. M. Crudden, *J. Am. Chem. Soc.* **2010**, *132*, 131 – 137.
[77] P.-F. Fu, L. Brard, Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **1995**, *117*, 7157 – 7168.
[78] S. C. Bart, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2004**, *126*, 13794 – 13807.
[79] A. M. Tondreau, C. C. H. Atienza, K. J. Weller, S. A. Nye, K. M. Lewis, J. G. P. Delis, P. J. Chirik, *Science* **2012**, *335*, 567 – 570.
[80] Y. Ura, G. Gao, F. Bao, M. Ogasawara, T. Takahashi, *Organometallics* **2004**, *23*, 4804 – 4806.
[81] For an earlier example, see: M. Larhed, C.-M. Andersson, A. Hallberg, *Tetrahedron* **1994**, *50*, 285 – 304.

[82] D. Tsvelikhovsky, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14048 – 14051.
[83] For some tactics to achieve good regiocontrol in intermolecular Heck reactions, see: a) J. Ruan, J. Xiao, *Acc. Chem. Res.* **2011**, *44*, 614 – 626; b) M. Oestreich, *Top. Organomet. Chem.* **2007**, *24*, 169 – 192. For a recently reported stoichiometric example of regiocontrol in Heck reactions of electron-poor alkenes, see: c) P. Wucher, L. Caporaso, P. Roesle, F. Ragone, L. Cavallo, S. Mecking, I. Göttker-Schnetmann, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 8955 – 8959.
[84] K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 400 – 402.
[85] G. Hilt, F.-X. du Mesnil, S. Lüers, *Angew. Chem.* **2001**, *113*, 408 – 410; *Angew. Chem. Int. Ed.* **2001**, *40*, 387 – 389.
[86] M. Arndt, M. Dindaroğlu, H.-G. Schmalz, G. Hilt, *Org. Lett.* **2011**, *13*, 6236 – 6239.
[87] B. Moreau, J. Y. Wu, T. Ritter, *Org. Lett.* **2009**, *11*, 337 – 339.
[88] F. Viton, G. Bernardinelli, E. P. Kündig, *J. Am. Chem. Soc.* **2002**, *124*, 4968 – 4969.
[89] D. Carmona, M. P. Lamata, F. Viguri, R. Rodríguez, L. A. Oro, A. I. Balana, F. J. Lahoz, T. Tejero, P. Merino, S. Franco, I. Montesa, *J. Am. Chem. Soc.* **2004**, *126*, 2716 – 2717.
[90] N. Marion, R. S. Ramón, S. P. Nolan, *J. Am. Chem. Soc.* **2009**, *131*, 448 – 449.
[91] F. Boeck, T. Kribber, L. Xiao, L. Hintermann, *J. Am. Chem. Soc.* **2011**, *133*, 8138 – 8141.
[92] M. Tokunaga, Y. Wakatsuki, *Angew. Chem.* **1998**, *110*, 3024 – 3027; *Angew. Chem. Int. Ed.* **1998**, *37*, 2867 – 2869.
[93] L. J. Goossen, J. Paetzold, D. Koley, *Chem. Commun.* **2003**, 706 – 707.
[94] H. Doucet, B. Martin-Vaca, C. Bruneau, P. H. Dixneuf, *J. Org. Chem.* **1995**, *60*, 7247 – 7255.
[95] R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407 – 1420.
[96] A. Ogawa, *Top. Organomet. Chem.* **2012**, DOI: 10.1007/3418_2011_19.
[97] a) M. J. Gainer, N. R. Bennett, Y. Takahashi, R. E. Looper, *Angew. Chem.* **2011**, *123*, 710 – 713; *Angew. Chem. Int. Ed.* **2011**, *50*, 684 – 687; b) A.-L. Girard, T. Enomoto, S. Yokouchi, C. Tsukano, Y. Takemoto, *Chem. Asian J.* **2011**, *6*, 1321 – 1324.
[98] H. Jang, A. R. Zhugralin, Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7859 – 7871.
[99] T. Ohmura, K. Oshima, H. Taniguchi, M. Suginome, *J. Am. Chem. Soc.* **2010**, *132*, 12194 – 12196.
[100] F. Gao, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10961 – 10963.
[101] U. Kazmaier, M. Pohlman, D. Schauß, *Eur. J. Org. Chem.* **2000**, 2761 – 2766.
[102] A. Darwish, A. Lang, T. Kim, J. M. Chong, *Org. Lett.* **2008**, *10*, 861 – 864.
[103] For an example of regioselective alkyne hydroacylation see: C. González-Rodríguez, R. J. Pawley, A. B. Chaplin, A. L. Thompson, A. S. Weller, M. C. Willis, *Angew. Chem.* **2011**, *123*, 5240 – 5244; *Angew. Chem. Int. Ed.* **2011**, *50*, 5134 – 5138.
[104] For a discussion of factors controlling the regioselectivity in such reactions, see: R. M. Moslin, K. Miller-Moslin, T. F. Jamison, *Chem. Commun.* **2007**, 4441 – 4449.
[105] K. M. Miller, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 15342 – 15343.
[106] H. A. Malik, G. J. Sormunen, J. Montgomery, *J. Am. Chem. Soc.* **2010**, *132*, 6304 – 6305.
[107] P. Liu, J. Montgomery, K. N. Houk, *J. Am. Chem. Soc.* **2011**, *133*, 6956 – 6959.
[108] A.-R. Shareef, D. H. Sherman, J. Montgomery, *Chem. Sci.* **2012**, *3*, 892 – 895.
[109] C. C. Bausch, R. L. Patman, B. Breit, M. J. Krische, *Angew. Chem.* **2011**, *123*, 5805 – 5808; *Angew. Chem. Int. Ed.* **2011**, *50*, 5687 – 5690.
[110] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057 – 3064.
[111] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708 – 2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596 – 2599.
[112] L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998 – 15999.
[113] B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923 – 8930.
[114] S. Kezuka, S. Tanaka, T. Ohe, Y. Nakaya, R. Takeuchi, *J. Org. Chem.* **2006**, *71*, 543 – 552.
[115] M. Satoh, Y. Nomoto, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1989**, *30*, 3789 – 3792.
[116] M. Zaidlewicz, J. Meller, *Tetrahedron Lett.* **1997**, *38*, 7279 – 7282.
[117] J. Y. Wu, B, Moreau, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 12915 – 12917.
[118] Y. Sasaki, Y. Horita, C. Zhong, M. Sawamura, H. Ito, *Angew. Chem.* **2011**, *123*, 2830 – 2834; *Angew. Chem. Int. Ed.* **2011**, *50*, 2778 – 2782.
[119] W. Yuan, H. Du, B. Zhao, Y. Shi, *Org. Lett.* **2007**, *9*, 2589 – 2591.
[120] H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 762 – 763.
[121] B. Zhao, X. Peng, Y. Zhu, T. A. Ramirez, R. G. Cornwall, Y. Shi, *J. Am. Chem. Soc.* **2011**, *133*, 20890 – 20900.
[122] B. Zhao, H. Du, S. Cui, Y. Shi, *J. Am. Chem. Soc.* **2010**, *132*, 3523 – 3532.
[123] R. G. Cornwall, B. Zhao, Y. Shi, *Org. Lett.* **2011**, *13*, 434 – 437.
[124] V. Komanduri, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 16448 – 16449.
[125] R. L. Patman, V. M. Williams, J. F. Bower, M. J. Krische, *Angew. Chem.* **2008**, *120*, 5298 – 5301; *Angew. Chem. Int. Ed.* **2008**, *47*, 5220 – 5223.
[126] For an early but impressive demonstration of such a reversal in the reaction of nitrostyrenes, see: P. V. Alston, R. M. Ottenbrite, *J. Org. Chem.* **1975**, *40*, 1111 – 1116.
[127] G. Hilt, F.-X. du Mesnil, *Tetrahedron Lett.* **2000**, *41*, 6757 – 6761.
[128] G. Hilt, J. Janikowski, W. Hess, *Angew. Chem.* **2006**, *118*, 5328 – 5331; *Angew. Chem. Int. Ed.* **2006**, *45*, 5204 – 5206.
[129] P. Mörschel, J. Janikowski, G. Hilt, G. Frenking, *J. Am. Chem. Soc.* **2008**, *130*, 8952 – 8966.
[130] While the authors try to adhere to the definition of different type of selectivities given by IUPAC (http://goldbook.iupac.org/), we acknowledge that certain terms such as "regioselective conjugate addition" are used colloquially throughout the literature and do not follow the strict IUPAC definition. For the sake of coherence of this Review in terms of content, we will, in this instance, use the colloquial "regioselective" modifier.
[131] a) J.-L. Luche, L. Rodriguez-Hahn, P. Crabbe, *J. Chem. Soc. Chem. Commun.* **1978**, 601 – 602; b) M. Lozanov, J. Montgomery, *Tetrahedron Lett.* **2001**, *42*, 3259 – 3261.
[132] Y. Kanazawa, H. Nishiyama, *Synlett* **2006**, 3343 – 3345.
[133] a) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32 – 33; b) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110 – 112; *Angew. Chem. Int. Ed.* **2005**, *44*, 108 – 110.
[134] K. R. Voigtritter, N. A. Isley, R. Moser, D. H. Aue, B. H. Lipshutz, *Tetrahedron* **2012**, *68*, 3410 – 3416.
[135] B. H. Lipshutz, J. M. Servesko, B. R. Taft, *J. Am. Chem. Soc.* **2004**, *126*, 8352 – 8353.
[136] C. Czekelius, E. M. Carreira, *Angew. Chem.* **2003**, *115*, 4941 – 4943; *Angew. Chem. Int. Ed.* **2003**, *42*, 4793 – 4795.
[137] S. L. Buchwald, Y. Aye, M. P. Rainka, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5821 – 5823.

[138] For extensive reviews, see a) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169 – 196; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829 – 2844.
[139] J.-F. Paquin, C. Defieber, C. R. J. Stephenson, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 10850 – 10851.
[140] M. Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450 – 4452.
[141] J. Lv, L. Zhang, Y. Zhou, Z. Nie, S. Luo, J.-P. Cheng, *Angew. Chem.* **2011**, *123*, 6740 – 6744; *Angew. Chem. Int. Ed.* **2011**, *50*, 6610 – 6614.
[142] "Transition-Metal Catalyzed Enantioselective Allylic Substitution in Organic Chemistry": *Topics in Organometallic Chemistry*, *Vol. 38* (Ed.: U. Kazmeier), Springer, Heidelberg, **2012**.
[143] P J. Harrington in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. Stone, G. Wilkinson), Elsevier, Oxford, **1995**.
[144] a) R. Takeuchi, M. Kashio, *Angew. Chem.* **1997**, *109*, 268 – 270; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 263 – 265; b) For a fundamental study on the nature of the intermediate in Ir-catalyzed allylations, see: S. T. Madrahimov, D. Markovic, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 7228 – 7229.
[145] For some previous examples of such reversals in Pd-catalyzed reactions, see: a) R. Prétôt, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 337 – 339; *Angew. Chem. Int. Ed.* **1998**, *37*, 323 – 325; b) S.-L. You, X.-Z. Zhu, Y.-M. Luo, X.-L. Hou, L.-X. Dai, *J. Am. Chem. Soc.* **2001**, *123*, 7471 – 7472.
[146] B. M. Trost, S. Malhotra, W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 7328 – 7331.
[147] B. Plietker, A. Dieskau, K. Möws, A. Jatsch, *Angew. Chem.* **2008**, *120*, 204 – 207; *Angew. Chem. Int. Ed.* **2008**, *47*, 198 – 201.
[148] M. Holzwarth, A. Dieskau, M. Tabassam, B. Plietker, *Angew. Chem.* **2009**, *121*, 7387 – 7391; *Angew. Chem. Int. Ed.* **2009**, *48*, 7251 – 7255.
[149] M. Pérez, M. Fañanás-Mastral, P. H. Bos, A. Rudolph, S. R. Harutyunyan, B. L. Feringa, *Nat. Chem.* **2011**, *3*, 377 – 381.
[150] Y. Sevryugina, B. Weaver, J. Hansen, J. Thompson, H. M. L. Davies, M. A. Petrukhina, *Organometallics* **2008**, *27*, 1750 – 1757.
[151] J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 457 – 461.
[152] M. P. Doyle, M. Yan, W. Hu, L. S. Gronenberg, *J. Am. Chem. Soc.* **2003**, *125*, 4692 – 4693.
[153] D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 14440 – 14441.
[154] For an excellent account on chemoselective reactions both catalytic and otherwise, see N. A. Afagh, A. K. Yudin, *Angew. Chem.* **2010**, *122*, 270 – 320; *Angew. Chem. Int. Ed.* **2010**, *49*, 262 – 310.
[155] For a review of chemoselectivity in esterifications, see M. Nahmany, A. Melman, *Org. Biomol. Chem.* **2004**, *2*, 1563 – 1572.
[156] For example, A. D. Worthy, X. Sun, K. L. Tan, *J. Am. Chem. Soc.* **2012**, *134*, 7321 – 7324.
[157] H. F. Olivo, M. S. Hemenway, M. H. Gezginci, *Tetrahedron Lett.* **1998**, *39*, 1309 – 1312.
[158] T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama, K. Mashima, *J. Am. Chem. Soc.* **2008**, *130*, 2944 – 2945.
[159] S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190 – 1191.
[160] a) K. Daigo, L. J. Reed, *J. Am. Chem. Soc.* **1962**, *84*, 659 – 662; b) T. C. Owen, A. Richards, *J. Am. Chem. Soc.* **1987**, *109*, 2520 – 2521; c) T. C. Owen, J. N. Harris, *J. Am. Chem. Soc.* **1990**, *112*, 6136 – 6137.
[161] A. Shafir, P. A. Lichtor, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3490 – 3491.
[162] G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3703 – 3706.
[163] D. Maiti, *Chem. Commun.* **2011**, *47*, 8340 – 8342.
[164] L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 3041 – 3043.
[165] C. B. Tripathi, S. Mukherjee, *J. Org. Chem.* **2012**, *77*, 1592 – 1598.
[166] For a recent general overview, see A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243 – 251.
[167] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370.
[168] S. P. Nolan, H. Clavier, *Chem. Soc. Rev.* **2010**, *39*, 3305 – 3316.
[169] A. Fürstner, L. Ackermann, B. Gabor, R. Goddard, C. W. Lehmann, R. Mynott, F. Stelzer, O. R. Thiel, *Chem. Eur. J.* **2001**, *7*, 3236 – 3253.
[170] C. W. Lee, R. H. Grubbs, *J. Org. Chem.* **2001**, *66*, 7155 – 7158.
[171] S. Ma, B. Ni, *Chem. Eur. J.* **2004**, *10*, 3286 – 3300.
[172] J. Holtsclaw, M. Koreeda, *Org. Lett.* **2004**, *6*, 3719 – 3722.
[173] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020 – 4028.
[174] F. Schoenebeck, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 2496 – 2497.
[175] a) F. Proutiere, F. Schoenebeck, *Angew. Chem.* **2011**, *123*, 8342 – 8345; *Angew. Chem. Int. Ed.* **2011**, *50*, 8192 – 8195; b) F. Proutiere, M. Aufiero, F. Schoenebeck, *J. Am. Chem. Soc.* **2012**, *134*, 606 – 612.
[176] T. Kamikawa, T. Hayashi, *Tetrahedron Lett.* **1997**, *38*, 7087 – 7090.
[177] N. Yoshikai, A. Matsumoto, J. Norinder, E. Nakamura, *Angew. Chem.* **2009**, *121*, 2969 – 2972; *Angew. Chem. Int. Ed.* **2009**, *48*, 2925 – 2928.
[178] I. N. Houpis, C. Huang, U. Nettekoven, J. G. Chen, R. Liu, M. Canters, *Org. Lett.* **2008**, *10*, 5601 – 5604.
[179] I. N. Houpis, R. Liu, Y. Wu, Y. Yuan, Y. Wang, U. Nettekoven, *J. Org. Chem.* **2010**, *75*, 6965 – 6968.
[180] I. N. Houpis, K. Weerts, U. Nettekoven, M. Canters, H. Tan, R. Liu, Y. Wang, *Adv. Synth. Catal.* **2011**, *353*, 538 – 544.
[181] L.-C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266 – 3267.
[182] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118 – 1126.
[183] D. J. Schipper, L.-C. Campeau, K. Fagnou, *Tetrahedron* **2009**, *65*, 3155 – 3164.
[184] D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234 – 245.
[185] R. A. Altman, A. M. Hyde, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 9613 – 9620.
[186] a) S. Lee, N. A. Beare, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 8410 – 8411; b) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 12557 – 12565.
[187] A. Renaudat, L. Jean-Gérard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem.* **2010**, *122*, 7419 – 7423; *Angew. Chem. Int. Ed.* **2010**, *49*, 7261 – 7265.
[188] P. Larini, C. E. Kefalidis, R. Jazzar, A. Renaudat, E. Clot, O. Baudoin, *Chem. Eur. J.* **2012**, *18*, 1932 – 1944.
[189] K. Williams Fiori, J. J. Fleming, J. Du Bois, *Angew. Chem.* **2004**, *116*, 4449 – 4452; *Angew. Chem. Int. Ed.* **2004**, *43*, 4349 – 4352.
[190] C. J. Hayes, P. W. Beavis, L. A. Humphries, *Chem. Commun.* **2006**, 4501 – 4502.
[191] T. Hatakeyama, Y. Okada, Y. Yoshimoto, M. Nakamura, *Angew. Chem.* **2011**, *123*, 11165 – 11168; *Angew. Chem. Int. Ed.* **2011**, *50*, 10973 – 10976.
[192] a) B. Alcaide, P. Almendros, T. Martínez del Campo, *Chem. Eur. J.* **2008**, *14*, 7756 – 7759; b) B. Alcaide, P. Almendros, T. Martínez del Campo, M. C. Redondo, I. Fernández, *Chem. Eur. J.* **2011**, *17*, 15005 – 15013.
[193] For recent reviews of N-heterocyclic carbene catalysis: a) P.-C. Chiang, J. W. Bode, *N-Heterocyclic Carbenes*, The Royal Society of Chemistry, London, **2011**, pp. 399 – 435; b) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511 – 3522; c) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617 – 1639.
[194] S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873 – 3876.

[195] J. Kaeobamrung, M. C. Kozlowski, J. W. Bode, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20661 – 20665.
[196] J. R. Struble, J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2008**, *10*, 957 – 960.
[197] J. Mahatthananchai, J. W. Bode, *Chem. Sci.* **2012**, *3*, 192 – 197.
[198] M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418 – 8420.
[199] J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2009**, *11*, 677 – 680.
[200] O. Winkelmann, C. Näther, U. Lüning, *Org. Biomol. Chem.* **2009**, *7*, 553 – 556.
[201] X.-Y. Chen, R.-C. Lin, S. Ye, *Chem. Commun.* **2012**, *48*, 1317 – 1319.
[202] S. Xu, R. Chen, Z. Qin, G. Wu, Z. He, *Org. Lett.* **2012**, *14*, 996 – 999.
[203] J.-J. Dai, J.-H. Liu, D.-F. Luo, L. Liu, *Chem. Commun.* **2011**, *47*, 677 – 679.
[204] C. J. Rieder, K. J. Winberg, F. G. West, *J. Org. Chem.* **2011**, *76*, 50 – 56.
[205] R. Zriba, V. Gandon, C. Aubert, L. Fensterbank, M. Malacria, *Chem. Eur. J.* **2008**, *14*, 1482 – 1491.
[206] B. Bolte, F. Gagosz, *J. Am. Chem. Soc.* **2011**, *133*, 7696 – 7699.
[207] R. T. Yu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 12370 – 12371.
[208] R. T. Yu, E. E. Lee, G. Malik, T. Rovis, *Angew. Chem.* **2009**, *121*, 2415 – 2418; *Angew. Chem. Int. Ed.* **2009**, *48*, 2379 – 2382.
[209] a) A. Lumbroso, N. R. Vautravers, B. Breit, *Org. Lett.* **2010**, *12*, 5498 – 5501; b) A. Lumbroso, P. Koschker, N. R. Vautravers, B. Breit, *J. Am. Chem. Soc.* **2011**, *133*, 2386 – 2389.
[210] P. Panne, J. M. Fox, *J. Am. Chem. Soc.* **2007**, *129*, 22 – 23.
[211] P. Klahn, S. F. Kirsch, *ChemCatChem* **2011**, *3*, 649 – 652.
[212] H. Seo, B. P. Roberts, K. A. Abboud, K. M. Merz, S. Hong, *Org. Lett.* **2010**, *12*, 4860 – 4863.
[213] B. Baskar, H. J. Bae, S. E. An, J. Y. Cheong, Y. H. Rhee, A. Duschek, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 2605 – 2607.
[214] a) S. Ma, J. Zhang, *Angew. Chem.* **2003**, *115*, 193 – 197; *Angew. Chem. Int. Ed.* **2003**, *42*, 183 – 187; b) S. Ma, L. Lu, J. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 9645 – 9660.
[215] K. K. Toh, Y.-F. Wang, E. P. J. Ng, S. Chiba, *J. Am. Chem. Soc.* **2011**, *133*, 13942 – 13945.
[216] J.-L. Zhou, Y. Liang, C. Deng, H. Zhou, Z. Wang, X.-L. Sun, J.-C. Zheng, Z.-X. Yu, Y. Tang, *Angew. Chem.* **2011**, *123*, 8020 – 8024; *Angew. Chem. Int. Ed.* **2011**, *50*, 7874 – 7878.
[217] S. K. Hanson, R. Wu, L. A. P. Silks, *Angew. Chem.* **2012**, *124*, 3466 – 3469; *Angew. Chem. Int. Ed.* **2012**, *51*, 3410 – 3413.
[218] C. Jäckel, D. Hilvert, *Curr. Opin. Biotechnol.* **2010**, *21*, 753 – 759.
[219] C. Wuensch, S. M. Glueck, J. Gross, D. Koszelewski, M. Schober, K. Faber, *Org. Lett.* **2012**, *14*, 1974 – 1977.
[220] P. K. Sydor, S. M. Barry, O. M. Odulate, F. Barona-Gomez, S. W. Haynes, C. Corre, L. Song, G. L. Challis, *Nat. Chem.* **2011**, *3*, 388 – 392.
[221] a) A. Corma, L. T. Nemeth, M. Renz, S. Valencia, *Nature* **2001**, *412*, 423 – 425; b) M. Renz, T. Blasco, A. Corma, V. Fornés, R. Jensen, L. Nemeth, *Chem. Eur. J.* **2002**, *8*, 4708 – 4717.
[222] Y. Kwon, Y. Birdja, I. Spanos, P. Rodriguez, M. T. M. Koper, *ACS Catal.* **2012**, *2*, 759 – 764.
[223] For an alternative approach with a homogeneous Pd catalyst, see R. M. Painter, D. M. Pearson, R. M. Waymouth, *Angew. Chem.* **2010**, *122*, 9646 – 9649; *Angew. Chem. Int. Ed.* **2010**, *49*, 9456 – 9459.
[224] C. F. Gorin, E. S. Beh, M. W. Kanan, *J. Am. Chem. Soc.* **2012**, *134*, 186 – 189.