Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis

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1. Introduction

The rise of green chemistry has drawn attention to bond construction strategies that promote atom economy and avoid mutagenic reagents.[1] For example, both goals are achieved by replacing highly reactive reagents such as RBr or ROTs with less reactive RH or ROH. Such strategies almost always include a C−H activation component, hence their relevance to this special issue. In the absence of an intrinsically reactive reagent, catalysis is the most appropriate alternative mode of activation of the less reactive substitute substrate and organometallic catalysis has thus taken a prominent role.

Atom economic reactions minimize waste formation, another goal of green chemistry. Processes that are carried out on an industrial scale naturally cause the most acute waste problems, hence the generally greater interest in industry than in academia. Given the stringent regulatory climate, problems of residual mutagens in the final product are probably most critical for pharmaceuticals. One very helpful response by the pharmaceutical industry has been the formation of the ACS GCI Pharmaceutical Roundtable "to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry".

Well-known cases of green catalysis include asymmetric catalysis, a strategy that provides the pharmacologically active form of a drug molecule and avoids production of the enantiomer that is at best inactive or at worst toxic. C−H, C−Si, and C−C bond construction via hydrogenation, hydrosilylation, hydrocyanation, and hydroformylation has also been widely adopted in industry.

In the reactions discussed in this review, the substrate is activated by catalytic dehydrogenative oxidation. This activation is followed by a bond construction step. These steps proceed under 'one-pot' conditions with a single catalyst or at most two catalysts acting together.

Alkane and alcohol substrates are the two best established reactants. In the first case, alkanes are dehydrogenated to alkenes, which then react further to give the final products. In the second case, alcohol dehydrogenation leads to aldehydes or ketones that then react further with nucleophiles. Amines also have also figured in dehydrogenative activation

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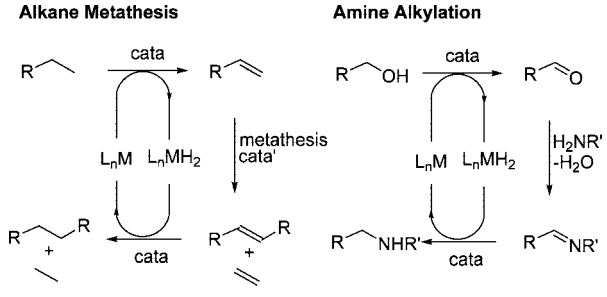
Bob Crabtree, educated at New College Oxford with Malcolm Green, did his Ph.D. studies with Joseph Chatt at Sussex University and spent four years in Paris in Hugh Felkin's lab at the CNRS Natural Products Institute, then headed by Derek Barton. In 1977 he became Assistant Professor at Yale, where he is now Professor of Chemistry. He has received the ACS and Royal Chemical Society prizes for organometallic chemistry and has been Chair of the Division of Inorganic Chemistry of the ACS. He has also been Dow lecturer (Berkeley), Williams lecturer (Oxford), Mond Lecturer (RSC), and Osborn lecturer (Strasbourg). He is the author of *The Organometallic Chemistry of the Transition Metals* and Editor in Chief of *Comprehensive Organometallic Chemistry* and *Encyclopedia of Inorganic Chemistry*. He has been most directly involved in organometallic and bioinorganic chemistry with early work on catalytic alkane C−H activation and functionalization chemistry and recent biomimetic C−H activation via molecular recognition.

reactions, although to a lesser extent, in which case reactive imines are generated as intermediates.

A number of characteristics are common to the reactions discussed. In each case a less reactive species, such as an alkane or alcohol, is converted to a more reactive one, an alkene or organic carbonyl compound, that then reacts further in a tandem 'one-pot' procedure. The first step is catalyzed by a transition-metal complex and involves a C−H bond cleavage; the following steps may or may not be catalyzed depending on the case. At least two aspects are green: the great majority of cases show very high atom economy and by using unfunctionalized alkanes and alcohols avoid the need to introduce activating groups such as bromide or tosylate.

The types of reaction involved can best be illustrated by two leading examples, alkane metathesis and amine alkylation, illustrated in Scheme 1, where 'cata' refers to the dehydrogenation/hydrogenation catalyst. Where the initial dehydrogenation is endoergic, particularly the case for alkane dehydrogenation, the resulting arrangement has a great thermodynamic advantage. The third step is necessarily exoergic to approximately the same extent as the first step is endoergic but with the opposite sign. The third step can therefore help drive the first step.

Scheme 1. Representative Reactions Featuring Dehydrogenative Activation



This review covers three areas of homogeneous C−H activation: the dehydrogenative oxidation of alkanes, alcohols, and amines. The last section contains specific information on the proposed reaction mechanisms involved.

Though much of the earliest work on such activations used heterogeneous catalysts, the emphasis of this review is homogeneous catalysis; heterogeneous counterparts are included for historical perspective.

2. Dehydrogenative Alkane Activation

This area has its roots in early work on heterogeneous systems. In 1973, Burnett and Hughes found that butane can be converted to lower and higher alkanes in contact with a combination of a dehydrogenation catalyst, platinum on alumina, and an olefin metathesis catalyst, tungsten oxide on silica.[2] Basset and co-workers[3] found that supported Ta and W hydride catalysts also bring about this reaction but by a more complex mechanism.

Homogeneous alkane activation is less explored than either alcohol or amine activation. Selective dehydrogenative activation of alkanes is particularly challenging because an initial C−H activation is required in a notoriously unreactive substrate to associate with metal species in the catalytic cycle. Once an alkene is formed, the alkane metathesis reaction (section 2.2) efficiently permutes alkylidene groups and leads to higher and lower hydrocarbons. A brief discussion of current alkane dehydrogenation methods follows.

2.1. Dehydrogenation of Alkanes

Early work showed the feasibility of homogeneous alkane dehydrogenation to alkenes by a reverse hydrogenation pathway.[4] The earliest report of such a dehydrogenation described the reaction of alkanes with $[Ir(H_2(Me_2CO)_2(PPh_3)_2]BF_4$ in the presence of a hydrogen acceptor.[5] It was proposed that the oxidative addition of an alkane C−H bond to the complex is followed by β-elimination to give final products derived from an intermediate alkene; the key oxidative addition was later shown experimentally by Janowicz and Bergman.[6] Later work by Felkin,[7] Jensen,[8] Goldman,[9] Saito,[10] and Crabtree[11] established that several low-valent metal complexes were capable of this type of activation.

First, an alkene was needed to act as a hydrogen acceptor to remove 2H from the intermediate dihydride, so no net dehydrogenation occurred. Later, conditions were found that allowed liberation of H_2 with net C=C bond formation. Reflux conditions[10b] and photolysis[11b] both proved effective for acceptorless dehydrogenation. The proposed role of the reflux is to sweep the H_2 out of the solvent and to displace the equilibrium toward products. In photolytic examples, the dehydrogenation reaction is driven by the photon energy in the photodissociation of H_2 from the otherwise thermally stable metal dihydride, recycling the active catalyst. In the absence of either of these special conditions, the endoergic character of the alkane dehydrogenation reaction always means that the equilibrium concentration of alkene is small.

Kaska and Jensen reported a particularly stable PCP pincer Ir complex capable of transfer dehydrogenation in the presence of hydrogen acceptor with a greatly improved turnover frequency; however, the reaction was still limited by the need for stoichiometric hydrogen acceptor (tbe) and by the buildup of hydrogenated product (tba).[12] The thermal stability of these complexes was improved in later work.[13]

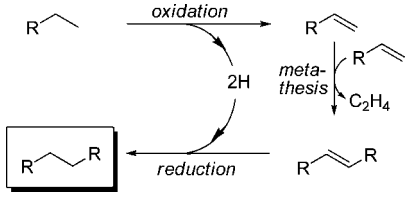
A key finding in acceptorless alkane dehydrogenation came from Goldman and Jensen and co-workers, who demonstrated that the dihydride analogue of the PCP Ir complex was highly active for dehydrogenation of alkanes, including *n*-alkanes.[14] Later versions of this system gave improved turnovers.[15] Bisphosphonite PCP pincer Ir complexes are also among the most active for this reaction, albeit with the requirement of a sacrificial hydrogen acceptor.[16]

2.2. Alkane Metathesis

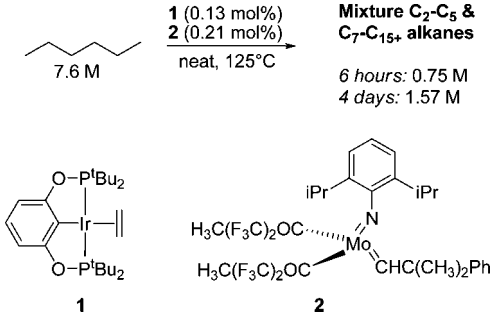
In a striking development, Goldman, Brookhart, and co-workers were able to bring about homogeneous *alkane metathesis* by a three-step one-pot process (Scheme 2).[17] In step 1, alkane dehydrogenation to the corresponding alkenes by one of Goldman's Ir-based alkene dehydrogenation catalysts produces a small equilibrium concentration of alkenes. A Schrock Mo-based alkene metathesis catalyst, also present in the medium, converts these alkenes to alkenes of higher and lower carbon number in step 2. In the third step, the resulting alkenes are hydrogenated by the Ir catalyst to form the higher and lower alkanes. By using the 2H from step 1 as the reductant for step 3, the system beats the usual thermodynamic limitation for alkane dehydrogenation, since the overall process is nearly thermodynamically neutral. A hydrogen acceptor is not required, but it was employed in some runs to increase the yield.

For example, *n*-hexane (7.6 M) was converted to a mixture of C_2-C_{15+} alkanes using catalysts **1** (10 mM) and **2** (16 mM) at 125° (Scheme 3). An impressive 0.75 M product mixture was attained in 6 h with a maximum of 1.57 M after 4 days. Addition of fresh catalyst **2** led to further conversion to give a total of 2.05 M products after 5 days, suggesting that Mo catalyst **2** has the higher deactivation rate under the conditions used. The Ir catalyst has a strong kinetic preference for formation of 1-alkenes, so the initial alkane metathesis products should be *n*-decane and ethane. The broad distribution of C numbers implies that catalytic isomerization of the double bond along the chain occurs. If so, cross metathesis of the isomerized products can then produce the wide distribution seen in the final product mixture. Alkane comproportionation is also possible: a mixture of *n*-hexane (4.36 M) and *n*-$C_{20}H_{42}$ (1.09 M) was converted to a mixture of C_2-C_{38} alkanes (1.97 M after 6 days) under similar conditions.

Scheme 2. Alkane Metathesis Sequence

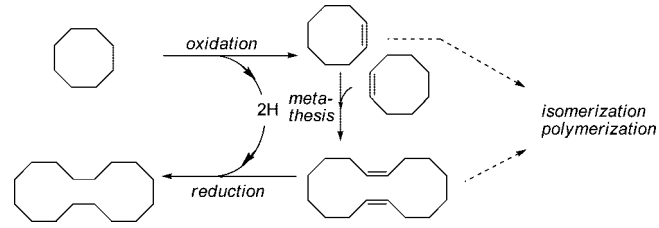


Scheme 3. Alkane Metathesis Reaction[17]



1 **2**

Scheme 4. Synthesis of Large Saturated Rings via Alkane Metathesis[19]



The two catalysts required, one for the metathesis step and the other for the dehydrogenation and hydrogenation steps, do not appear to interfere with one another. Few prior examples of catalysis have employed two catalysts together rather than in separate steps. In a second version of this reaction, the same homogeneous Ir catalyst was combined with a heterogeneous metathesis catalyst, Re_2O_7/Al_2O_3. The latter has the advantage of greater stability after long reaction times and the temperature could be raised to 175 °C without loss of catalytic activity, a point that also demonstrates the high stability of the PCP pincer−Ir catalyst employed. Later work[18] has led to the identification of improved homogeneous metathesis catalysts for this reaction.

A similar combination of homogeneous catalysts has been used with cyclic alkanes with the aim of synthesizing large saturated rings (Scheme 4).[19] A conversion of up to 37% of the initial cyclooctane proved possible under similar conditions to those used for the linear alkanes; however, the reaction was performed exclusively with the use of a hydrogen acceptor. The hydrocarbon-soluble fraction showed a distribution of cycloalkanes from C_6H_{12} to $C_{40}H_{80}$ with no linear species detectable. The formation of products having C numbers that are not multiples of 8 implies that alkene isomerization must occur as before. The major component of the hydrocarbon-insoluble product is high molecular weight polyethylene (M_w = 49 600; M_n = 29 700; PDI = 1.67). This was ascribed to ring-opening metathesis polymerization (ROMP) of cyclooctene, followed by hydrogenation of the C=C bonds in the chain. It could not be determined if the polyethylene was linear or cyclic. For cycloalkanes, no prior examples of the metathesis or ROMP reactions, either homogeneous or heterogeneous, have been reported.

It might at first be thought that a reaction in which a single compound is converted to a cocktail of products might have limited scope for practical application. The spectacular development of the related alkene metathesis reaction argues otherwise. The alkene version has been successfully applied to myriad problems in organic synthesis, industrial production, and polymer science. In the Shell Higher Olefins Process, alkene isomerization and alkene metathesis convert a mixture of short- and long-chain alkenes into a full spectrum of chain lengths, from which desirable detergent alcohols of intermediate chain length can be produced by hydroformylation.

Many applications of alkene metathesis avoid the formation of a multiplicity of products and rely on specificity, however. These predominantly form single products, such as in the many known ring-closing reactions. To introduce this specificity into alkane metathesis it will therefore be necessary to enhance catalyst selectivity. The step that leads to the multiplicity of products is the alkene isomerization, so hydrogenation/dehydrogenation catalysts must be devel-

oped that have low alkene isomerization activity, a goal that is likely to be more easily attained for homogeneous rather than heterogeneous catalysts.

Applications in the polymer field are also promising, particularly if the polymers formed prove to have a microstructure usefully distinct from any of the classical types of polyethylene. Entangled rings (catenanes) are possible targets, for example.

3. Dehydrogenative Alcohol Activation

The insight that a dehydrogenative step could function as a mode of alcohol activation is a more recent development. Though several groups have demonstrated many useful examples of alcohol activation, Fujita and Yamaguchi,[20] Ramón and Yus,[21] and Williams[22] have been the leaders in making the method general for many different types of transformations and have formalized the concept. This type of transformation has been referred to as "hydrogen borrowing methodology",[22a] the "hydrogen autotransfer process",[21] or simply "hydrogen transfer".[20] In general, alcohol activation reactions, after a dehydrogenation event, functionalize the carbonyl generated to form a substrate for a last hydrogenation step (Scheme 5). Rather than performing a final dehydrogenation of the functionalized carbonyl, the hydrogen can be alternatively liberated or transferred to a sacrificial hydrogen acceptor.

3.1. Dehydrogenation of Alcohols

By dehydrogenating alcohols to their more reactive aldehyde or ketone oxidation products, subsequent bond construction steps are possible that would not occur for the parent alcohols. The earliest known examples of hydrogen transfer date back more than 100 years. The dehydrogenative activation and concomitant dimerization of alcohols is a nineteenth century development, now known as Guerbet chemistry after its discoverer.[23] The beta-branched primary alcohols formed in this way, also known as Guerbet alcohols, still have great practical value for the production of detergent alcohols, lubricants, and personal care products. Their hydrophobic double tails result in very favorable surfactant properties, along with low melting points. Oxidation to the corresponding Guerbet acids and conversion to their esters, a much newer development, has extended their applications even further.[24] Much of this work has been discussed only in the patent literature and may have escaped the notice of a wider audience.

In the Guerbet reaction, a linear primary alcohol is heated to 130−180 °C in a basic medium with a hydrogen transfer catalyst, typically heterogeneous. A three-step reaction is proposed (Scheme 6). The alcohol first dehydrogenates to the aldehyde; the aldehyde then undergoes nucleophilic attack by the aldehyde enolate in an aldol reaction. After loss of water, an α,β-unsaturated aldehyde is formed. In the final step, the unsaturated aldehyde is hydrogenated by hydrogen transfer from the starting alcohol. Since the 4H that need to be removed to dehydrogenate the two alcohol molecules exactly supply the 4H that are also needed for complete hydrogenation of the α,β-unsaturated aldehyde, this closes the hydrogen transfer loop and ensures high atom efficiency. The third step also helps drive the endothermic initial step by ensuring a thermodynamic near neutrality for the sum of the first and third steps.

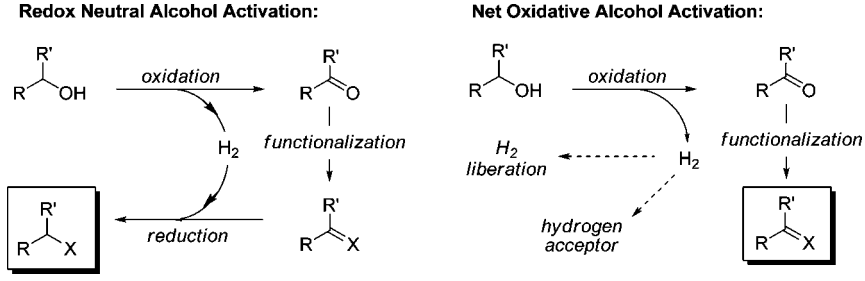
Hydrogen transfer in the context of alcohol oxidation in organic chemistry has been studied and developed since the 1930s, albeit outside the framework of homogeneous transition-metal processes. An early milestone in the chemistry of catalyzed hydrogen transfer from an alcohol is Oppenauer's report of aluminum *tert*-butoxide oxidation of secondary alcohols in the presence of acetone.[25]

Though aluminum alkoxides had been previously utilized in the reduction of aldehydes and ketones by Meerwein, Ponndorf, and Verley, Oppenauer was the first to use the method for oxidizing an alcohol to ketone. Many other catalysts have proven useful in this transformation, including alkali metal alkoxides[26] and lanthanide alkoxides.[27] Generally, the 'catalysts' used in classical Oppenauer oxidations are simple bases added in stoichiometric quantities.

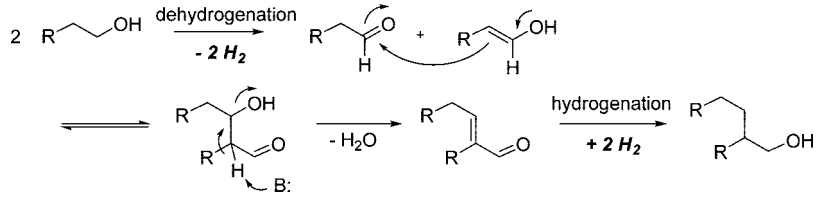
The homogeneous dehydrogenative catalytic activation of alcohols can be seen as a development of hydrogen transfer catalysis. In its original form this reaction led to transfer of 2H from a sacrificial secondary alcohol to a ketone facilitated by a transition-metal catalyst. One H is removed from a CH bond, hence the relevance to CH activation, and the other comes from the alcohol OH proton. Only a brief overview of the field will be provided here.

The classic early examples employed secondary alcohols such as isopropanol, in part because of their greater reducing

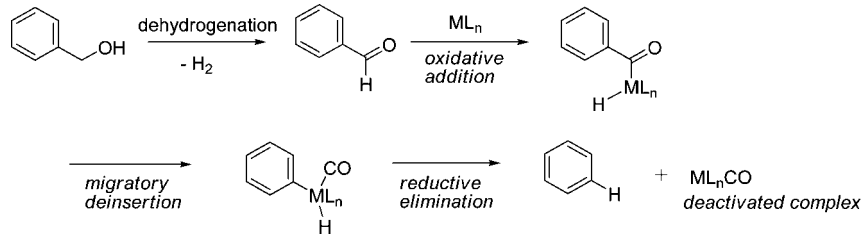
Scheme 5. Alcohol Activation: A Schematic View



Scheme 6. Idealized Mechanism of the Guerbet Reaction



Scheme 7. Decarbonylation as a Potential Inhibiting Pathway in Alcohol Activation: A Possible Mechanism



character relative to primary alcohols.[28] In addition, the acetone formed when using isopropanol as hydrogen donor is not subject to decarbonylation, as can be the case for aldehydes.[29] The volatile acetone is also sometimes removed by distillation to help drive the reaction. Guerbet alcohols are not seen because of the low temperature and the avoidance of primary alcohols as reductants. Some homogeneous hydrogen transfer catalysts are so active that aldol chemistry is avoided even with reactive aldol substrates such as $PhCH_2CHO$.[30]

Hydrogen transfer catalysis tended to be limited to the reduction of ketones and alkenes rather than of aldehydes and imines. Aldehyde and imine reduction, very relevant to alcohol activation pathways, proves to be harder than ketone reduction. If reactive H−C(CHO) bonds are present in the substrate, a potential problem is diversion of the reaction toward the aldol products rather than simple reduction, base typically being needed for both reactions. Catalysts capable of selectively reducing aldehydes and imines by hydrogen transfer, without interference from the aldol path, have been developed however, so there is no fundamental barrier to this process.[30,31]

For aldehydes, decarbonylation of the aldehyde by the catalyst may be one complicating factor (Scheme 7). In the case of transfer dehydrogenation reactions, the formation of alkanes from sequential dehydrogenation and decarbonylation of alcohols is well established. It is currently unclear exactly to what extent decarbonylation affects catalytic cycles for alcohol activation. Decarbonylation has been seen in several ruthenium systems in the presence of alcohols.[32]

Hydrogen transfer catalysis was normally viewed as a means of reducing a carbonyl compound or olefin to the corresponding alcohol or alkane. The concomitant oxidation of the alcohol reductant, typically isopropanol, was not of particular interest and even detracted from the atom economy of the reaction compared with its natural alternative, hydrogenation with H_2.

Several groups have demonstrated transition-metal-catalyzed systems that show Oppenauer-type alcohol oxidation reactivity. Many of the first catalysts discovered for hydrogen transfer from alcohols to carbonyls incorporated iridium, rhodium, or ruthenium. These catalysts tend to require harsh conditions for good conversion. Among the first Oppenauer oxidation catalysts were $[RhCl(PPh_3)_3]$ (Wilkinson's catalyst)[33] and $[IrCl_3(dmso)_3]$.[34] Zassinovich and Mestroni introduced the first in a generation of more active transfer hydrogenation catalysts in 1979 with their phenanthroline Ir complexes activated by KOH that are active for hydrogen transfer.[35]

Blum and Sasson[36] and Whitesides[37] had shown $[RuCl_2(PPh_3)_3]$ to be competent for oxidation of alcohols, among other substrates, but the catalyst required high temperatures. It was subsequently found that the complex is more active in basic conditions[32c,38] and that $[RuH_2(PPh_3)_4]$ is a more active catalyst for transfer hydrogenation.[39] Indeed, base often serves as an activator of hydrogen transfer catalysts and as a promoter for hydrogen transfer reactions.[35,40,41] As a result, the majority of alcohol activation reactions require at least catalytic amounts of base. In some cases, the catalyst can be activated prior to use and used at neutral conditions.

Noyori's catalysts, thought to operate via outer-sphere transfer of 2H from a Ru−H and an adjacent NH to the substrate aldehyde, have the special characteristic of giving high enantiomeric excess in asymmetric reactions.[42] Other catalysts thought to function via outer-sphere or metal−ligand bifunctional mechanisms have been utilized in hydrogen transfer, including Shvo's diruthenium complex.[43] Reviews on the mechanistic details of hydrogen transfer are available.[44] So far, asymmetric complexes such as Noyori's catalysts have not been converted to alcohol activation catalysts, but they may provide useful asymmetric versions for future development.

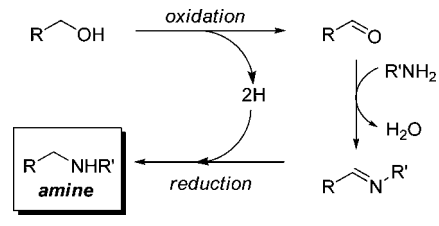
Another oxidative path for alcohols is the extrusion of molecular hydrogen. Though the hydrogen removed is no longer available to the catalytic system for a successive hydrogenation, this mode of oxidation avoids the need for a stoichiometric oxidant. The acceptorless dehydrogenation of alcohols is a far less common case, but several examples are known. In 1970, Charman reported a rhodium−tin complex capable of dehydrogenating isopropyl alcohol to acetone without a hydrogen acceptor.[45] Several ruthenium[46] and iridium[47] catalysts were subsequently shown to perform catalytic acceptorless dehydrogenation.

3.2. N-Alkylation by Alcohols

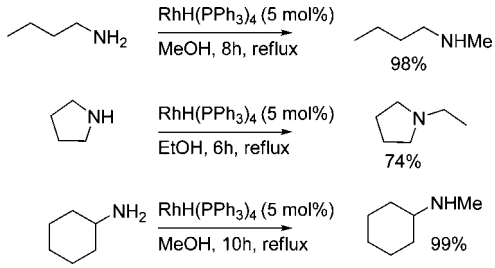
Several different types of products can be obtained via the amination of activated alcohols (Scheme 8). The alcohol functional group, once oxidized and attacked by an amine nucleophile, yields a hemiaminal. This intermediate can dehydrate to an imine and be hydrogenated, generating an amine. The synthetic scope of these reactions spans the range from simple amines to quinolines, indoles, and other heterocycles, with more complex products being generated through tandem multistep sequences.

Catalysts for these reactions are generally complexes of ruthenium and iridium. Conditions vary, but often base and moderate heating are required. Though it is currently unclear

Scheme 8. Schematic of the Alkylation of Amines by Primary Alcohols



Scheme 9. N-Alkylation Products Generated Using $[RhH(PPh_3)_4]$ as Catalyst[48]



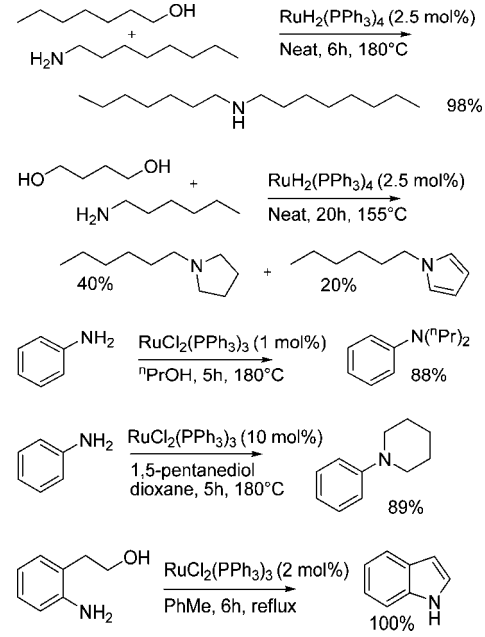
which catalytic steps *require* base, a basic moiety (located within a bifunctional ligand, or as a reactant) is seen as a requirement for a dehydrogenation mechanism via a monohydride intermediate.[41]

The first report of N-alkylation via homogeneous catalysis was by Grigg and co-workers in 1981.[48] Heterogeneous catalysts such as Cu[49] and Pd[50] had previously shown activity for this reaction. After finding that imines could be hydrogenated by alcohols via hydrogen transfer catalyzed by $[RhH(PPh_3)_4]$,[51] Grigg and co-workers attempted an N-alkylation of alcohols, no doubt with the expectation that the aldehyde generated from oxidizing the alcohol would react with an amine to form an imine in situ. Several iridium, rhodium, and ruthenium complexes were shown to be competent for the formation of secondary and tertiary amines from alcohols and primary or secondary alkyl amines under mild conditions (Scheme 9).[48] The synthesis of N-heterocycles from amino alcohols was also reported. Watanabe demonstrated an N-alkylation of an azole with methanol using $[RhH(PPh_3)_4]$ under harsh conditions.[52] Several ruthenium complexes and iridium catalysts were also capable of the transformation with higher yields.

3.2.1. Ruthenium Catalysis

Several ruthenium compounds (Chart 1) give N-alkylation of alcohols, with much early work performed by Murahashi and co-workers and Watanabe and co-workers (Scheme 10).[53] A wide variety of amines have been utilized in N-alkylation reactions. In 1982, Murahashi and co-workers showed aliphatic amines are competent substrates for N-alkylation using a $[RuH_2(PPh_3)_4]$ catalyst (**3**).[54] Curiously, aryl amines were ineffective substrates for this catalytic system, as they were for Grigg's Rh hydride complex. However, aminoarenes were used with success both by Watanabe et al. and by others using $[RuCl_2(PPh_3)_3]$ (**4**)[55] and monophosphine complexes of type $[RuCl_3L]$.[56] N-Alkylation of heterocyclic aryl amines has also been reported using a variety of ruthenium complexes.[57] Ammonium salts have been utilized as a nitrogen source in a N-alkylation reaction using $[RuH_2(PPh_3)_4]$.[58]

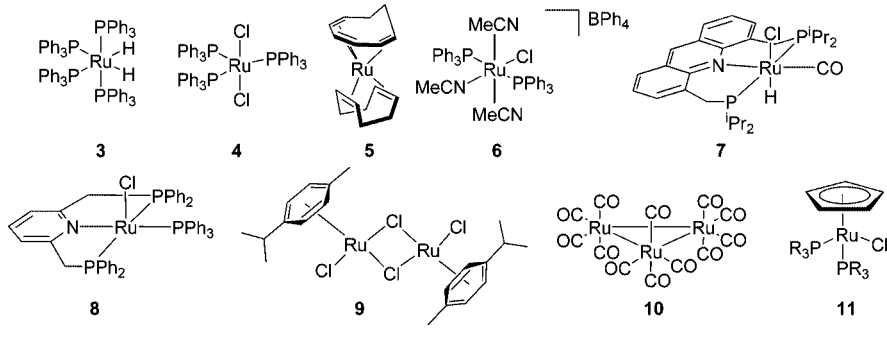
Scheme 10. Ruthenium-Catalyzed Amine Alkylation Reactions[54,55a,d,e]



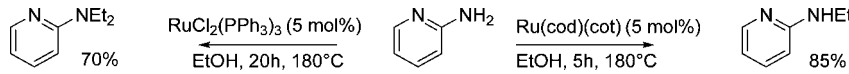
Watanabe identified a selectivity advantage in an early N-alkylation report.[55c] Selectivity for conventional monoalkylation of primary amines poses a challenge where the monosubstituted amine product from the first alkylation, being a more nucleophilic base than the amine starting material, can preferentially attack the electrophile. This effect is seen in conventional N-alkylations using alkyl halides, leading to a mixture of differently alkylated products. A great advantage of the alcohol activation strategy is that the initial secondary amines formed by alkylation of a primary amine tend not to react further because this would require the formation of an iminium cation as an intermediate; its formation tends to be unfavorable, particularly in the nonpolar solvents often used for N-alkylation reactions. Watanabe demonstrated that different ruthenium catalysts show widely varying selectivity in N-alkylations with both mono- and dialkylated amines possible, depending on the complex employed and the conditions used (Scheme 11).[57] Additionally, it was shown that more sterically encumbered amines are generally poorer substrates for N-alkylation.

Selectivity for monoalkylation has been well established in several systems. The $[RuCl_2(PPh_3)_3]$ complex was shown to selectively convert primary amines to N,N-dialkylated amines with longer reaction times and excess alcohol;[55a] conversely, monoalkylated amines can be generated in good yield by utilizing equimolar amounts of alcohol.[55c] Watanabe and co-workers found that of several ruthenium complexes,

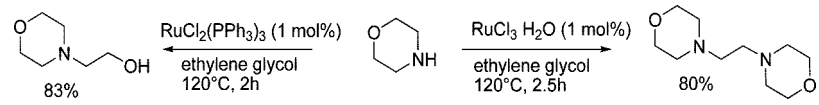
Chart 1. Ruthenium Catalyst Precursors for the Alkylation of Amines with Alcohols



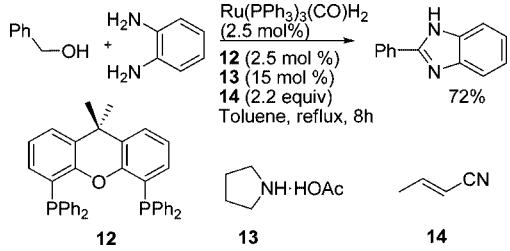
Scheme 11. Selectivity for Mono- and Dialkylation of Amines in N-Alkylation Reactions[57]



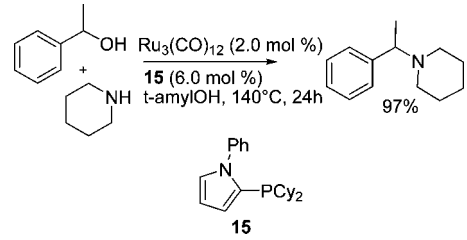
Scheme 12. Selectivity of Mono- and Diamination of Ethylene Glycol[62]



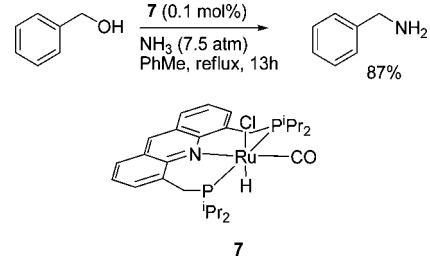
Scheme 13. Benzimidazole Synthesis via N-Alkylation[65]



Scheme 14. Synthesis of Tertiary Amines via N-Alkylation of Secondary Amines by Alcohols[66c]



Scheme 15. Synthesis of Primary Amines Directly from Alcohols and Ammonia[68]



[Ru(cod)(cot)] (**5**, Chart 1) was the most selective for monoalkylation of heteroaromatic amines.[57] $[(PPh_3)_2Ru(CH_3CN)_3Cl]BPh_4$ (**6**) performs selective monoalkylation of anilines.[59] Cp Ru complexes (**11**) were screened for dimethylation of aliphatic amine by methanol.[60] Triarylphosphine complexes of type $[RuCl(Cp)L_2]$ were found to be the most active versus aliphatic and chelating phosphines; the authors suggest the nonchelating, bulky phosphines are required to allow the chloride and phosphine ligand dissociation required to reach the active metal species.

Van Koten et al. reported N-heterocycle formation via N-alkylation of aromatic amines with diols using pincer ruthenium complexes (e.g., **8**, Chart 1).[61] Selectivity for N-monoalkylation of aniline was achieved by utilizing a NNN pincer ligand.

The selectivity for N-alkylation of secondary amines by diols was studied by Marsella (Scheme 12).[62] Diols in the presence of secondary amines can be either monosubstituted or disubstituted, forming amino alcohols or diamines, respectively, depending on the ruthenium catalyst used. Phosphine ruthenium complexes generated diamines, while ruthenium chloride hydrate forms the amino alcohol. Selectivity for diamines using $[RuCl_3 \cdot nH_2O]$ catalyst decreases as PPh_3 is added to the reaction.

Williams and co-workers demonstrated a $[Ru(p\text{-cymene})Cl_2]_2$ (**9**, Chart 1) and bis(diphenylphosphino)ferrocene (dppf) catalyst system for the alkylation of amines by primary alcohols.[63] The use of other chelating phosphines resulted in a large amount of ester side product. Several primary and secondary amines were utilized, including anilines; no secondary amines or alcohols were reported as substrates. A $[Ru(p\text{-cymene})Cl_2]_2$/DPEphos combination was later found to be active for the formation of sulfonamides and *N*-alkylbenylamines via N-alkylation.[64] Recent work by Williams and co-workers employs $Ru(PPh_3)_3(CO)H_2$ and xantphos (**12**) for hydrogen transfer reactions, including a benzimidazole synthesis via N-alkylation (Scheme 13).[65] The addition of piperidinium acetate (**13**) may activate an intermediate imine as an iminium ion to facilitate nucleophilic attack.

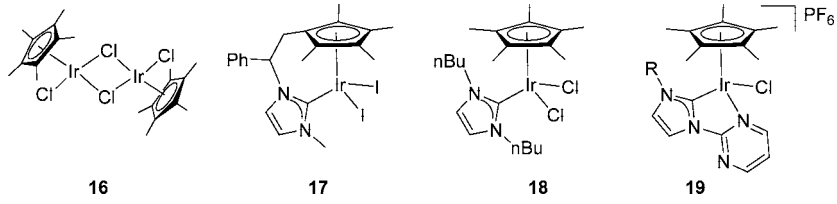
N-Alkylation of secondary alcohols is more difficult than that of primary alcohols. Though the oxidation potential of secondary versus primary alcohols makes dehydrogenation more favorable, the resulting ketone is a poorer electrophile than an aldehyde. Beller et al. report N-alkylation of primary amines using both primary and secondary alcohols with $[Ru_3(CO)_{12}]$ (**10**) (Scheme 14).[66] Shvo's diruthenium complex was also capable of the transformation, but with lower yields, due to competing transamination.[67] Other ruthenium complexes gave an increased yield of imines, as did lowering the reaction temperatures with $[Ru_3(CO)_{12}]$; transfer hydrogenation of C═N is harder than for C═O in comparable situations. Because of this difficulty an excess of alcohol (the hydrogen donor) was used to improve the yields. Bulkier amines had lower yields, suggesting a steric effect; aniline as amine yielded no conversion. A ligand screen showed $[Ru_3(CO)_{12}]$/*N*-phenyl-2-(PCy_2)pyrrole (**15**) to be the most active and selective catalyst. When alkyl secondary amines were employed, transamination occurs, providing alternatively substituted side products.

Milstein and co-workers developed a convenient and potentially very important method for generating primary amines from primary alcohols and ammonia (Scheme 15).[68] An air-stable ruthenium PNP pincer complex **7** is capable of generating amine in mild conditions, without base, and functions in organic/aqueous biphasic conditions. Water-soluble alcohol substrates were found to be unreactive when the reaction was run in water. The reaction requires several atmospheres of ammonia (7.5 atm). Formation of secondary amines via transamination was a competing pathway. Dihexylamine was generated in 86.5% yield from a neat reaction of the catalyst in hexylamine at reflux for 18 h.

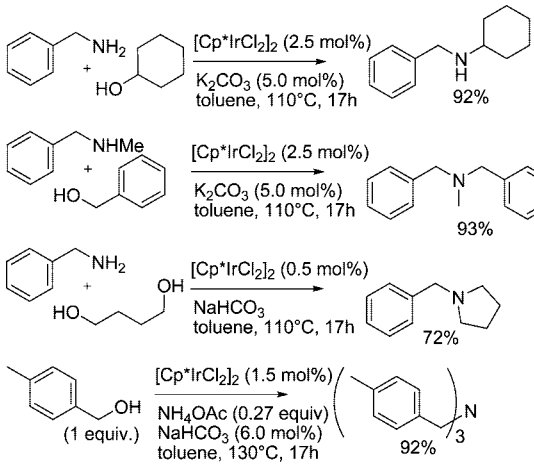
3.2.2. Iridium Catalysis

Pentamethylcyclopentadienyl (Cp*) complexes of iridium have shown good activity for N-alkylation reactions (Chart

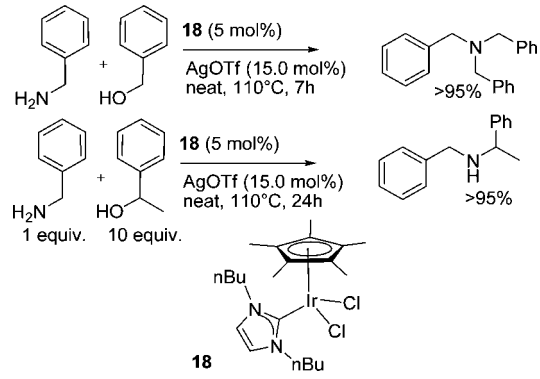
Chart 2. Cp*Ir Complexes Employed in Alcohol Amination Reactions



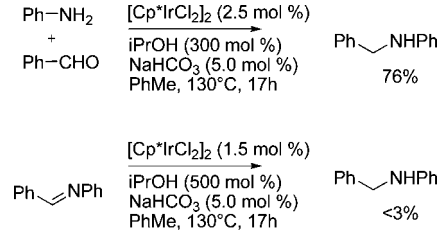
Scheme 16. $[Cp^*IrCl_2]_2$ in N-Alkylation Reactions[73,75a,76]



Scheme 17. N-Alkylation with Iridium Complexes without the Addition of Base[81]



Scheme 18. Mechanistic Experiments on the $[Cp^*IrCl_2]_2$-Catalyzed N-Alkylation Reaction[69a]



2). Fujita and Yamaguchi have shown several alcohol activation reactions with Cp*Ir complexes.[69] An Oppenauer-type oxidation of primary and secondary alcohols utilizing catalytic amounts of $[Cp^*IrCl_2]_2$ in acetone and in the presence of base was reported by Fujita and Yamaguchi in 2002.[70] Yamaguchi and co-workers found a Cp*Ir−NHC complex had higher activity for the reaction;[71] additionally, a NHC Ir complex with a functionalized Cp* ring with a tethered amine was active for transfer hydrogenation under neutral conditions.[72]

$[Cp^*IrCl_2]_2$ (**16**, Chart 2) was later used by Fujita and Yamaguchi in hydrogen transfer reactions, including N-alkylation by alcohols (Scheme 16).[73] A wide range of substrates are compatible, including primary and secondary amines and both primary and secondary alcohols. The reaction is run with catalytic base, likely for activating the catalyst. The catalyst loading was as high as 5%, but excellent yields of monoalkylated product are obtained. The cyclization of amino alcohols[74] and the cyclization of primary amines with diols[75] were subsequently reported. Under more harsh conditions, quarternary ammonium salts can be di- and trialkylated to form secondary and tertiary amines, respectively, using $[Cp^*IrCl_2]_2$.[76] Fujita and Yamaguchi and co-workers also successfully alkylated primary amides and carbamates using the $[Cp^*IrCl_2]_2$ system in neat conditions and elevated temperatures with the use of sodium acetate as base.[77]

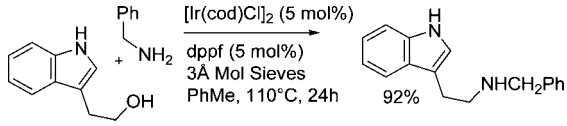
Other groups have explored the use of Cp*Ir for N-alkylation. Nordstrøm and Madsen reported a piperazine synthesis via N-alkylation using diols and amines.[78] $[Cp^*IrCl_2]_2$ was competent as catalyst; notably, the reaction was performed successfully in basic aqueous media. Crabtree and co-workers developed Cp*Ir complexes with chelating NHC ligands (e.g., **19**, Chart 2) capable of N-alkylation with $NaHCO_3$ in excellent yields and short reaction times relative to most other systems.[79]

Tejeda, Peris, Royo, and co-workers performed an N-alkylation using an Ir complex featuring a Cp*-functionalized N-heterocyclic carbene (NHC) (**17**, Chart 2).[80] Peris et al. also demonstrated the competency of untethered Cp*Ir NHC complexes (e.g., **18**) for the N-alkylation reaction, which notably do not require base when catalytic silver triflate is added (Scheme 17).[81] The selectivity of the reaction for secondary versus tertiary amines was dependent on the substrate alcohol and amine used.

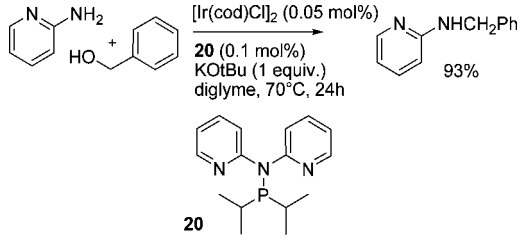
Little is known from experiment about the active species for the $[Cp^*IrCl_2]_2$ N-alkylation except that $[Cp^*IrCl_2]_2$ can react with alcohol and base to form $[Cp^*Ir(\mu\text{-}H)Cl]_2$.[82] Fujita and Yamaguchi and co-workers performed a few experiments to explore the mechanism of $[Cp^*IrCl_2]_2$ N-alkylation (Scheme 18).[69a] When a chiral secondary alcohol was used as a substrate with an amine, the racemic alkylated amine was obtained, in agreement with in-situ generation of a carbonyl during alcohol activation. The addition of an amine (aniline), an aldehyde (benzaldehyde), and a hydrogen donor (2-propanol) to the alcohol activation reaction mixture generated the alkylated amine, again suggesting the aldehyde is an intermediate in the reaction. The addition of an imine and a hydrogen donor failed to generate amine under the same conditions. Presumably the imine is a suitable ligand for the active metal complex, and if more than one imine binds to a complex it may inhibit catalysis. Crabtree and co-workers report the use of a bulky Cp*Ir NHC complex for the transfer hydrogenation of imines under near identical conditions which may be less prone to this type of inhibition.[79]

Eisenstein et al. performed a DFT study on iridium-catalyzed carbonate-promoted amine alkylation.[83] The com-

Scheme 19. [Ir(cod)Cl]$_2$-Catalyzed N-Alkylation[86]



Scheme 20. N-Alkylation with [Ir(cod)Cl]$_2$ and a P,N Chelating Ligand[87]



putational results suggest that amine starting material and products are both stronger Lewis bases than imine or alcohol and thus tend to block the sites at the metal. The relatively high temperatures needed may be required to open sites via amine dissociation to allow the reaction to occur. One possible role of iridium-bound base (e.g., carbonate) is promotion of the dehydrogenation of alcohol by deprotonation and amine hydrogenation via proton transfer. Dehydrogenation of alcohol had a smaller barrier than dehydrogenation of amine; the imine was hydrogenated more easily than the aldehyde, showing that the forward N-alkylation process is thermodynamically favored. Thus, the third step helps drive the endoergic first step.

Ishii identified another iridium catalyst system for transfer hydrogenation:[84] [Ir(cod)Cl]$_2$ with a chelating phosphine (dppp) in the presence of Cs_2CO_3. Williams reported that [Ir(cod)Cl]$_2$ can be used to accomplish N-alkylation; another phosphine, bis(diphenylphosphino)ferrocene (dppf), was used by Williams and co-workers for monoalkylation of primary amines by primary alcohols (Scheme 19).[85] Imine side product was formed when using benzyl alcohol as substrate, suggesting incomplete hydrogenation. Williams also performed a C−N bond formation through a dehydrogenation−aza-Wittig−hydrogenation process, a variant of similar C−C bond-forming Wittig chemistry (section 3.3.2).[86]

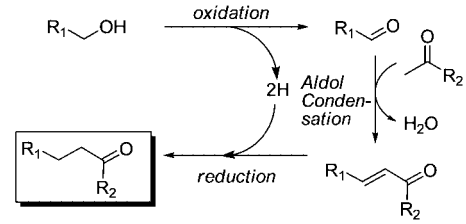
Kempe et al. performed a study of the [Ir(cod)Cl]$_2$ N-alkylation of aromatic amines (Scheme 20).[87] Employing P,N chelating ligand **20**, excellent yields were obtained for the monoalkylation of aromatic and heteroaromatic primary amines at low catalyst loadings (0.05%) and mild temperatures (70 °C) with stoichiometric amounts of alkoxide as base. N,N-Dialkylated diamines were also successfully synthesized. No secondary amines or alcohols were reported as substrates.

3.3. C−C Bond Formation

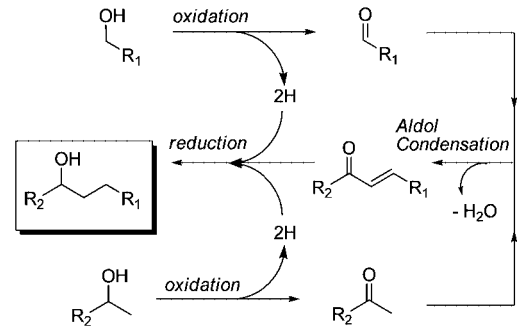
Several different classes of carbon nucleophiles have been employed in the same manner as amines in hydrogen transfer reactions.[21] The precursor reagents generally require deprotonation or oxidation prior to electrophilic attack, such as those employed in aldol-type reactivity. Alternatively, activated C−C bond-forming reagents, such as phosophinium ylides, can be employed in the presence of hydrogen transfer catalysts to effect other products, such as Wittig-type adducts. β-Alkylation of alcohols is also a relevant redox neutral process and can be performed in a regioselective manner with a judicious choice of substrates.

Scheme 21. Modes of Aldol-Based C−C Bond Formation in the Activation of Alcohols

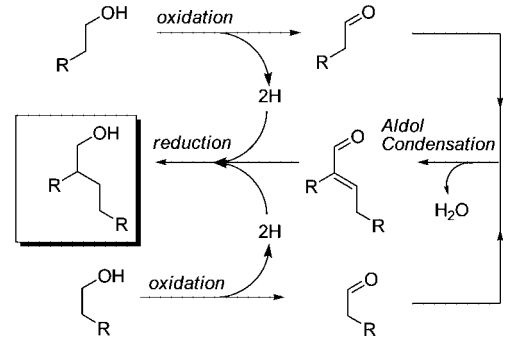
General Aldol Pathway (Ketone Alkylation):



Crossed Aldol Pathway (β-alkylation):



Guerbet Pathway:



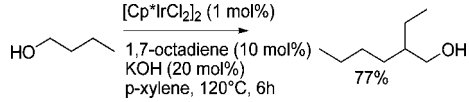
3.3.1. Enolate Nucleophiles

The so-called *β-alkylation* of alcohols has traditionally been performed with heterogeneous species or stoichiometric reagents. Recent developments in the field of hydrogen transfer have brought this reaction within the realm of homogeneous transition-metal catalysis. The reaction can be effected either by forming a carbonyl in situ from an alcohol or by adding a carbonyl substrate as a starting material (Scheme 21). Reaction stoichiometry suggests that unless hydrogen is transferred to another species or liberated as gas the products of an alcohol−alcohol coupling are alcohols. If an alcohol is reacted with a ketone, either the ketone or the alcohol product can be obtained, the latter only if excess alcohol or hydrogen donor is added to reduce the ketone. Excellent selectivities are often achieved for these reactions, with very little Guerbet product.

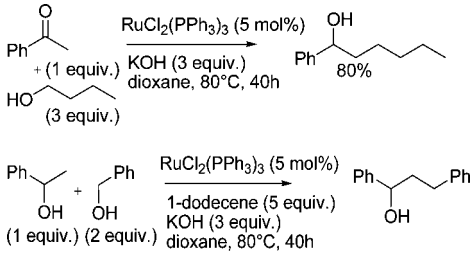
Guerbet-type products have been seen with several different metal complexes in the presence of metal alkoxides and alkali hydroxides. Complexes of Ru and Rh have been demonstrated.[88] [Pd(PPh$_3$)$_4$] and [PdCl$_2$(dppe)][89] and [Cp*IrCl$_2$]$_2$ (Scheme 22) and [Ir(cod)Cl]$_2$[90] have also been used as catalysts for the dimerization of primary alcohols.

These reactions stand in contrast to recently reported alcohol cross-coupling reactions that utilize a strong Lewis

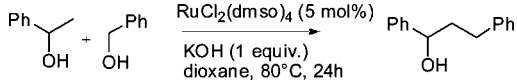
Scheme 22. Guerbet Reaction of Primary Alcohols[90]



Scheme 23. C−C Bond Formation via Alcohol Dehydrogenation[92,93]



Scheme 24. Beta Alkylation Using [$RuCl_2(dmso)_4$] as Catalyst[94]



acid.[91] These reactions form different isomeric products from those seen in the hydrogen transfer reactions reported here. Current mechanistic proposals feature a radical pathway as opposed to a dehydrogenation−functionalization−hydrogenation cycle.

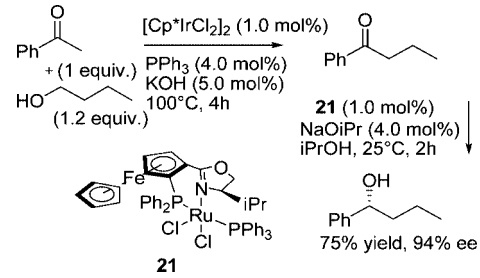
Several C−C bond-forming products were shown by Cho et al. through in-situ alcohol dehydrogenation (Scheme 23).[92] The alkylation of benzyl alcohols with various ketones resulted in α-alkylated ketone products. [$RuCl_2(PPh_3)_3$] and several other ruthenium catalysts gave good selectivity for the hydrogenated alcohol product with dioxane as hydrogen donor. Alternatively, an excess of 1-dodecene was required for good yields of the ketone product. This same catalytic system was also found to be active for the β-alkylation of primary and secondary alcohols.[93]

[$RuCl_2(dmso)_4$] has also been employed in both the beta alkylation (Scheme 24) and ketone alkylation reactions.[94] High yields were obtained when 1,4-dioxane was used as a solvent, which has been implicated as a hydrogen donor in other studies.[95] Experiments by Ramón and Yus suggest that the α,β unsaturated ketone product of the aldol condensation is reduced by hydride attack rather than a formal dihydride hydrogenation.[94b] This type of reduction may be applicable to other β-alkylation catalysts and other hydrogen transfer reactions, including imine reduction in N-alkylation reactions.

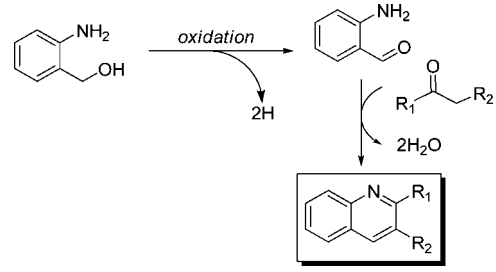
Though the ketone alkylation and β-alkylation reactions are related, not all catalysts active for one process have been reported to have activity for the other. Several complexes have given β-alkylations, including [$IrCp^*Cl_2]_2$,[96] Ru and Ir NHC complexes,[79,80,97] Ru alkylidenes,[46h] and Ir and Ru terpyridine complexes.[98] [Ir(cod)Cl]$_2$ in the presence of PPh_3 and base is reported to be active for ketone alkylation, but the system has not yet given beta alkylation.[99] Several Cp, bipy, and Tp ruthenium complexes have also given beta alkylation in the presence of 20 mol % NaOH.[100] Peris and co-workers reported a tandem, one-pot Suzuki coupling/alpha alkylation reaction using a heterobimetallic Pd/Ir species.[101]

An asymmetric approach to ketone alkylation was employed using a two-catalyst stepwise procedure (Scheme 25).[102] [$Cp^*IrCl_2]_2$ was used to perform the condensation of an alcohol and a ketone. The resulting ketone was then hydrogenated at room temperature via stereoselective hydrogen transfer using Ru complex **21** featuring a chiral P,N chelating ligand.

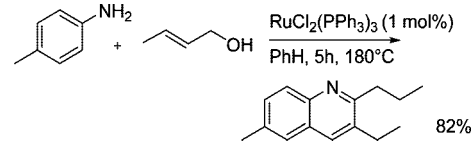
Scheme 25. Asymmetric Alcohols via a Two-Step Alkylation/Hydrogenation Sequence[102]



Scheme 26. Schematic of the Modified Friedländer Quinoline Synthesis



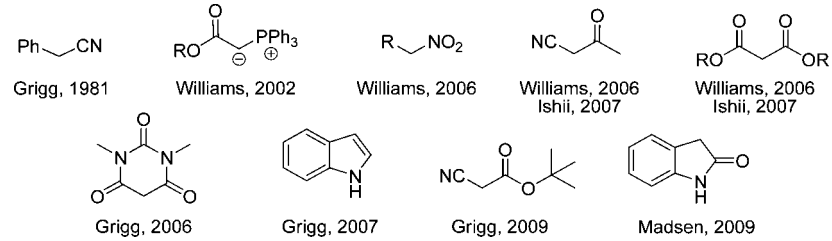
Scheme 27. Formation of Quinolines Through an N-Alkylation Process[112]



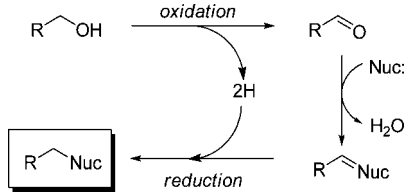
More complex products including heterocycles can be generated using C−C bond-forming processes via alcohol activation. The Friedländer quinoline synthesis (Scheme 26) typically employs an amino benzaldehyde in the presence of a ketone to furnish quinoline derivatives via a tandem condensation.[103] This process has been modified for use with hydrogen transfer catalysts, where an amino benzyl alcohol is dehydrogenated, forming a substrate competent for a tandem Friedländer-type condensation. Stoichiometry dictates that hydrogen removed from the alcohol starting material must be transferred to a hydrogen acceptor or liberated as H_2. The ketone coupling partner is either added directly or formed in situ from a secondary alcohol. [$RuCl_2(PPh_3)_3$] generated the highest yields when a secondary alcohol was employed and oxidized in situ.[104] Several complexes have been demonstrated to perform this reaction, including ruthenium alkylidenes,[105] [$RuCl_2(dmso)_4$],[106] $Pd(OAc)_2$,[107] as well as $IrCl_3$, [Ir(cod)Cl]$_2$ and [$IrCl_2H(cod)]_2$,[108] and [RhCl-($PPh_3)_3$].[109] $CuCl_2$ has also been used for this quinoline formation.[110] Most of the reported reactions require stoichiometric strong base, such as KOH or KO^{t}Bu. A modified Friedländer quinoline synthesis has even been reported without any transition-metal catalyst but using only a strong base.[111]

The ruthenium complex [$RuCl_2(PPh_3)_3$] is competent for a different alcohol activation sequence, leading to quinoline formation (Scheme 27).[55a,112] N-Alkylation of an aryl amine by an allylic alcohol results in an α,β unsaturated imine that is thought to cyclize to form the fused ring. If [$PtCl_2(PPh_3)_2$] and tin chloride are used in the place of [$RuCl_2(PPh_3)_3$], the

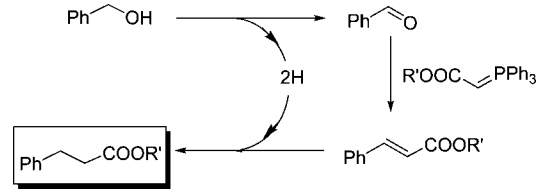
Chart 3. Representative Activated Nucleophiles Employed in Alcohol Activation Reactions



Scheme 28. Alkylation of Activated Nucleophiles by Alcohols



Scheme 29. An Oxidation−Wittig−Reduction Pathway for Alcohols



α,β unsaturated imine is apparently reduced to the amine; no quinoline is isolated.[113]

3.3.2. Activated Methylene Nucleophiles

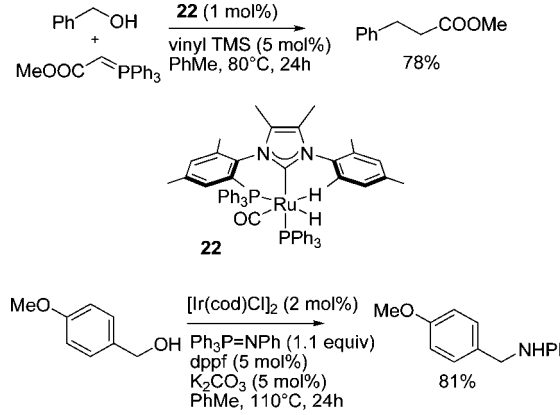
Beyond enolate chemistry, several Knoevenagel-type additions have been performed within the context of dehydrogenative activation (Chart 3 and Scheme 28). Early work found that fluorene alkylation could be achieved with ethanol using sodium ethoxide at high temperatures (210−220 °C).[114] Grigg and co-workers reported some of the first examples of homogeneous transition-metal-catalyzed C−C bond formation via alcohol activation.[115] An aryl acetonitrile was alkylated by primary alcohols in the presence of stoichiometric base using several rhodium catalysts as well as $[RuH_2(PPh_3)_4]$. Grigg later reported this transformation using $[Cp^*IrCl_2]_2$ with stoichiometric KOH,[116] and it has been reported elsewhere using iridium and rhenium hydrides.[117] Grigg and co-workers also reported the use of other activated nucleophiles,[118] including indoles.[119] Madsen recently reported an analogous addition using oxindoles as activated nucleophiles.[120]

Ishii and co-workers also investigated the activity of $[Ir(cod)Cl_2]$ in the presence of PPh_3 for alkylation and found that several activated methylene species, including alkyl cyanoacetates and β-keto nitriles, could be utilized in the absence of base, albeit at slightly higher temperatures.[121] The ability of this catalyst to function without base suggests that unlike many other alcohol activation catalysts, a metal dihydride intermediate may be formed in the catalytic cycle, with hydride now acting as an internal base. Williams achieved a similar result with $[Ru(PPh_3)_3(CO)H_2]$ and xantphos in the presence of a mild base.[122]

Williams explored the nitro aldol reaction in the context of hydrogen transfer reactions as well as analogous reactions with other nucleophiles.[122,123] $[Ir(cod)Cl_2]$ and dppf are added to form the active catalyst in situ in the presence of mild base. It was found that the addition of a suitable hydrogen acceptor, such as crotononitrile, allows access to the unsaturated products prior to their reduction.[124]

Williams and co-workers also explored ruthenium complexes for alkylation of activated methylene species with alcohols.[32e] Mild base, $[Ru(PPh_3)_3(CO)H_2]$, and xantphos effected the reaction in good yield. In an interesting mechanistic result, alkane side products were traced to an

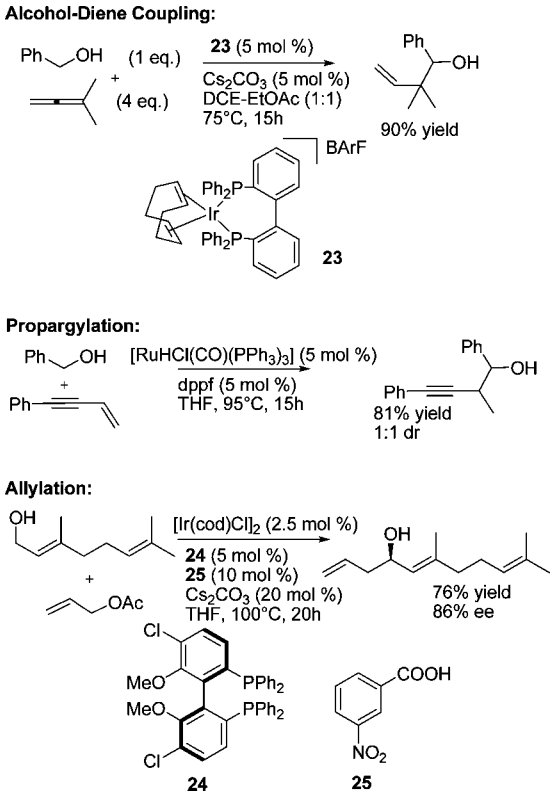
Scheme 30. Wittig-Type Processes within an Alcohol Activation Sequence[86,127b]



inhibiting decarbonylation side reaction in transfer hydrogenation reactions of primary alcohols. Williams saw decarbonylation products when the active catalysts was exposed to an aldehyde and suggested that the ability of a complex to perform decarbonylation is related to its capacity for certain alcohol activation processes. Other results support this claim: $[Ir(cod)Cl]_2$, a precursor to catalysts active for alcohol activation, has been used in a decarbonylation of aldehydes under similar reaction conditions.[125] Ruthenium phosphine hydride species, similar to complexes employed in alcohol activation reactions, have also been seen to perform decarbonylation.[32b] Williams and co-workers later attempted to improve the reaction by synthesizing a Ru−NHC xantphos catalyst but found that the resulting complexes were susceptible to intramolecular C−H activation of the NHC side chains.[126]

An interesting advance from Williams and co-workers uses generated aldehydes as coupling partners in Wittig-type reactions (Scheme 29).[123a,127] The nascent aldehyde generated from dehydrogenation reacts with a phosphonium ylide, and the resulting adduct is reduced. By the aza-Wittig reaction,[128] amine products were also generated using this strategy by analogous reaction with an iminophosphorane (Scheme 30).[86] In addition to $[Ir(cod)Cl]_2$/dppf, Williams et al. also utilized $[Ru(PPh_3)_3(CO)H_2]$ and Ru−NHC complex **22** successfully for this transformation, which could perform the reaction in

Scheme 31. Carbonyl Addition Reactions Utilizing Dehydrogenative Activation[129b,h,i]



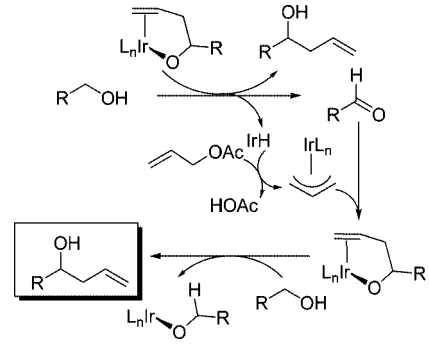
more mild conditions. One drawback from a green perspective is the production of stoichiometric triphenylphosphine oxide.

3.3.3. Other Nucleophiles

Beyond utilizing organic nucleophiles to react with an aldehyde or ketone generated by oxidation, alternative reactivity can be seen by using in-situ-generated carbonyls in other transition-metal processes. Krische and co-workers developed several metal-mediated carbonyl addition reactions that rely on dehydrogenative activation of alcohols (Scheme 31).[132] Aldehydes generated in situ from an alcohol react with unsaturated substrates in the presence of Ru or Ir catalysts, forming C−C bonds. Hydrogen removed from the alcohol starting material is reintroduced to molecular unsaturation within the catalytic cycle in net 'redox neutral' processes. Carbonyl allylations, crotylations, vinylations, and propargylations can be effected using this approach. The precursors $[RuHCl(CO)(PPh_3)_3]$ and $[Ir(cod)Cl]_2$ are used in the presence of chelating phosphines; some preformed complexes have also been employed, such as **23** in an alcohol/diene coupling (Scheme 31).[129b]

By reacting the oxidized alcohol in a transition-metal-catalyzed functionalization, catalyst-controlled asymmetric carbonyl attack becomes possible with the use of chiral ligands. Stereoselective product formation has been seen for allylations using allyl acetate as an achiral allyl donor; the active catalyst is formed in situ with chelating chiral phosphine ligand **24** as well as a benzoic acid derivative (**25**) that is thought to form a metallocyclic species with the metal precursor (Scheme 31).[129i] Asymmetric induction can be achieved with a variety of aryl alcohols in good yield and

Scheme 32. Carbonyl Additions of Aldehydes within an Alcohol Activation Reaction: A Possible Pathway[129i]



excellent stereoselectivity. A possible pathway for a dehydrogenation/functionalization sequence is shown in Scheme 32.

3.4. Net Oxidation of Alcohols

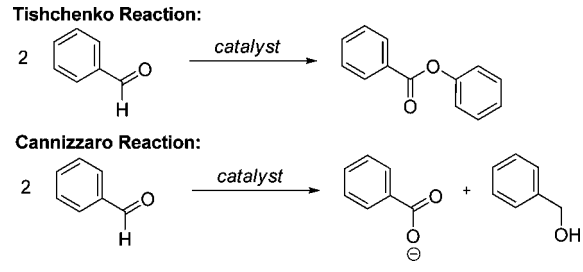
For the reactions discussed so far, the hydrogen that is removed from the substrate is returned to form the product. In a few cases the final hydrogenation step does not occur, leading to some novel net oxidation processes. In such cases the dehydrogenation and subsequent functionalization proceed to give a product that is more oxidized than the starting materials. For example, esters can be formed in this way from alcohols, and amides can be formed from alcohols and amine.

3.4.1. Ester Formation

Relevant organic reactions in this respect include the Tishchenko and the Cannizzaro reactions (Scheme 33). In the Tishchenko process esters are formed from the dimerization of aldehydes, catalyzed by transition-metal species, lanthanide alkoxides, or alkali alkoxides. The Cannizzaro reaction is traditionally a strong base-catalyzed disproportionation of aldehydes, forming a carboxylate and an alcohol. As many hydrogen transfer reactions occur at elevated temperature in the presence of strong base, these processes are possible side products where aldehydes are produced in situ.

The reactivity of metal complexes for the Tishchenko reaction appears to parallel reactivity for ester formation via the oxidative activation and dimerization of alcohols, including lactonization by diol oxidation (Scheme 34). Catalyst precursors found to have activity for oxidative esterification are shown in Chart 4. $[RuH_2(PPh_3)_4]$ is a known catalyst for both the Tishchenko reaction[131] and the formation of esters and lactones from the dehydrogenative activation of alcohols.[132] However, Murahashi suggested the alcohol esterification reaction does not operate via a Tishchenko-type

Scheme 33. Organic Reactions Related to the Formation of Esters from Primary Alcohols



Scheme 34. Oxidative Esterification of Primary Alcohols[132c,136]

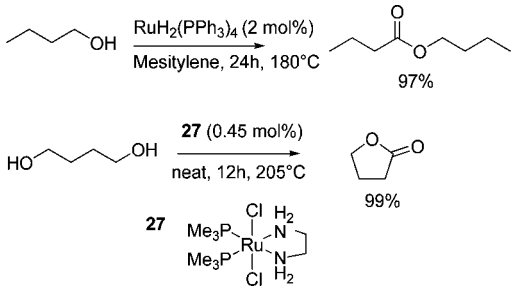
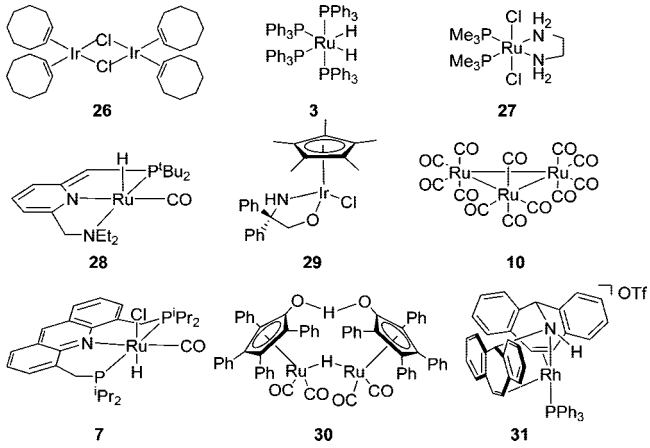
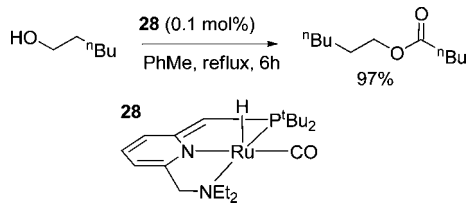


Chart 4. Catalyst Precursors for the Oxidative Esterification of Primary Alcohols



Scheme 35. Acceptorless Oxidative Esterification of Primary Alcohols[137]

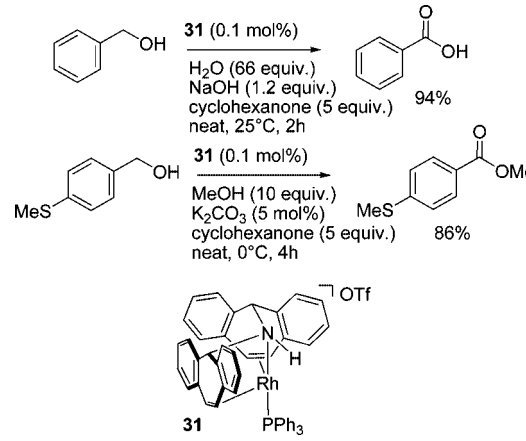


mechanism due to the inability of $[RuH_2(PPh_3)_4]$ to form esters from aldehydes in substantial yields under the conditions employed for alcohol esterification.[132c] Shvo's complex, $[(\eta^4\text{-}C_4Ph_4CO)Ru(CO)_3]_2$ (**30**), is capable of Tishchenko reactions[133] as well as oxidative esterification.[43] These ruthenium complexes as well as $Ru_3(CO)_{12}$[134] are capable of ester and lactone formation at elevated temperatures in the absence of base. Shvo's complex and $RuH_2(PPh_3)_4$ are capable of performing acceptorless dehydrogenation (presumably through formation of a ruthenium hydride), where $Ru_3(CO)_{12}$ requires a hydrogen acceptor. If $Ru_3(CO)_{12}$ is reacted with diols besides 1,4 and 1,5 diols, polyesters are synthesized.[135] Lactone formation was performed using ruthenium bis-phosphine diamine complex **27**, capable of an acceptorless dehydrogenation at elevated temperatures.[136]

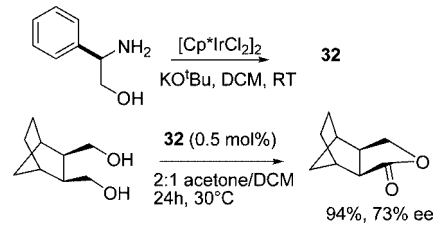
Another complex with activity for oxidative esterification is Ru PNN pincer complex **28** developed by Milstein and co-workers, which gives dehydrogenation of primary alcohols to esters in the absence of base (Scheme 35).[137] This same complex was found to perform acceptorless oxidative amidation as well (see section 3.4.2).

Heterocoupled products have also been seen in oxidative esterification using ruthenium catalysts by using methanol as a coupling partner. Williams and co-workers demonstrated

Scheme 36. Dehydrogenative Activation Products in the Carboxylic Acid Oxidation State[139]



Scheme 37. Asymmetric Lactone Formation from a Meso-Diol[143]



the synthesis of methyl esters from primary alcohols in the presence of methanol. The $[Ru(PPh_3)_3(CO)H_2]$/xantphos system demonstrated good activity for this reaction in the presence of a hydrogen acceptor (crotonitrile).[124b,138] Grützmacher and co-workers have seen oxidations to esters and carboxylic acids using cationic rhodium catalyst precursor **31** at room temperature using a hydrogen acceptor (Scheme 36).[139] The neutral complex is competent for oxidative amidation (section 3.4.2).

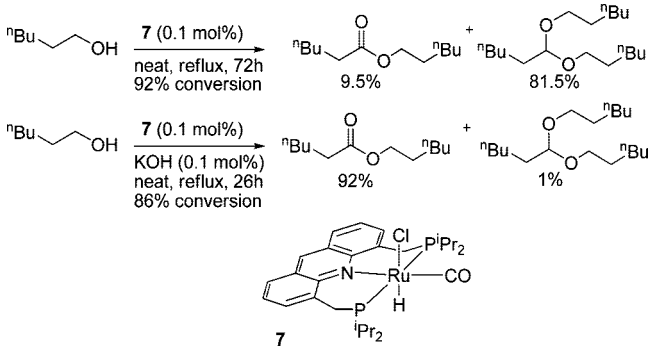
Several iridium metal species are also known to catalyze this reaction, including an iridium hydride species[140] and a Cp*Ir complex with a chelating N,O ligand (**29**, Chart 4) capable of reaction at room temperature in the presence of acetone.[141] A similar catalyst was employed for a Tishchenko reaction of aldehydes at room temperature in the presence of base.[142] An asymmetric variant of this lactonization methodology was successfully performed using a chiral N,O ligand from prochiral diols (Scheme 37).[143] Ishii et al. have shown that $[Ir(coe)Cl]_2$ (**26**, Chart 4) can perform the oxidative dimerization of primary alcohols to esters without base in the presence of air.[144]

Two alcohols can form other products besides esters via dehydrogenative activation. Milstein and co-workers found the formation of acetals upon reaction of alcohols with Ru PNP pincer complex **7** with extrusion of dihydrogen (Scheme 38).[145] The ester is obtained in the presence of base, while at neutral conditions the acetal is formed. Peris and co-workers found that a Cp*Ir NHC complex can perform etherification of alcohols (an alcohol/alcohol coupling).[81]

3.4.2. Amide Formation

Amide bond construction appears to be conceptually similar to ester formation from the perspective of the oxidation state changes, but the competing N-alkylation process greatly complicates the picture (Scheme 39). Currently there is little mechanistic information suggesting to

Scheme 38. Base-Dependent Selectivity in an Acetal and Ester Formation[145]

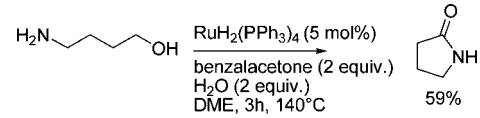


what extent the N-alkylation and alcohol amidation pathways may overlap. The number of complexes so far found to be active for amide formation is far smaller than the wide array of catalysts active for N-alkylation (Chart 5).

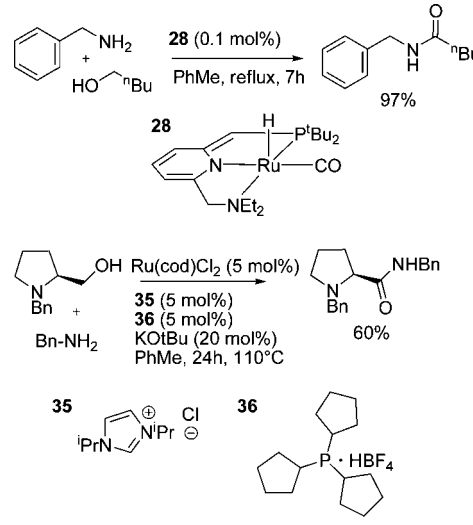
Murahashi saw the formation of an amide from alcohol and amine using $[RuH_2(PPh_3)_4]$ in the presence of a hydrogen acceptor (Scheme 40).[146] Five- and six-membered lactam rings were synthesized from amino alcohols in an intramolecular process. The addition of two equivalents of water to the reaction mixture was required to form the lactam product; without it, the authors report forming cyclic amines. As both N-alkylation and amidation likely proceed through a hemiaminal intermediate, presumably the presence of water inhibits dehydration to generate the imine. Instead, the hemiaminal is irreversibly dehydrogenated, forming an amide. It is currently unclear what properties predispose a complex for one pathway or the other, and more mechanistic studies are needed. Water has an inhibitory effect on the same catalyst in the Tishchenko reaction of aldehydes.[131] A rhodium-based catalyst was later found to generate cyclic 5-, 6-, and 7-membered lactams from aromatic amino alcohols.[147] $[Cp^*RhCl_2]_2$ was employed as a catalyst in the presence of acetone as a hydrogen acceptor and mild base. A sealed tube was required to attain temperatures (100 °C) where good yields could be reached.

Milstein and co-workers performed a similar transformation in the absence of a hydrogen acceptor (Scheme 41).[148] Dihydrogen gas is evolved as the substrate is oxidized. Notably, the reaction can be performed in an intermolecular fashion; aliphatic primary alcohols and primary and secondary amines were successfully used to form secondary and tertiary amides in excellent yields. The PNN-pincer ruthenium complex **28** employed as catalyst functions in the

Scheme 40. Lactam Synthesis from Amino Alcohols[146]



Scheme 41. Intermolecular Amide Bond Formation via Dehydrogenative Alcohol Activation[148,149]



absence of base or catalyst activators. The authors think that the pincer ligand, which contains an unusual dearomatized ring, can alternatively aromatize and dearomatize during the catalytic cycle to facilitate the formation of dihydrogen. This reaction can also be performed in the presence of a Ru−NHC complex, as reported by Madsen and co-workers (Scheme 41).[149] They form the active complex in situ from $[Ru(cod)Cl_2]$ (**34**, Chart 5), imidazolium salt **35**, phosphine **36**, and catalytic base added to the reaction mixture. Secondary amides were formed in good to excellent yields, and a single tertiary amide was reported in fair yield. Longer reaction times were needed than in the Milstein report. Williams and co-workers reported the formation of amides from alcohols and amines from $[Ru(p\text{-cymene})Cl]_2$ in the presence of dppb and Cs_2CO_3 and a hydrogen acceptor in refluxing *tert*-butanol.[150]

Grützmacher and co-workers have seen an array of net oxidations of alcohols to amides using hydrogen acceptor **37** and rhodium complex **33** with unprecedented activity at room temperature (Scheme 42).[139] Both primary amines and ammonia were successfully employed to generate primary

Scheme 39. Possible Products from Alcohol Activation in the Presence of Amine

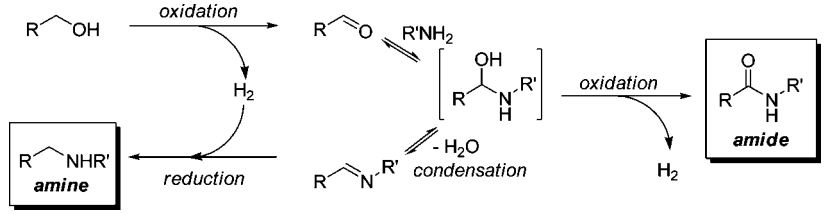
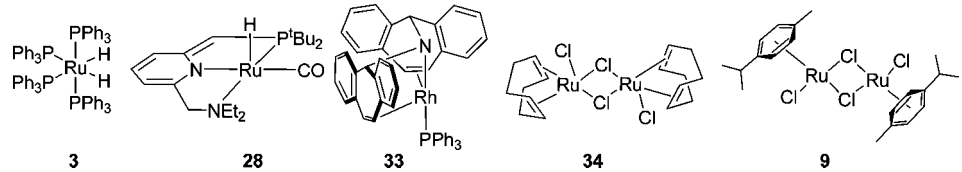
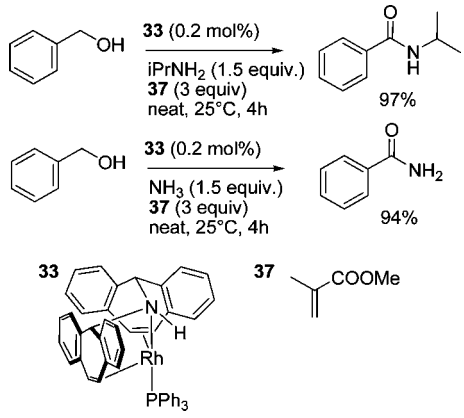


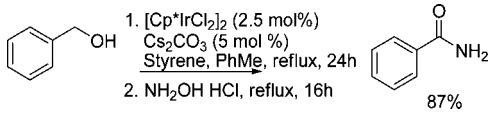
Chart 5. Precursor Complexes Implicated in the Amide Formation from Amines and Alcohols



Scheme 42. Mild Synthesis of Primary and Secondary Amides via Oxidative Amidation[139]



Scheme 43. Primary Amide Synthesis via an Oxime Rearrangement[151]



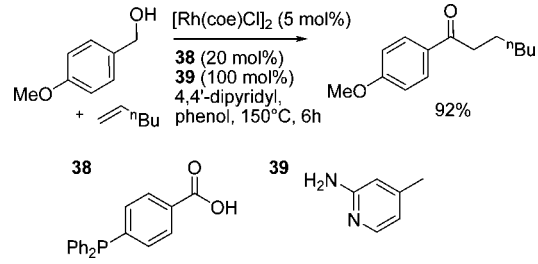
and secondary amides, respectively. This species is proposed to contain a ligand-based Lewis basic site that may play a crucial role during the catalytic cycle. A computational study suggests that this basic site allows the complex to dehydrogenate via a monohydride mechanism. For the formation of carboxylic acid products, a ruthenium hydroxo species is invoked as a local nucleophile capable of attacking a metal-coordinated aldehyde; the resulting hemiacetal undergoes β-elimination, forming the product. This mechanistic hypothesis is significant because it suggests the metal is fully involved in the pathway, including the hemiacetal intermediate.

Williams and co-workers identified an indirect one-pot synthesis of primary amides from hydroxylamine and alcohols (Scheme 43).[151] This relies on a Beckmann rearrangement of an oxime intermediate. First, an alcohol is oxidized to the aldehyde via $[Cp^*IrCl_2]_2$ and Cs_2CO_3 in refluxing toluene; in a subsequent reaction with hydroxylamine the oxime is formed and then undergoes rearrangement to the primary amide.

3.4.3. Hydroacylation

Hydroacylation,[152] the coupling of alkenes to carbonyls and imines, has been employed within an alcohol activation procedure.[153] Jun and co-workers found that in-situ-generated aldehydes can participate in a so-called *chelation-assisted hydroimination* reaction by temporarily forming a chelating imine that is hydrolyzed after the coupling step in the catalytic cycle (Scheme 44). A coupling of this type was first reported using a $RhCl_3H_2O/PPh_3$ system in the presence

Scheme 45. Coupling of Primary Alcohols and Terminal Olefins via Hydroacylation[155]



of 2-amino-4-picoline to couple a benzyl alcohol with a terminal olefin.[154] An unconventional biphasic solvent system was later employed by Jun and co-workers for the hydroacylation of primary alcohols that allows for catalyst recycling.[155] This system uses $[Rh(coe)Cl]_2$ in the presence of phosphine **38** and 2-amino-4-picoline (**39**), with 4,4-dipyridyl and phenol added to form a biphasic mixture (Scheme 45). An elegant variant of this work was reported using a recyclable self-assembling organic catalyst.[156]

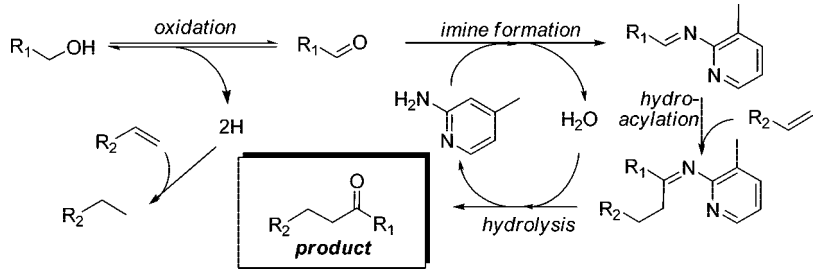
4. Dehydrogenative Amine Activation

In principle, amines can be activated in much the same manner as alcohols and alkanes. Imines and iminium ions are reactive functional groups which see utility in a variety of organic transformations, including cyclization reactions and reactions with nucleophiles. Thus, a one-pot reaction sequence that (1) oxidizes an amine substrate, generating an imine or iminium ion, and (2) utilizes this functionality in a second chemical process offers an approach to generating molecular complexity that reduces the total number of steps and eliminates activating groups. This concept has been briefly described by Beller and co-workers.[157]

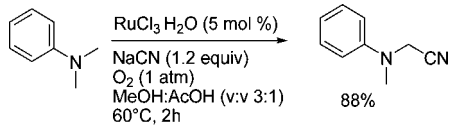
Many of the existing examples of amine activation reported in the literature require the use of stoichiometric oxidants to promote the reaction. A representative example of this type is the oxidative cyanation of a tertiary amine to generate an α-aminonitrile, molecules useful in the synthesis of α-amino acids (Scheme 46).[158] Catalytic $RuCl_3$ is employed using 1 atm O_2 as a stoichiometric oxidant in mild acid conditions. This sequence offers an alternative to the classical Strecker reaction in which an iminium cation, generated in situ from a ketone and an amine, is attacked by cyanide anion. This class of reaction will not be discussed further since recent reviews of this area are available[159] and because the catalysis requires a traditional external oxidant.

Amine activation reactions through dehydrogenation are less prevalent in the literature than those for alcohols. One factor is the slower β-elimination from amines and amido complexes. Another is the high nucleophilicity of amines, particularly that of primary amines, a complicating property

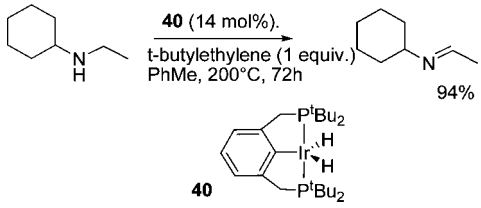
Scheme 44. Hydroacylation via Dehydrogenative Activation of Primary Alcohols[155]



Scheme 46. Representative Reaction for Oxidant-Promoted Amine Activation[158]



Scheme 47. Amine Dehydrogenation Using an Ir Pincer Complex[160]



in the presence of electrophilic imines and in the basic conditions in which dehydrogenations are often performed.

4.1. Dehydrogenation of Amines

Catalytic homogeneous amine transfer dehydrogenation has been demonstrated for iridium pincer complex **40** by Jensen and co-workers (Scheme 47).[160] A PCP pincer ligand that earlier dehydrogenated alkanes[12] was employed in the dehydrogenation of secondary amines with good to excellent yields and selectivity. It was found that imine generation inhibited the reaction, and high dilution was required to overcome inhibition.

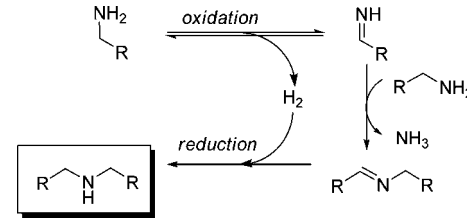
Jensen identified multiple possible pathways for the apparent C−N bond dehydrogenation of secondary amines to afford imines, including (a) direct C−N bond dehydrogenation and (b) C−C bond dehydrogenation, followed by isomerization. The ability of 2,2,2′,2′-tetramethyldibutylamine to undergo apparent amine dehydrogenation lends credence to the former pathway. Additionally, it was reported that tertiary amines could not react under the conditions used; however, Goldman reported C−C bond dehydrogenation of tertiary amines to afford enamines using an identical catalyst.[161] Though the mechanistic details of this reaction are still to be fully understood, it currently appears to involve a C−N bond dehydrogenation event. This reactivity is not limited to iridium species; amine dehydrogenation has been reported by Yi and co-workers using a highly active tetranuclear ruthenium cluster.[162]

Several metal species are competent for amine racemization, which is believed to go by rapid dehydrogenation−hydrogenation via a short-lived imine intermediate. Rhodium complexes, including $[RhCl(PPh_3)_3]$, $[Rh(cod)Cl]_2$, and $[Rh(cod)_2BF_4]$, were shown to have good activity for the racemization of primary amines in the presence of PCy_3.[163] $[Pd(PPh_3)_4]$ was found to perform this reaction more rapidly.[164] Bäckvall demonstrated similar reactivity with the Shvo complex.[165]

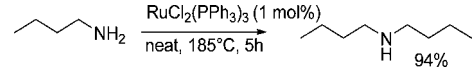
4.2. Transamination

Imines formed through the activation of amines should in principle react with any available nucleophile. The characteristic nucleophilicity of the amine substrate makes the transamination pathway available within the amine activation manifold. Transamination, also known as *amine exchange*, allows for the formation of highly substituted amines without the need for typical activating groups seen within the contemporary organic literature. Transaminations that feature

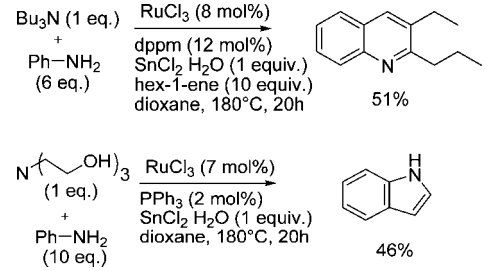
Scheme 48. Schematic Mechanism of Transamination



Scheme 49. Transamination of Primary Amines[168]



Scheme 50. Heterocycle Synthesis via Transamination of Aryl and Alkyl Amines[172,175]



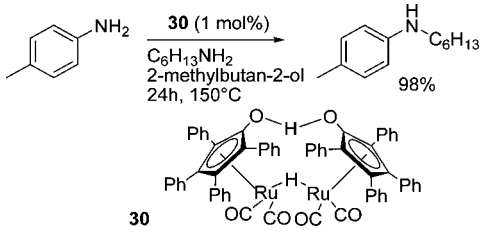
more than one amine species can be successful with careful choice of substrates.

A schematic mechanism for the reaction is shown in Scheme 48. An amine, once oxidized to the imine by hydrogen transfer, reacts with another equivalent of the substrate amine. The resulting imine is then hydrogenated by hydrogen transfer to the product amine.

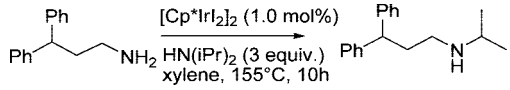
Murahashi and co-workers used palladium black for performing the first reported alkyl exchange between substituted amines.[166] Among the first homogeneous complexes found for this reaction were $[Ru_3(CO)_{12}]$, $[Os_3(CO)_{12}]$, and $[Ir_4(CO)_{12}]$ as reported by Shvo and Laine.[167] Porzi and coworkers reported many of the earliest transamination reactions, using $RuCl_2(PPh_3)_3$ as the active catalyst (Scheme 49). Primary amines were self-coupled with extrusion of ammonia.[168] Alkyl group transfer between two identical secondary amines or two identical tertiary amines was reported in good yield.[169] Additionally N-heterocycles were formed from the respective aliphatic diamines in an intramolecular transamination reaction.[170] A study of the $RuCl_3$/phosphine catalyst system found that in the transamination reaction imine hydrogenation is approximately 200 times faster than the overall reaction,[171] suggesting that amine dehydrogenation is the rate-determining step.

Shim, Cho, and co-workers have seen amine exchange reactions with ruthenium complexes (Scheme 50). For example, quinolines were formed by an exchange reaction of aniline and a trialkylamine.[172] The catalyst is formed in situ from $RuCl_3$ and bis(diphenylphosphino)methane (dppm) with $SnCl_2 \cdot 2H_2O$ as an additive and a superstoichiometric amount of hex-1-ene as hydrogen acceptor. Initial formation of imine via dehydrogenation is presumed, and the authors suggest an organic Schiff-base dimerization, followed by a ruthenium-catalyzed heteroannulation, to give the quinoline product. A similar formation of quinolines from a triallylamine starting material was also reported.[173] Indoles were successfully synthesized from triethanolamine and an N-substituted aniline in the presence of $[RuCl_2(PPh_3)_3]$ via a transamination reaction.[174] The reaction could be performed

Scheme 51. Transamination of Primary Amines Catalyzed by the Shvo Complex[179a]



Scheme 52. $[Cp^*IrCl_2]_2$-Catalyzed Transamination of Two Amines Capable of Oxidation[181]



from primary anilines in the presence of tin chloride dehydrate with $RuCl_3$ and PPh_3.[175] Cho and co-workers developed a related reaction for the synthesis of 1,2-disubstituted benzimidazoles from *N*-alkyl-1,2-diamino benzenes.[176]

Platinum(II) bromide was found to catalyze the formation of quinolines from *N*-alkyl anilines and trialkylamines in the presence of tin chloride.[177] The reaction requires 1-hexene as a hydrogen acceptor as well as $[R_4P]Br$. The authors suggest that 1-hexene may also have a role in promoting catalysis beyond accepting dihydrogen.

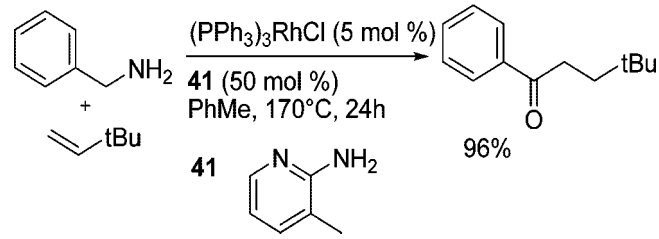
The Shvo complex (**30**), previously shown to perform racemization of primary amines, is also competent for transamination reactions (Scheme 51).[178] The formation of secondary amines was accomplished by condensation of a primary amine and an aryl amine, with liberation of ammonia at 140 °C.[179] The use of an aniline as one of the amine coupling partners reduces the possible number of products from the transamination process. The Shvo complex was also used in transamination reactions coupling amines to *tert*-alkyl amines.[180] The authors report that many of the ruthenium complexes employed in the alkylation of amines by alcohols (see section 3.2) were not able to perform the transamination reaction under their conditions. A similar reaction was reported by Peris and co-workers using Cp*Ir NHC complexes to couple aryl amines to primary amines.[81]

Transamination of aryl amines has also been achieved using the iridium species $[Cp^*IrI_2]_2$ (Scheme 52). Williams and co-workers report the formation of substituted amines via the transamination pathway.[181] The authors were capable of selectively coupling a primary and secondary amine, two amines capable of oxidation, without significant generation of homocoupled products. Additionally, aryl amines were reacted with secondary amines, and self-coupling of primary amines was also reported. $[Cp^*IrCl_2]_2$ was found to be a poor catalyst versus $[Cp^*IrI_2]_2$. The authors note that this complex has been previously employed as an amine racemization catalyst, presumably via a dehydrogenation/hydrogenation pathway with intermediate imine formation. This reactivity matches that known for the Shvo complex, which is also active for both processes.

4.3. Hydroimination and Hydroaminoalkylation

The intermediate imine product generated in the transamination reaction can be further functionalized. An example of tandem functionalization of this type is the coupling of an unsaturated hydrocarbon with an imine (so-called *hydroimination*).

Scheme 53. Amine Activation within a Hydroimination Protocol[182]



Jun and co-workers demonstrated a reaction where a substrate suitable for directed hydroimination is generated as the product of two alkyl transfer steps (Scheme 53).[182] The first transfer occurs with the substrate amine and the second with 2-amino-3-picoline (**41**), generating a substrate for hydroimination. The hydroiminated product undergoes another alkyl transfer, and the resulting ketimine is hydrolyzed to generate a ketone product and an equivalent of amine starting material (Scheme 54). This net C−C bond formation has a maximum theoretical yield of 50% due to the use of alkene as a sacrificial hydrogen acceptor for the initial oxidation as well as the incorporation of an equivalent of amine substrate in the ketimine that is recovered upon workup.

Coupling of amines with ethylene has been known for several decades. Coulson reported an addition of ethylene to secondary amines using homogeneous iridium and rhodium catalysts in 1971.[183] More recently, Jun and cowokers[184] and Murai and co-workers[185] demonstrated a coupling of activated amines and olefins with $Ru_3(CO)_{12}$ (Scheme 55).

A Ru complex, $[(PCy_3)_2(CO)RuHCl]$, has been reported to perform amine−olefin coupling to afford a mixture of imine and amine products, depending on the selected amine and olefin substrates (Scheme 56).[186] The olefin substrate (added in large excess) can apparently act as a hydrogen acceptor as well as a coupling partner within the reaction.

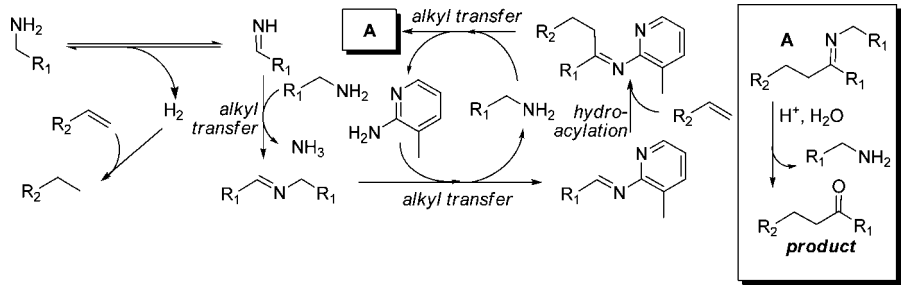
A related process was first described by Nugent and co-workers[187] as well as Maspero and Clerici[188] using early transition-metal dimethylamines, including $[Ta(NMe_2)_5]$. An $\eta-2$ imine complex is formed after C−H activation of the amine substrate; the resulting species undergoes insertion by the olefin to create a five-membered metallacycle that is protonated by substrate amines to give the product (Scheme 57). Though the proposed tantalum-catalyzed reaction mechanism does not feature a metal hydride species as an intermediate, the mechanism includes an imine formation from an unactivated amine without the need for an external oxidant and thus is mentioned here.

The so-called *hydroaminoalkylation* reaction was later described by Herzon and Hartwig, who found that amines with aryl substituents were more active substrates than their aliphatic counterparts, and reported $[TaCl_3(NEt_2)_2]$ as a novel catalyst (Scheme 58).[189] Similar chemistry has been reported in the lanthanide literature[190] and has also been performed with a titanium catalyst.[191]

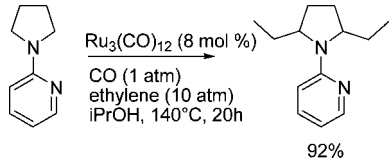
4.4. Amine Oxidation to Nitriles

Another pathway for the functionalization of an oxidized amine is a further oxidation to a nitrile species (Scheme 59). Goldman reported that the PCP pincer Ir complex **40** is capable of dehydrogenation of amines to form nitriles with *tert*-butyl ethylene as hydrogen acceptor (Scheme 60).[192] The proposed reaction mechanism, supported by mechanistic data,

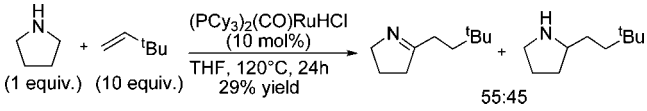
Scheme 54. Amine Activation within a Hydroimination Protocol: A Possible Mechanism[182]



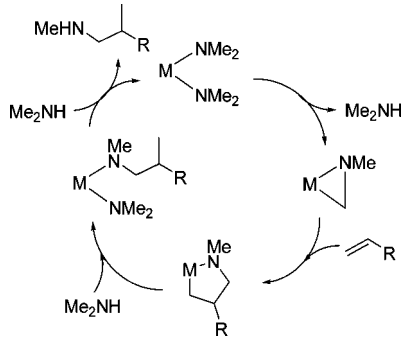
Scheme 55. Olefin−Amine Coupling with $Ru_3(CO)_{12}$[185]



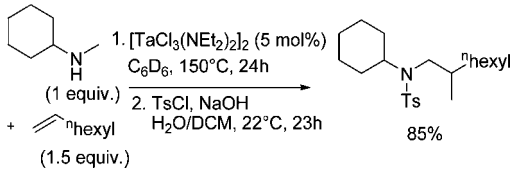
Scheme 56. Selectivity in Amine−Olefin Coupling Reactions[186]



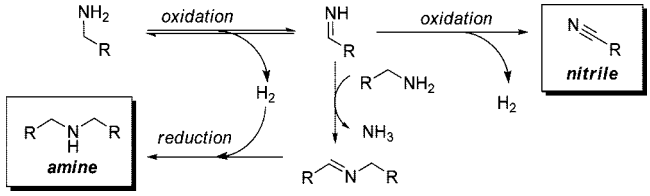
Scheme 57. Hydroaminoalkylation Reaction (Adapted with Permission from Ref 187. Copyright 1983 American Chemical Society)



Scheme 58. Hydroaminoalkylation with $[TaCl_3(NEt_2)_2]$[189]

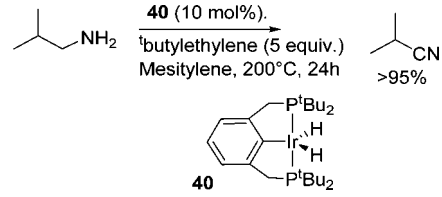


Scheme 59. Established Pathways for the Dehydrogenative Activation of Amines



features an amine oxidation via stepwise oxidative addition and β-elimination, generating an iridium dihydride intermediate which is reduced by the hydrogen acceptor. The intermediate imine is oxidized in the same manner as the imine, again requiring an equivalent of hydrogen acceptor. High temperature was required, likely in part due to the thermodynamic barrier of displacing product nitrile with substrate amine in the catalytic cycle.

Scheme 60. Nitriles via Dehydrogenative Activation of Amines[192]



5. Mechanisms of Dehydrogenative Activation

The mechanism of dehydrogenative activation via homogeneous transition-metal complexes varies greatly, depending on the substrate and catalyst employed as well as the conditions chosen. The two H atoms extruded can be delivered to the metal complex or directly to a hydrogen acceptor. The pathways for stepwise mechanisms generally consist of two separate components: association of the substrate with the catalyst followed by cleavage of a C−H bond. A saturated molecule must first coordinate in some manner to a transition-metal complex, a step that often requires direct activation of a C−H bond for alkanes or for alcohols and amines of a O−H or N−H bond. Alcohol or amine binding to the metal catalyst is typically followed by a deprotonation event. The resulting metal alkoxide or amine complex then undergoes a β C−H bond cleavage, resulting in a metal hydride and a dehydrogenated organic species.

Following the dehydrogenative step, a functionalization occurs. This process can be catalyzed by the same catalyst as that employed for dehydrogenation, catalyzed by a different species added to the reaction mixture for this purpose, or simply occur without the need for a catalyst. Once generated, the resulting intermediate can then react with additional reagents and be oxidized or reduced depending on the specific reaction sequence.

The known roles of transition metals in the various mechanisms of dehydrogenative activation are described in more detail below, with the classes of dehydrogenative activation discussed by substrate type.

5.1. Alkane Mechanisms

Alkane activation, unlike that of alcohols or amines, requires an initial activation of a C−H bond. For the complexes employed for the dehydrogenation of alkanes, mechanistic studies have been performed that support a reverse-hydrogenation mechanism for the alkane dehydrogenation sequence.[193] The oxidation state of the intermediates, however, remains controversial. In early work on Ir hydrogenation catalysts, an Ir(I)/Ir(III) cycle was assumed

by analogy with the Rh(I) catalysts. The properties of the Rh and Ir catalysts are so different, however, that this assumption always remained troubling. More recent computational work[194] implicates Ir(III)/Ir(V) cycles. This would explain the substantial differences in properties since Rh(V) is far less easily accessible. For example, $[IrH_5(PR_3)_2]$ forms a perfectly stable series of complexes, while efforts to make the analogous Rh complexes have so far failed.

Goldman and co-workers[195] and Hall and co-workers[196] carried out extensive computational studies on alkane dehydrogenation.

Combined computational and experimental work[194a] has also helped understanding of photochemical and thermal alkane activation with $[IrH_2(O_2CCF_3)(PAr_3)_2]$ (Ar = *p*-FC_6H_4); H/D isotope scrambling between alkenes and $[IrD_2(O_2CCF_3)(PAr_3)_2]$ was studied. No unique interpretation of the experimental data was possible, so DFT(B3PW91) calculations on the exchange process on the quantum model system $[IrH_2(O_2CCF_3)(PH_3)_2(C_2H_4)]$ were carried out to distinguish between the possibilities allowed by experiment. The preferred pathway proposed involves the insertion of the olefin to give an alkyl hydride that reductively eliminates to lead to a transition state that contains an η^3-bound alkane. This transition state, which leads to a 1,1′ geminal H/D exchange in the alkane complex, is significantly lower in energy than the alternative dihydrido carbene, located as a secondary minimum, eliminating the previously favored alternative carbene mechanism. The unexpectedly large binding energy (BDE) of the alkane to the $[IrH_2(O_2CCF_3)(PH_3)_2]$ fragment (BDE = 11.9 kcal mol^{-1}) in this transition state is ascribed in part to the presence of a weakly σ- and π-donating (O_2CCF_3) group trans to the alkane binding site. The observed experimental H/D exchange selectivity requires 1,1′bshifts (i.e., M moving to a geminal C−H bond) but excludes 1,3 shifts in the alkane complex. In a key finding, a 1,3 shift in which the metal moves down the alkane chain is indeed found to have a much higher activation energy than the 1,1′ process and is therefore slow in our system. A 1,2 shift was not considered since it would involve a large degree of steric hindrance at a tertiary carbon. This mechanism, involving a strongly bound alkane, provides insight into the closely related photochemical and catalytic thermal alkane dehydrogenation processes mediated by $[IrH_2(O_2CCF_3)(PAr_3)_2]$. Only the thermal route requires t-BuCH=CH_2 as the hydrogen acceptor. In the photochemical process energy is supplied by the photon absorption mediating reductive elimination of H_2. These two alkane reactions have the same intermediate alkane complex. Remarkably, the rate-determining step of the thermal (150 °C) alkane dehydrogenation process is predicted to be substitution of the t-$BuCH_2$−CH_3 alkane complex, derived from hydrogenation of the hydrogen acceptor, by the alkane substrate.

5.2. Alcohol and Amine Mechanisms

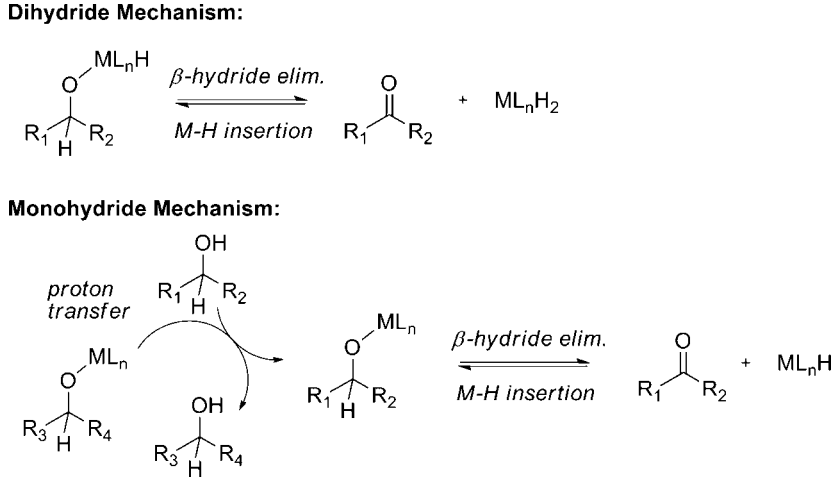
Alcohol and amine activation reactions typically rely on three steps: (i) dehydrogenation, (ii) functionalization, and (iii) hydrogenation. Since the functionalization of step ii is usually a standard organic reaction involving nucleophilic attack of a reactant on a dehydrogenated substrate such as an aldehyde, no intervention by the metal is necessarily involved. This is an assumption, however, and may not in fact hold because aldehyde binding to an electrophilic metal fragment should greatly increase the electrophilicity of the carbonyl carbon and thus enhance nucleophilic attack. Since the first and third steps are generally considered more challenging, we will discuss these steps in what follows. Step iii does not necessarily occur, as in the transformation of amine and alcohol to the amide, in which case the overall transformation is oxidative.

Alcohol activations rely on repeated hydrogen transfer to and from the reactants and the intermediates involved. Homogeneous hydrogen transfer catalysis has been known for many years, and the mechanistic aspects have been reviewed several times.[44,197] In spite of much work, the situation remains to be clarified because several possibilities have been suggested. Indeed, each may operate in specific catalysts. The possibilities may be broadly classified as inner sphere, intermediate sphere, and outer sphere. They differ in the way they transfer 2H to and from the substrate. Assuming reversibilty, we need only discuss one of the two directions, and assuming analogy between the different classes of substrate, we need only discuss one class.

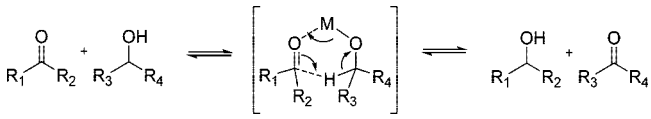
The inner-sphere mechanism relies on insertion of the aldehyde into an M−H bond present on the catalyst (Scheme 61). The resulting alkoxide can then be liberated as the free alcohol by reacting with a substrate alcohol.

In the intermediate-sphere case, a pathway taken from classical organic chemistry is invoked, the Meerwein−Ponndorf−Verley (MPV) mechanism (Scheme 62). In this case the metal acts as template to hold the H-donor and H-acceptor species together, so that a hydride can be effectively transferred from one to the other.

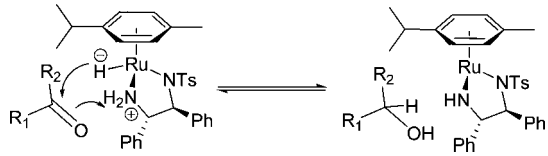
Scheme 61. Prototypical Inner-Sphere Transfer Hydrogenation Pathways



Scheme 62. Mechanism of the Meerwein−Pondorf−Verley Reduction and Oppenauer Oxidation



Scheme 63. Outer-Sphere Hydrogen Transfer Mechanism of Noyori's Catalyst



An outer-sphere mechanism has been invoked to account for the activity of the Noyori's Catalyst which have no open site on the metal for substrate binding that would be required prior to any insertion (Scheme 63). These catalysts all have a protonic hydrogen in a position cis to the hydride, typically in the form of a coordinated R_2NH ligand. This arrangement allows for concerted transfer of H^- from the metal and H^+ from the R_2NH ligand to the substrate.

It might be thought that this transfer would not be energetically favorable because it leaves behind a 16e d^6 metal fragment. As shown by Caulton, however, such a fragment can be greatly stabilized by the presence of a basic lone pair on a ligand.[198] This lone pair is considered to be partially donated to the metal, filling the $2e^-$ vacancy that would otherwise be present. This effect has been invoked to account for the low M−P bond energy on the grounds that the $16e^-$ d^6 metal fragment left behind is stabilized by the halide lone pair.

If the alcohol is readily dehydrogenated, why does the amine not similarly dehydrogenate where a reactant amine is present, such as in the amine alkylation reaction, for example? If this occurred, a more complex product spectrum would be expected. Regarding the β-elimination inner-sphere mechanism, it is possible to understand a preference for the reaction of an alcohol over an amine. Computational backing for this qualitative picture has been provided by Macgregor and co-workers,[199] who have shown that an alkoxide more easily β-eliminates than an amide because of the need to liberate an open site cis to the alkoxide or amide. In any such 16e precursor, there will be a competition between H^- transfer to the open site and lone pair binding. The amide having a more basic lone pair is thus seen as raising the barrier for β-elimination.

The standard MPV reaction has not been seen for amines, so that amine alkylation, at least, seems unlikely to proceed in this way. On the basis that a common mechanism is more plausible than separate mechanisms for each specific subtype of alcohol activation, the MPV mechanism seems less likely to contribute. In addition, no extensive series of alcohol activations has been reported for standard main-group MPV catalysts, where the mechanisms invoking hydride intermediates seem implausible.

Since the catalysts for alcohol activation do not in general possess an acidic proton cis to the presumed substrate binding site, the outer-sphere mechanism also seems less likely, at least as a general explanation.

An apparent objection to the inner-sphere mechanism is the paucity of examples in which imines are reduced, a step implied in the amine alkylation pathway. Fortunately, an increasing number of cases of hydrogen transfer reduction of imines have now been found.[79,200]

The class of reactions in which net oxidation occurs provides further mechanistic clues. In a reaction such as Milstein's amide synthesis from alcohol and amine,[148] hydrogen must be evolved. The MPV mechanism seems incapable of H_2 formation on any reasonable hypothesis. For the outer-sphere mechanism to operate, the hydrogenated form of the catalyst would have to eliminate H_2, a reaction that has not been documented. The objection that the known amidation catalysts do not systematically have protonic NH groups on cis ligands loses some of its force because such a group could be provided by an amine substrate after its coordination to the metal.

Amine alkylation and amidation reactions start from the same reactants yet produce quite different products, secondary amine or amide, so a mechanistic change must be invoked. In alkylation an intermediate imine is hydrogenated, while in amidation an intermediate hemiaminal is dehydrogenated (Scheme 39). One possibility is that once the hemiaminal has lost H_2O, its fate is sealed and secondary imine must be formed. In that case it may be that the hemiaminal is never released from the metal in amidation. One way this could happen is formation of a chelated hemiaminalate, which could β-eliminate to form the amide, similar to the intermediate proposed by Grützmacher et al. for the formation of esters from alcohols.[139] If, in contrast, imine is released into solution, the imine and hemiaminal are still in equilibrium so amide formation is not in principle excluded. In solution, the outcome should now depend on the imine to hemiaminal equilibrium ratio and the ratio of the imine hydrogenation to hemiaminal dehydrogenation rates. Since the equilibrium is so strongly in favor of the imine, the rate ratio would have to be very strongly in favor of hemiaminal dehydrogenation. While not impossible, this seems the less likely assumption.

Finally, if there is a mechanistic analogy between the homogeneous alcohol activations and the heterogeneous Guerbet reaction, the inner-sphere and outer-sphere pathways seem to be most readily envisaged on a surface. The temperature is substantially higher for the heterogeneous process, however, so the analogy may be false.

6. Conclusion

The types of reaction discussed here may be specific cases of a more general strategy for the promotion of greener organic chemistry. It is not yet clear how far we may be able to push the strategy of replacing activating groups such as the X in RX (X = Br or OTs) and instead obtain the required transformations from RH, ROH, or even RCOOH. The activation would no longer come from the presence of the reactive C−X bond but now instead come from catalytic activation.

The advantages of oxidative activations of organic molecules of the types covered here are clear. They often lead to lower waste processes and involve lower toxicity starting materials. The extra step involved in introducing the X group is also avoided. They are still somewhat high-barrier processes, however, and often require higher temperatures than classical reactions. The challenge therefore is to define catalysts and conditions that lead to the same transformations under milder conditions and with efficient asymmetric induction. In so doing, more difficult reactions may become possible.

7. Acknowledgments

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