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Induced Intramolecularity: An Effective Strategy in Catalysis

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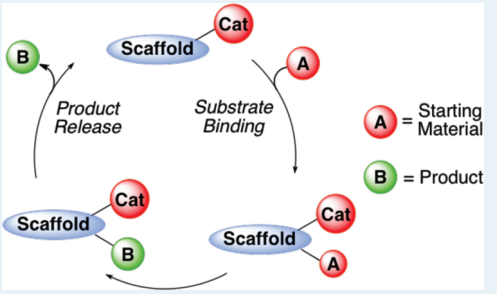
ABSTRACT: The use of reversibly formed covalent bonds to induce intramolecular reactions is a powerful way of controlling regio- and stereoselectivity, as well as accelerating reactions. Although this mode of activation was demonstrated in catalytic systems over 60 years ago, it is infrequently used in catalyst design. This review will focus on highlighting examples of reversible covalent bonding in organic catalysts as well as ligands for metal catalysis. A key aspect of this type of catalysis is that it is an entropically driven process, so it has the potential to be applied to a broad variety of reactions. Furthermore, this design element can be used in concert with more traditional forms of catalyst activation.



KEYWORDS: catalysis, intramolecular, reversible covalent, stereoselectivity, entropy, preassociation

1. INTRODUCTION

How can catalysts accelerate reactions? Answering this fundamental question underpins the development of any new catalyst system. One strategy involves the stabilization of the transition state or the destabilization of the ground state to achieve this goal. Alternatively, chemists may discuss activation of the substrate(s) and preorganization of the substrate(s) as means of accelerating reactions. In organic transformations, activation of the substrate can be carried out in numerous ways (e.g., Lewis acid or base activation, hydrogen bond activation, enamine formation, iminium formation, metal complexation, etc.).[1−3] Rate acceleration through the preorganize of substrate(s) occurs in both unimolecular and bimolecular reactions, with enzymes[4] and supramolecular catalysts[5−8] being paragons for this type of catalysis. In a seminal report, Jencks summarized how enzymes can achieve large rate accelerations through preorganization, "... enzymes can carry out a large fraction of their extraordinary rate accelerations by virtue of their ability to utilize substrate-binding forces to act as an entropy trap."[9] In essence, enzymes use a favorable binding step to orient substrates in a reactive arrangement, which costs significant amounts of entropy; however, this down payment in entropy is then used to accelerate the subsequent step. Preorganization is often achieved through noncovalent interactions, but reversible-covalent bonding is used as well. This brief review will focus on nonenzymatic catalysts that use reversible covalent bonding to increase reaction rate through induced intramolecularity.[10−14] The first section will survey organic catalysts that make a reversible covalent bond with a substrate and then through an intramolecular process accelerate the subsequent functionalization step. Although iminium and enamine catalysis, as well as *N*-heterocyclic carbene catalysts, uses reversible covalent bonds, it is not covered in this review, since it has been extensively reviewed in other reports[15−19] and in most cases does not involve acceleration through an intramolecular step in the mechanism. The second part of this review will survey the application of reversible covalent bonds between a substrate and ligand in transition metal catalysis.

2. NON-METAL CATALYSTS

The application of reversible covalent bonds to organic catalysis is often inspired by enzymes. As stated above, induced intramolecularity is a significant contributor to the overall acceleration observed in enzyme-catalyzed reactions. From a practical standpoint, a catalyst or enzyme that can convert a bimolecular step into a unimolecular reaction gains 15−35 entropy units (eu). Such harnessing of entropy corresponds to a potential rate enhancement of 10^4−10^8 M at room temperature. Notably, this effect is independent of any other activation of the substrate and is only a result of prepaying the entropic penalty for bringing two molecules together; therefore, it can be applied to any bimolecular step. In most of the cases in this review, a binding step will bring the catalyst and a substrate together, followed by intramolecular activation of the substrate. The intramolecular activation leads to significant rate enhancements that allow the catalyst to perform challenging reactions under mild conditions.

2.1. Carbonyl-Based Catalysts. *2.1.1. Hydrolysis and Alcoholysis of Esters.* In 1956, Wieland and co-workers reported the hydrolysis of a glycine ester using bicarbonate as a catalyst.[20,21] The proposed mechanism involves formation of a carbamic acid from the free amine and carbon dioxide (Scheme 1, eq 1). Cyclization to form Leuchs anhydride **2**, followed by hydrolysis, forms the acid product **3** and releases a molecule of carbon dioxide, thus completing the catalytic cycle. After Wieland's initial discovery, several groups reported that aromatic aldehydes increase the rate of hydrolysis of the *p*-nitrophenyl esters of amino acids.[22,23] Similar to the carbon dioxide catalyzed reaction, addition of the amine to the aldehyde forms a carbinol that cyclizes to form oxazolidinone **4** (Scheme 1, eq 2), which forms the carboxylic acid product upon hydrolysis.

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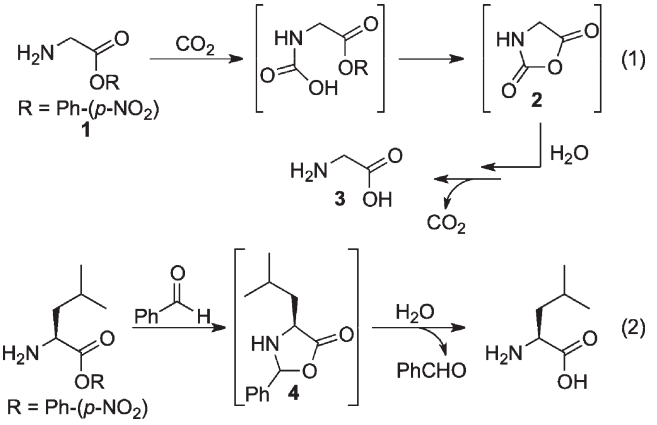
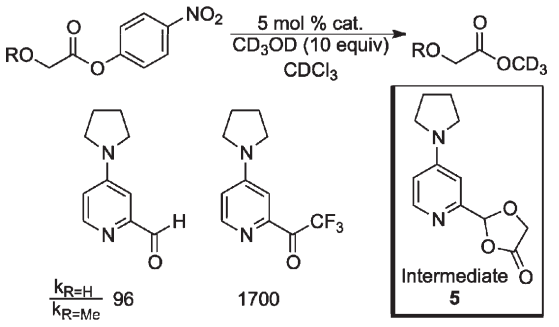
Scheme 1. CO_2 and Aldehyde-Promoted Ester Hydrolysis



Scheme 2. α-Hydroxy Ester Alcoholysis

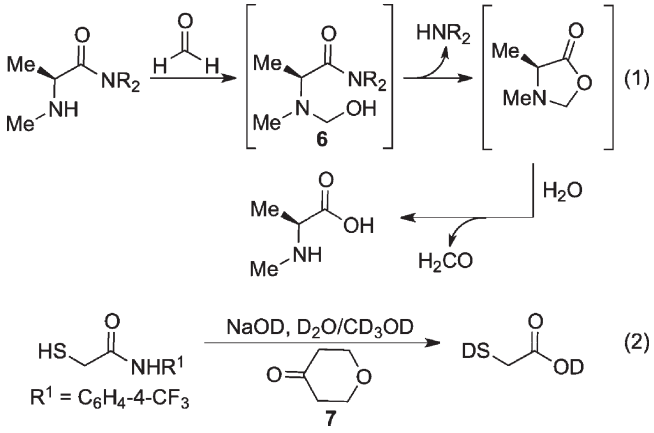


Such intramolecular activation reactions have been extended to the methanolysis of α-hydroxy esters. Using both aldehydes and ketones, Sammakia and co-workers demonstrated that α-hydroxy esters undergo transesterification at a rate 1700 times greater than the methyl ether substrate (Scheme 2).[24−26] Consistent with the mechanism of other carbonyl-based catalysts, intermediate **5** was observed under the reaction conditions. The basic nitrogen was found to be necessary for catalysis and likely serves as a general base rather than a nucleophilic catalyst. The addition of the CF_3 group to the catalyst was found to increase both the relative and absolute rate of catalysis. The electron-withdrawing nature of the CF_3 group is thought to accelerate methanolysis of the dioxolane intermediate **5**, which is the resting state of the catalyst.

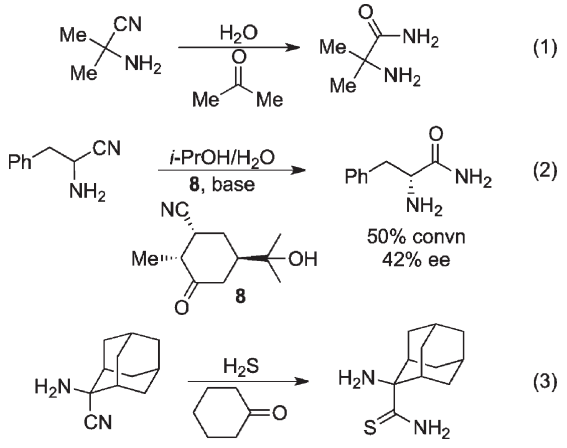
2.1.2. Amide Hydrolysis. The mild hydrolysis of amide bonds has been a long-standing goal for organic chemists. Reversible covalent interactions have been employed as means of meeting this challenge. Commeyras and co-workers found that α-amino amides react with formaldehyde to form a hemiaminal (**6**), which cyclizes to form an oxazolidinone intermediate (Scheme 3, eq 1).[27] Subsequent addition of water (similar to the proposed ester hydrolysis mechanism above) affords the carboxylic acid product. This concept was extended by the Seto group to the hydrolysis of α-mercaptoamides. Using ketone **7**, α-mercatopamides are hydrolyzed at a rate ~15 000 times faster than they are with no ketone present (Scheme 3, eq 2).[28]

2.1.3. Nitrile Hydration. The hydration or hydrolysis of α-amino nitriles is an important synthetic reaction that provides access to natural and unnatural amino amide and acid derivatives.

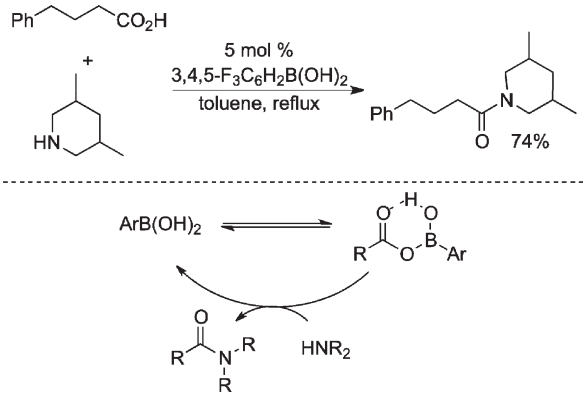
Scheme 3. Amide Hydrolysis with Carbonyl-Containing Catalysts



Scheme 4. Ketone-Catalyzed Nitrile Hydration



Scheme 5. Boronic Acid-Catalyzed Amidation



Notably, the α-amino nitriles are readily accessible through the addition of HCN to imines (Strecker reaction); this reaction is implicated in the synthesis of amino acids prebiotically.[29−31] α-Amino nitriles have been discovered to react at a significantly faster rate toward hydration than unfunctionalized nitriles. The rate acceleration arises from the presence of aldehydes and

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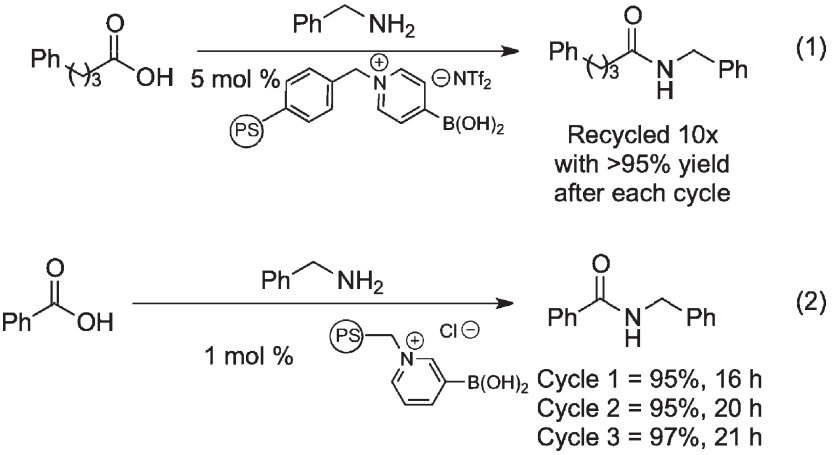
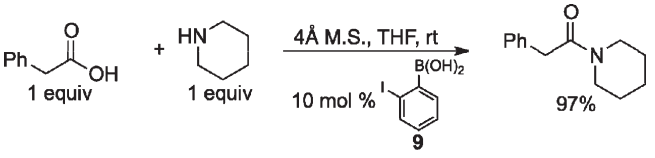
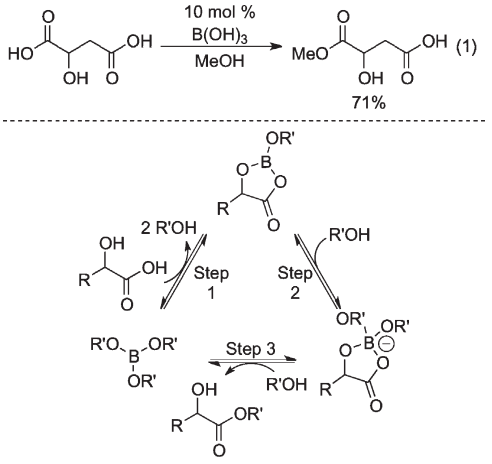
Scheme 6. Recycling of solid phase catalysts



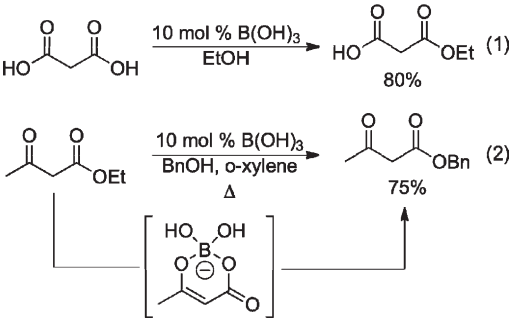
Scheme 7. Amidation with 9



Scheme 8. Site-Selective Boric Acid-Catalyzed Esterification



Scheme 9. Alcoholysis Catalyzed by Boric Acid



ketones formed through decomposition of α-amino nitriles, which serve as catalysts for the reaction.[32] To improve the efficiency of the hydrolysis process, a modified protocol was developed in which ketones, such as acetone, were added to the reaction (Scheme 4, eq 1).[33−35] Building on these discoveries, enantiopure ketone **8** was employed as a catalyst in the kinetic resolution of α-amino nitriles, yielding the α-amino amide in modest enantioselectivity (42% ee, Scheme 4, eq 2).[36] In a mechanistically similar process, Edward demonstrated that in the presence of hydrogen sulfide, 2-aminoadamantane-2-carbonitrile can be converted to the thioamide (Scheme 4, eq 3). For most other nitriles a two-step procedure is required, in which initially an imidazolidin-4-thione is formed, followed by hydrolysis to the thioamide.[37,38]

2.2. Boron-Based Catalysts. *2.2.1. Amidation and Transesterification.* Boronic acids and esters have been reported to readily exchange with protic functionalities. Yamamoto exploited the reversible exchange between aryl boronic acids and carboxylic acids to achieve catalytic amidation reactions.[39,40] Upon covalent bonding between a boronic acid and a carboxylic acid, intramolecular activation of the carbonyl occurs through a hydrogen bond; subsequent nucleophilic attack forms the amide product (Scheme 5). This methodology offers an advantage over traditional amide bond-forming reactions in that no stoichiometric activating agents are necessary, thereby avoiding the formation of undesirable byproduct. The practicality of these catalysts was greatly improved by development of pyridinium-based catalysts by both Yamamoto (Scheme 6, eq 1) and Wang (Scheme 6, eq 2).[41−43] These new catalysts are active in both amidation and esterification reactions and can be recycled several times either through solution phase methods or attachment to a solid support without loss of activity (Scheme 6). More recently, Hall and co-workers reported that 2-iodophenyl boronic acid (**9**) is also a highly effective catalyst for the amidation of carboxylic acids at room temperature (Scheme 7).[44]

Boric acid is uniquely effective at catalyzing the site-selective esterification of α-hydroxycarboxylic acids (Scheme 8, eq 1).[45−47] The specificity of the reaction has led to the mechanistic proposal that boric acid initially exchanges onto the alcohol. An intramolecular reaction follows, forming the Lewis acid activated ester,

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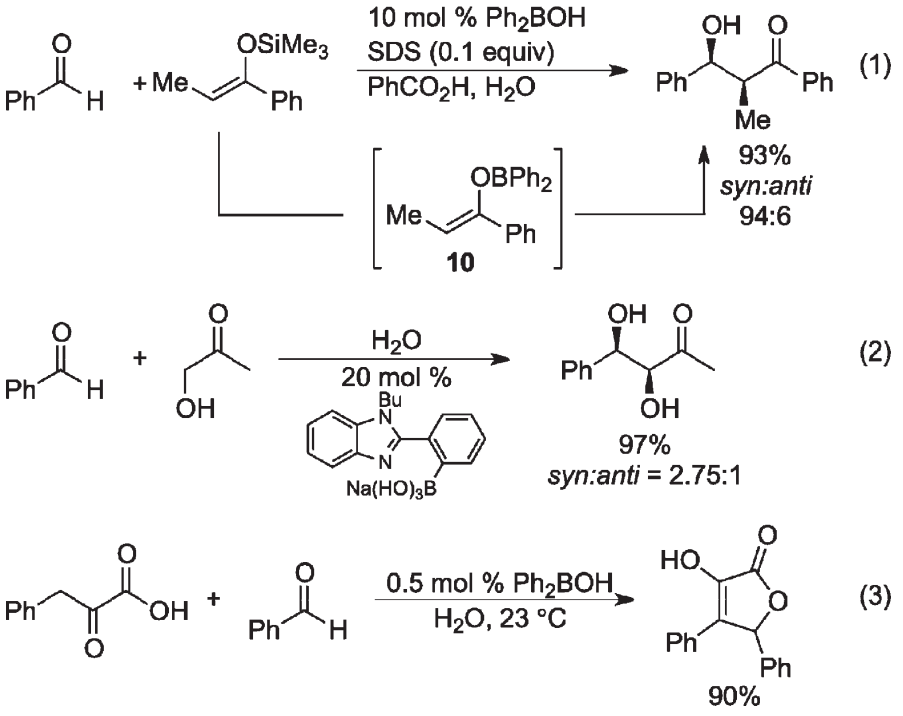
Scheme 10. Boron-Catalyzed Mukiyama Aldol

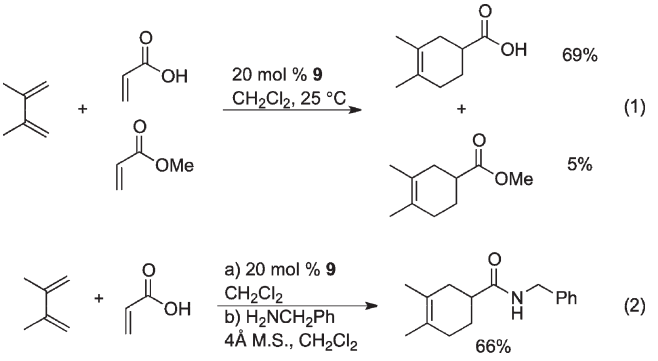


which then undergoes alcoholysis (Scheme 8). Notably, because cyclization preceeds the alcoholysis, it is possible to achieve a site-selective reaction. In a related mechanism, Houston performed a monoesterification of malonic acid (Scheme 9, eq 1).[48] Similarly, Anand and co-workers reported that β-keto esters undergo transesterification with boric acid, presumably through trapping of the enol (Scheme 9, eq 2).[49]

2.2.3. Carbon−Carbon-Bond-Forming Reactions. The reversible covalent bonding to boron-based catalysts has also been employed in carbon−carbon-bond-forming reactions. Both Yamamoto and Kobayashi applied diphenyl borinic acid catalysts to the Mukaiyama aldol reaction (Scheme 10).[50,51] In the Kobayashi example, the reaction is diastereoselective and takes place in water; the mechanism of the reaction is proposed to go through boron-based enolate **10** via exchange with a silyl enol ether (Scheme 10, eq 1). Lewis acid activation of the aldehyde results in a chairlike transition state that is responsible for the high syn selectivity observed in the aldol reaction. More recently, Whiting (Scheme 11, eq 2)[52] and Taylor (Scheme 10, eq 3)[53] have shown that boron-based catalysts promote the direct aldol reaction.

Hall and co-workers reported a variety of cycloaddition reactions with acrylic acid derivatives catalyzed by 2-iodophenyl boronic acid (**9**).[54−56] In one example, they demonstrate that acrylic acid reacts preferentially over the corresponding esters with diene substrates (Scheme 11, eq 1), consistent with covalent bond formation between the acid and **9**.[56] Similar to the reactions in Schemes 5−7, bonding between the boronic acid and carboxylic acid leads to the formation of a Bronsted-activated intermediate, accelerating the Diels−Alder reaction. Furthermore, a tandem Diels−Alder/amidation reaction can be performed using the boronic acid catalyst **9** (Scheme 11, eq 2).

Scheme 11. Boronic Acid-Catalyzed Diels−Alder reaction



3. APPLICATION OF REVERSIBLE COVALENT BONDS IN METAL ORGANIC COOPERATIVE CATALYSIS

The simultaneous application of metal and organic catalysts to promote organic transformations has been accomplished with great success.[57,58] This section of the review surveys transformations in which a ligand forms a reversible covalent bond to the substrate, inducing an intramolecular reaction. A key advantage of this type of transformation is the potential to gain further rate enhancement beyond traditional ligand-accelerated catalysis (LAC).[59] In LAC, the binding of the ligand to the metal generates a more active catalyst for the desired transformation (Scheme 12, eq 1). Therefore, even if there is free metal in solution, the reaction can still proceed via the metal−ligand complex. In reactions in which substrate binding to the catalyst occurs prior to the rate-determining step, meaning the concentration of substrate-bound catalyst is important to the overall rate, ligands that make a reversible covalent bond with the

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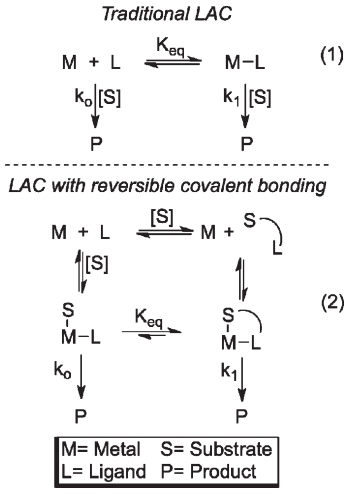
Scheme 12. Ligand-Accelerated Catalysis



substrate can significantly accelerate the rate beyond that of traditional LAC. In these cases, the substrate-bound ligand is a chelating ligand, which will have increased affinity for the metal (Scheme 12, eq 2). This increased affinity raises the concentration of substrate-bound catalyst and also helps to avoid formation of undesired catalyst species. It is important to differentiate the fact that these ligands can accelerate the reaction through steric and electronic perturbation of the metal ($k_1 > k_0$, Scheme 12, eq 2), and have the ability to gain additional acceleration through induced intramolecularity (K_{eq}, Scheme 12, eq 2). We have named these compounds scaffolding ligands to highlight that they accelerate reactions through induced intramolecularity. We use the term scaffolding ligand because of their functional similarity to scaffolding proteins. The major role of scaffolding proteins is to localize specific proteins in a functional cluster.[60−62] Similarly, the scaffolding ligands are designed to recognize specific substrates and colocalize them with a metal catalyst. The acceleration of the reaction combined with the stability and rigidity of the ligand−substrate chelate allows for abnormal modes of reactivity, high stereoselectivity, and suppression of undesired reactions.

3.1. Applications of Reversible Covalent Bonding in C−H Activation. *3.1.1. Ortho Functionalization of Phenols.* Catalytic C−H activation and subsequent functionalization has been an area of chemistry that has grown tremendously over the past 30 years.[63−68] The 2-fold synthetic challenge in this area is the development of catalysts that are able to insert into relatively inert C−H bonds and then selectively functionalize a specific C−H bond in the presence of numerous others. The most common method for achieving this selectivity has been through the application of directing groups. Although they have provided a means of obtaining selective C−H functionalization, directing groups inherently bring limitations to the substrate scope of the reaction. The development of ligands that covalently and reversibly bind to common organic functionalities provides a means of circumventing this problem.

In 1985, Lewis reported that deuterium is incorporated into the ortho positions of phenol using complex **11** (Scheme 13).[69] Although the reaction was reported in 1969,[70] Lewis discovered that a catalytic amount of KOPh was necessary to reproduce the reaction. It was found that the KOPh promoted rapid transesterification between triphenyl phosphite and phenol (Figure 1).

Scheme 13. Catalytic Deuteration of Phenol

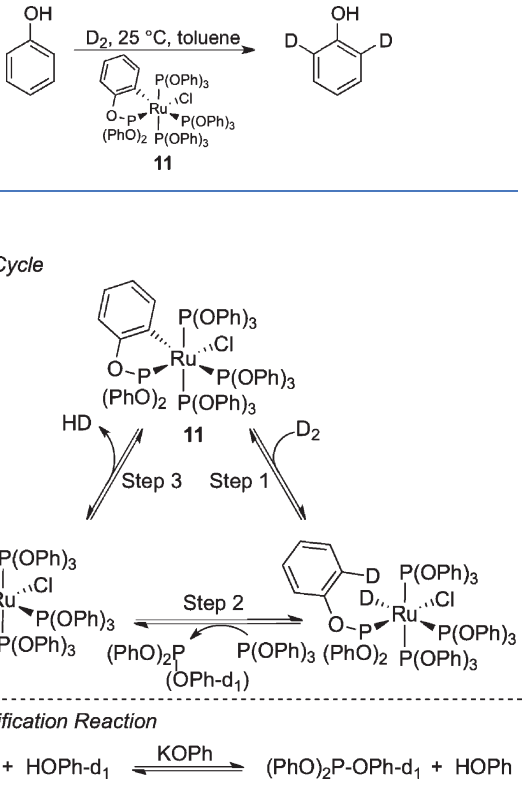
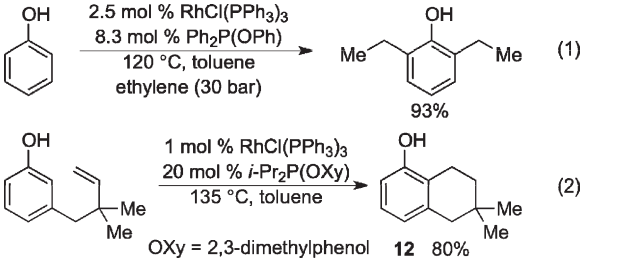


Figure 1. Mechanism of catalytic deuteration.

Scheme 14. Phosphonite-Directed C−H/Olefin coupling



The mechanism consists of cyclometalation, followed by addition of D_2 to afford the labeled phosphite (Figure 1). Ligand exchange and transesterification then allow for the catalytic incorporation of deuterium into phenol. After this initial publication, Lewis and Smith reported that **11** catalyzes coupling of phenol with alkenes such as ethylene and propene to form the ortho alkylated products.[71] More recently, Cole-Hamilton and co-workers have reported a more efficient Rh(I) complex for the coupling of ethylene to phenol as well as modest turnover with aniline (Scheme 14, eq 1).[72] Bergman and Ellman have also demonstrated the intramolecular coupling of phenol to an olefin to form the bicyclic **12** (Scheme 14, eq 2).[73]

Bedford and co-workers have used the phosphinite/phenol exchange reaction to perform the direct intermolecular coupling of aryl halides to the ortho C−H bond of phenolic derivatives (Scheme 15, eq 1).[74,75] The reaction procedure can be further simplified by employing commercially available $ClP(i\text{-}Pr)_2$, which generates the phosphinite in situ.[76] Similarly, Bedford

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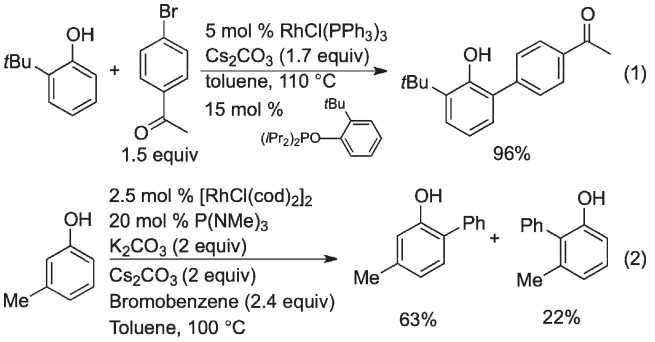
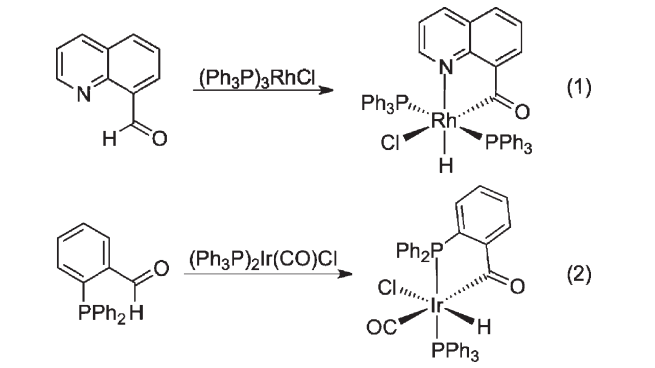
Scheme 15. Phenol Coupling with Aryl Bromides



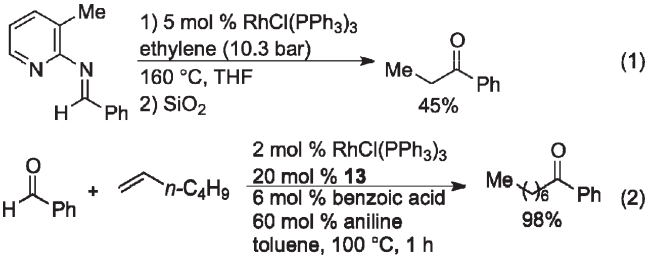
Scheme 16. Rh(I) and Ir(I) Cyclometalated Acyl Complexes



and Inoue showed that $P(NMe_2)_3$ is also a viable ligand for the cross-coupling reaction (Scheme 15, eq 2).[75,77] A broad range of aryl bromides can be employed in the cross-coupling. The utility of this method was demonstrated in the derivatization of tyrosine analogues.[78] A limitation of the procedure is that generally, to avoid bis arylation, only ortho-substituted phenols are employed.

3.1.2. Application to Hydroacylation and Carbon−Carbon Bond Activation. Hydroacylation is a powerful means of converting aldehydes into ketones. A significant challenge in this area has been the suppression of decarbonylation[79,80] during the catalytic cycle, which renders the catalyst inactive. Cationic Rh complexes have been effective catalysts for intramolecular hydroacylation; the effectiveness of cationic catalysts can be attributed, in part, to the destabilization of the carbonyl complex that results from decarbonylation of the substrate.[81−83] However, this class of catalysts has not been effective for the intermolecular coupling of olefins to aldehydes. For intermolecular reactions, high ethylene or carbon monoxide pressure can lead to catalyst turnover.[84−88] These conditions favor the formation of coordinatively saturated complexes that do not undergo decarbonylation. Similarly, work by Suggs (Scheme 16, eq 1) and Rauchfuss (Scheme 16, eq 2) demonstrated that decarbonylation in Rh(I) and Ir(I) complexes can be prevented through the introduction of an additional binding element in the substrate.[89−91] Subsequent to this discovery, Suggs reported that the same strategy could be used to promote intermolecular hydroacylation.[92] Recent work by several groups has demonstrated that incorporation of a variety of chelating functional groups onto the aldehyde or the olefin coupling partner is an effective means of promoting intermolecular hydroacylation.[93−99] However, the use of chelating groups limits the breadth of substrates that can be used in the reaction.

Scheme 17. 2-Amino-3-picoline-Catalyzed Hydroacylation



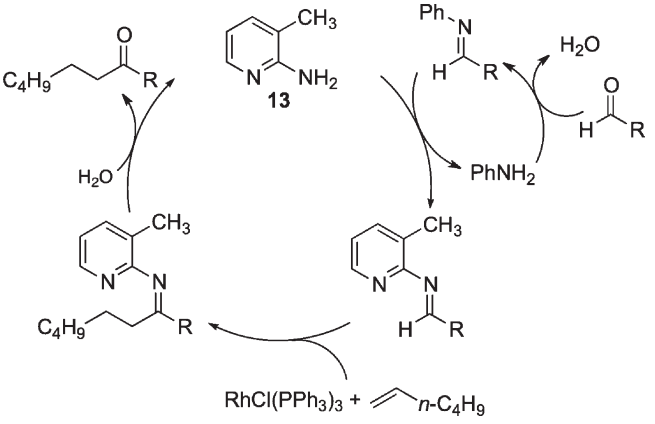


Figure 2. Transimination catalytic cycle.

Alternatively, Suggs found that preformation of pyridyl imines both suppresses decarbonylation and can be used in the coupling to ethylene (Scheme 17, eq 1). An obvious advantage is that the ketone can be unmasked through simple hydrolysis. Although use of the pyridyl imines increases the potential scope of aldehyde coupling partners, the method requires stoichiometric quantities of 2-amino-3-picoline (**13**, see Figure 2). In 1997, Jun and co-workers reported the use of reversible covalent bonding as a means of overcoming that limitation.[100,101] Utilizing a catalytic quantity of 2-amino-3-picoline, hydroacylation between aldehydes and terminal olefins was achieved. Improvements in the efficiency of the reaction were obtained through the addition of catalytic quantities of benzoic acid and aniline (Scheme 17, eq 2).[102] These additives promote rapid transimination of the 2-amino-3-picoline (**13**) onto the aldehyde substrate (Figure 2). The chelation-assisted reaction was extended to the coupling of alkynes and aldehydes as well as the hydrative dimerization of alkynes (Scheme 18).[103,104]

Jun and co-workers have extended the hydroacylation substrate scope by demonstrating that alcohols and amines can be used as precursors to the desired aldehyde substrate. Two mechanistic pathways have been proposed for the reactions. Alcohols and amines are oxidized in situ by a Rh(I) catalyst via transfer hydrogenation, with the olefin substrate serving as the hydrogen acceptor (Scheme 19, eq 1 and 2).[105,106] Alternatively, an allylic alcohol can be employed such that metal-catalyzed isomerization leads to in situ formation of the aldehyde (Scheme 19, eq 3).[107]

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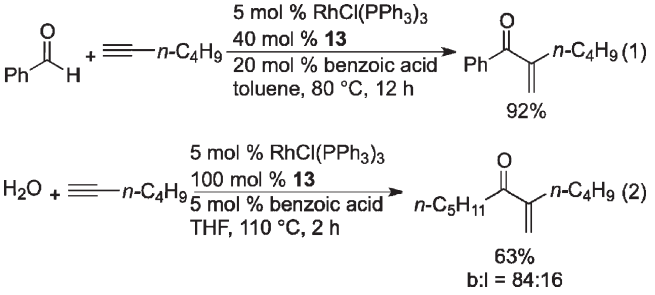
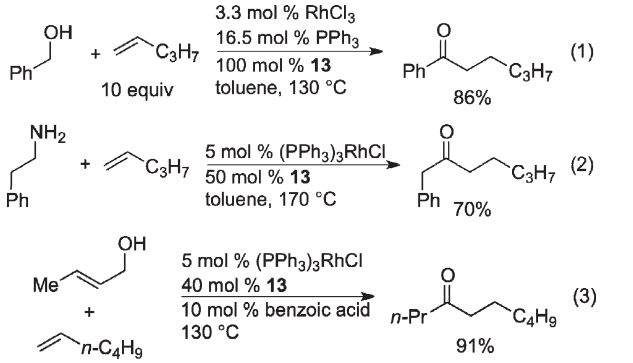
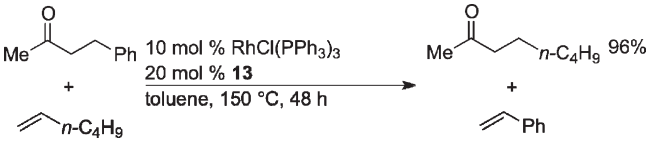
Scheme 18. Aldehyde C−H Bond Additions to Alkynes



Scheme 19. Tandem Transfer Hydrogenation or Isomerization/Hydroacylation



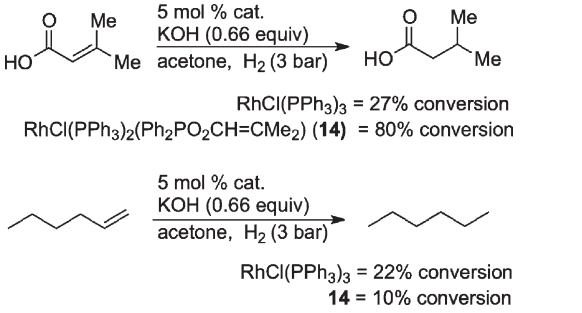
Scheme 20. Rh(I)-Catalyzed Carbon−Carbon Bond Activation



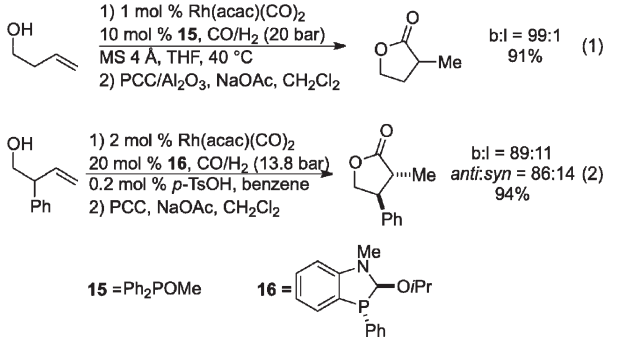
With the success in hydroacylation, the Jun group applied the power of directed metalation to the activation of carbon−carbon bonds (Scheme 20).[108] In this case, carbon−carbon bond activation is the microscopic reverse of the reductive elimination step in hydroacylation. Upon reversion to a Rh-hydride complex, an exogenous alkene is coupled to form the new ketone product. The reaction is driven to high conversion through either the generation of a conjugated olefin, such as styrene, or addition of an excess of the desired coupling partner. Furthermore, styrene was found to polymerize under the reaction conditions helping to drive the reaction.

3.2. Hydrogenation. At the same time that Lewis was developing phenol/phosphite exchange as a means of catalytically incorporating deuterium into the ortho positions of phenol, Cole-Hamilton and co-workers developed a catalytic hydrogenation of α,β-unsaturated acids utilizing the exchange between diphenylphosphinous acids and carboxylic acids.[109,110] Similar to the reports of Lewis, they found it necessary to perform the reaction under basic conditions. They found $RhCl(PPh_3)_2(Ph_2PO_2CH{=}CMe_2)$ (**14**) shows significant rate enhancement

Scheme 21. Hydrogenation with Catalyst $RhCl(PPh_3)_3$ and 14



Scheme 22. Regio- and Diastereoselective Hydroformylation



for hydrogenation of acrylic acid derivates compared with $RhCl(PPh_3)_3$ (Scheme 21). Conversely, catalyst **14** shows lower activity for simple alkenes, such as hex-1-ene. These data are consistent with the diphenylphosphinous acid ligand accelerating the hydrogenation via binding of the carboxylic acid, forming a chelating ligand.

3.3. Regio- and Stereoselective Hydroformylation. Hydroformylation is one of the most efficient means of generating aldehyde products. The utility of the reaction is evident from the millions of tons of aldehyde products produced each year via hydroformylation.[111,112] The vast majority of the products are linear aldehydes because of their desirability in commodity chemical synthesis. On the other hand, aldehydes can be formed at a branched carbon using either symmetrical or electronically activated olefins; however, use of unsymmetrical or terminal olefins affords poor regioselectivity or forms the linear isomer preferentially. A reliable means of controlling regioselectivity in hydroformylation has been the use of phosphorus-based directing groups.[113−127] Although effective in controlling regio- and stereoselectivity, the need for stoichiometric quantities of these groups has significantly diminished the synthetic practicality of the method. In 2008, the Breit group (Scheme 22, eq 1) and our group (Scheme 22, eq 2) simultaneously addressed this long-standing problem by utilizing reversible covalent bonds to transiently bind homoallylic alcohols to a phosphorus-based ligand.[128,129] Subsequent directed hydroformylation and oxidation form the five-membered ring lactone product; most importantly, the phosphine-based directing group is employed in catalytic quantities without erosion of branched selectivity.

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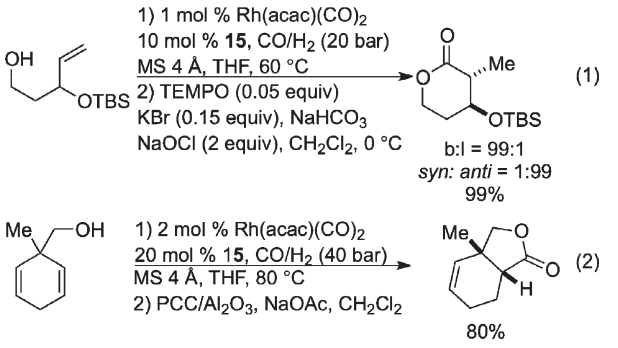
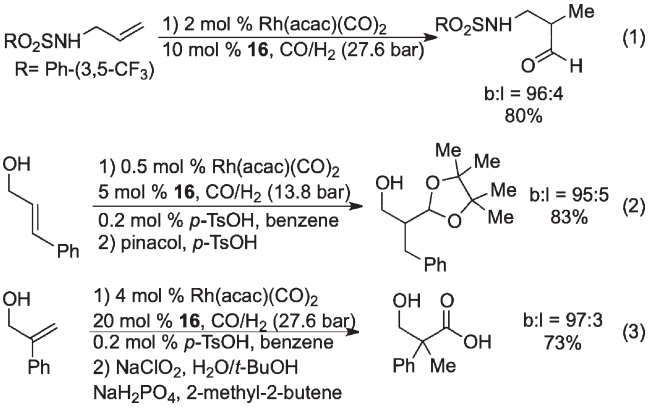
Scheme 23. Hydroformylation of Homoallylic and Bishomoallylic Alcohols



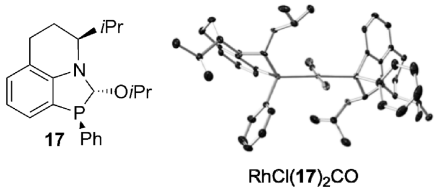
Scheme 24. Hydroformylation of Allylic Substrates



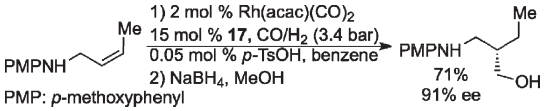
Mechanistically, ligand **15** utilizes the transesterification reaction developed by Lewis and co-workers. In a significant improvement to the exchange reaction, the Breit group showed that aliphatic alcohols (rather than only phenol) can exchange onto the phosphorus-based ligand in the presence of molecular sieves rather than using a base. The Breit system benefits from a short distance between the phosphorus atom and the olefin, allowing for excellent regioselectivities for both the homo- and bis homoallylic alcohols (Scheme 23). The bis homoallylic alcohols undergo hydroformylation to form the six-membered ring heterocycles, in which excellent diastereocontrol for the anti product is observed when an allylic stereocenter is present.[130] Most recently, ligand **14** has been applied to the diastereoselective hydroformylation of cyclohexadienyl substrates with high stereocontrol.[131] In this case, the directing group not only controls the selectivity of the reaction but also improves the overall efficiency of the transformation.

The design of our ligand relies on an acid-catalyzed exchange at a carbon in the orthoformate oxidation state. An advantage of this exchange mechanism is that a diverse set of functional groups can bind to the ligand. In addition to alcohols, **16** is amenable to exchange with sulfonamides, anilines, and secondary amines. In the case of sulfonamides, the rate of exchange correlates with the acidity of the NH bond, with more acidic substrates exchanging faster. The sulfonamide substrates can be hydroformylated with high regioselectivity to form the β-amino aldehyde products (Scheme 24, eq 1).[132] Ligand **16** has also been successfully

Scheme 25. Second-Generation Chiral Ligand



Scheme 26. Enantioselective Hydroformylation



applied to the hydroformylation of 1,2- and 1,1-disubstituted olefins to form β-hydroxyaldehydes and carboxylic acids (Scheme 24, eqs 2 and 3).[133,134] The 1,1-disubstituted olefin substrates have been particularly challenging in hydroformylation as a result of their low reactivity and high selectivity for the linear isomer. Utilizing **16**, the isomer with a quaternary carbon forms selectively under mild conditions (35−45 °C), highlighting the power of directing groups to control selectivity and enhance rate.

The catalytic directing group strategies discussed above have been applied mainly to regioselective reactions. In hydroformylation, the challenge of diastereoselectivity has been addressed; however, the development of enantioselective catalysis remains a significant challenge. Ligand **16** is an excellent candidate for enantioselective catalysis because it contains two stereogenic centers. Early attempts to resolve the ligand through exchange with an enantiopure alcohol led to the conclusion that both the phosphorus and carbon stereocenters undergo epimerization. To circumvent the epimerization issue, a second-generation ligand was developed that incorporates a third nonepimerizable stereocenter, whose conformation is thermodynamically geared to have the adjacent phosphorus and carbon stereocenters anti, respectively (Scheme 25). Application of **17** to the hydroformylation of *p*-methoxyphenyl (PMP) protected amines yields the β-amino alcohol products in good yield and excellent enantioselectivity. The highest selectivities were observed with cis olefins (up to 93% ee), whereas terminal and trans olefins afforded 70−80% ee (Scheme 26).[135]

4. SUMMARY AND OUTLOOK

Reversible covalent bonds provide a unique opportunity to accelerate reactions through either collocation of two reactants or intramolecular activation of a substrate. Through these reversible-binding events, significant rate enhancements can be achieved, such that challenging reactions can be performed under mild conditions (e.g., amide hydrolysis under neutral conditions). Furthermore, the conformational restrictions imposed by covalent bonds provide a means of inducing asymmetry in molecules in a general and highly selective fashion. Although there are currently few examples of using this mode of catalysis in enantioselective reactions, we believe this strategy holds great promise for controlling absolute stereoselectivity while enhancing the rate of a broad set of reactions.

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