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Transition Metal and Enzyme Catalyzed Reactions involving Reactions with Ammonia and Amines

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I. Scope

This review is written to provide the reader with an entry into the range of catalytic reactions involving

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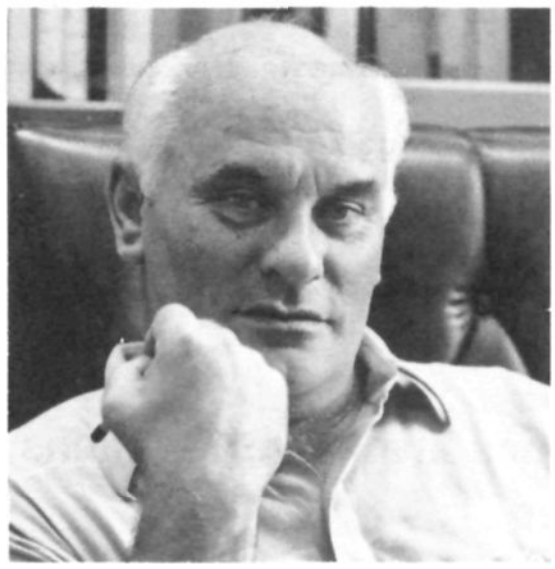

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ammonia and amines as synthetic reagents. We will compare and contrast reactions which are catalyzed by metals and metal compounds occluded into oxides, metal complexes in solution, and enzymatic processes which use ammonia as a reagent. Much of the literature for this review is available in patent form. In this article these patent reports are incorporated into the results published in the primary journals.

Throughout this review we will emphasize reaction types and mechanistic aspects of the different transformations. In many cases the detailed mechanisms of the reactions have not been elucidated, but where possible we will discuss the pathways insofar as the metal center is involved. Some reactions are catalyzed by enzymes rather than by transition metals and their compounds. These enzymatic reactions will be discussed especially with respect to their mechanistic features and to their potential commercial applications through biotechnology. These enzymatic and chemical methods are combined in the same review because they both involve the use of metals, and because both approaches have the potential to become primary routes for the functionalization of ammonia and amines. In conjunction with this article we suggest that the reader consult other relevant reviews which cover either catalytic processes or stoichiometric reactions.[1]

II. Introduction

Ammonia and amines are reagent sources which have the potential to be synthetic precursors for a wide range of commercially useful products. Among these products are amines, amides, ammonium and alkylammonium salts, ureas, carbamates, isocyanates, and amino acids. Ammonia and amines are moderate bases ($pK_b \sim 5$–6) and very weak acids ($pK_a \sim 30$–35).[2] The N–H bond enthalpy in ammonia is 107 kcal/mol, and for amines the N–H enthalpies for primary amines range from 88 to 100 kcal/mol, and for secondary amines they range from 87 to 91 kcal/mol.[3] These data suggest that ammonia and amines can react as electron pair donors, but that their reactivities as proton or hydrogen atom donors will be poor. Similarly the compounds do not undergo reversible electron transfer, and oxidation of aliphatic amines occurs at potentials in the region of 1.0 V.[4] In this article we will review the range of catalyzed reactions involving ammonia and amines, as well as attempting throughout to compare and contrast the mechanistic features involved in each reaction. In many cases there have been no detailed mechanistic studies published, but the reactions can nevertheless be categorized by reaction type.

III. Catalyzed Condensation Reactions of Ammonia or Amines with Alcohols

A. Ammonia

1. Formation of Primary Amines

Ammonia undergoes a catalyzed condensation reaction with alcohols (ROH) to give primary amines (eq 1). The reaction has been used to prepare both short- and long-chain amines, and also to prepare vicinal diamines from both diols and amino alcohols. Since the reaction involves the loss of water, catalysts have been employed which can readily undergo hydration. Frequently used heterogeneous catalysts are materials which contain either metals or metal oxides impregnated into silica, alumina, or similar supports. The reaction has been used for a wide variety of R groups ranging from methyl (C_1) to primary alkyl groups in the hexadecyl (C_{16}) detergent range. The temperature of the catalyst bed has been kept anywhere from 100 to 500 °C, and the reactor design uses a flow system where the water can be continuously removed from contact with the catalyst system. For a recent review of these catalytic transformations the reader should consult ref 1a.

$$RCH_2OH + NH_3 \rightarrow RCH_2NH_2 + H_2O \qquad (1)$$

If we take the bond enthalpy data from ref 3 and apply it to reaction 1, we conclude that the transformation is close to thermoneutral. The reaction involves the cleavage of a C–O bond in a primary alcohol and a N–H bond in ammonia. If we take these respective enthalpies as 92 and 107 kcal/mol, the bond-breakage steps requires 199 kcal/mol. The bond-making steps involve the formation of both a C–N bond in a primary amine and an O–H bond in water. Taking the respective enthalpies of these bonds as 82 and 119 kcal/mol, the bond-making steps releases 201 kcal/mol. Within experimental error, the bond breaking and making steps are equal. In the absence of a significant entropy change therefore, the reaction will be close to being an equilibrium process. The use of dehydration catalysts for these reactions will result in the formation of the amine as water is removed from the equilibrium reaction. A group of such catalysts which can be classified in this manner are listed in the following paragraph.

A common group of heterogeneous catalysts for reaction 1 include metals impregnated into alumina.[5–10] Among the metals used in combinations in these catalysts are cobalt, chromium, copper, sodium, tin, nickel, molybdenum, antimony, manganese, ruthenium, palladium, rhenium, and iridium. In some cases a pro-

moter such as phosphorus pentoxide or ammonium vanadate is used. These catalysts have been used to prepare amines in the C_2–C_{25} range. Conversions of up to 100% and selectivities of up to 97% have been achieved using these catalysts. Other promoter supports for these metal catalysts include aluminosilicates,[11-13] silicoaluminophosphate molecular sieves,[14] alkali and alkaline earth compounds,[15-17] and bochmite-kaolin.[18] Other catalysts include fused iron[19,20] and copper chromium oxides,[21-23] and catalysts activated with organometallic reducing agents such as aluminum alkyls.[24] In addition to primary alcohols, amines can be prepared by a similar catalytic procedure from secondary alcohols (eq 2) such as 2-propanol[25] and cyclohexanol.[26] The amination reaction is tolerant to

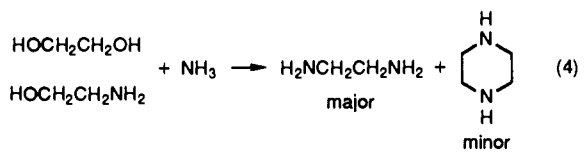
$$R_2CHOH + NH_3 \rightarrow R_2CHNH_2 + H_2O \quad (2)$$

substituent groups such as ethers, since a heterogeneous transition-metal catalyst can be used to give a 72.9% conversion of $BuOCH_2CH_2OH$ and ammonia into $BuOCH_2CH_2NH_2$ with 93.8% selectivity.[27]

Catalyzed amination reactions with ammonia have been used to convert diols and amino alcohols into diamines (eq 3). The most common example is when

$$HO(CH_2)_nOH \xrightarrow[-H_2O]{NH_3} HO(CH_2)_nNH_2 \xrightarrow[-H_2O]{NH_3} H_2N(CH_2)_nNH_2 \quad (3)$$

$n = 2$. For 2-ethanolamine the only primary amine product is ethylenediamine, but for ethylene glycol as the primary alcohol, either 2-aminoethanol or ethylenediamine can be formed. A wide variety of metal catalysts have been used to convert both ethylene glycol and 2-aminoethanol with ammonia into ethylenediamine.[28-38] A byproduct is the cyclic compound piperazine (eq 4). The reaction can be extended to po-



(4)

lypropylene glycols which can be converted to the amine at 95% conversion.[39]

The condensation reaction between alcohols and ammonia can be catalyzed in homogeneous solution by using a mixture of ruthenium trichloride and triphenylphosphine; reaction conditions which give the complex $RuCl_2(PPh_3)_3$.[40] This catalyst system has been used for the selective conversion of ethylene glycol and ammonia into 2-ethanolamine. Carbonyl complexes of ruthenium, osmium, iridium, rhodium, and rhenium have similarly been used as homogeneous solution catalysts for the manufacture of hydroxyalkylamines and (hydroxyalkyl)piperazines from alkylene glycols and ammonia.[41] Two other methods to convert alcohols into amines with ammonia involve using a barrier discharge or a photochemical method.[42,43] Under photolytic conditions the yield of amine follows the sequence EtOH > MeOH > *i*-PrOH > *t*-BuOH.

2. Formation of Secondary and Tertiary Amines

Lowered selectivity in the formation of primary amines from the condensation reaction between ammonia and primary alcohols is observed because the amine products undergo further reaction with the primary alcohol to give secondary and then tertiary amines (eqs 5 and 6). Alternately these transformations can be effected by the direct use of a primary or a secondary amine in the reaction with alcohols instead of ammonia. Analogous catalysts are used for these amine reactions as for those which use ammonia as the reactant. Both primary and secondary alcohols have been used, and the substituents on the alcohol and the amine may be the same or different.

$$RCH_2NH_2 + RCH_2OH \rightarrow (RCH_2)_2NH + H_2O \quad (5)$$

$$(RCH_2)_2NH + RCH_2OH \rightarrow (RCH_2)_3N + H_2O \quad (6)$$

The lowered selectivity can be explained, at least partially, by thermodynamic arguments. In reactions 5 and 6 a primary alcohol is converted into water and an amine. The only difference between the two reactions is that in reaction 5 a primary amine is converted into a secondary amine, and in reaction 6 a secondary amine is converted into a tertiary amine. For reaction 5, the respective N–H, C–O, C–N, and O–H bond enthalpies are 100, 92, 80, and 119 kcal/mol, thereby making the reaction exothermic by 7 kcal/mol. For reaction 6, these respective bond enthalpies are 92, 92, 72, and 119 kcal/mol, thereby making the reaction exothermic by 7 kcal/mol again. These estimates of the enthalpies suggest that the enthalpies for the conversion of primary amines into secondary amines, and of secondary amines into tertiary amines, are thermodynamically more favored by a small margin than the conversion of ammonia into primary amines.

In the previous section, many of the catalytic transformations which lead to primary amines give smaller quantities of secondary and tertiary amines. In other cases these amines are the desired products from ammonia, and catalytic conditions have been developed which yield these compounds in higher selectivity. Examples are the use of catalysts containing Cu, Ni, and Pt group elements for the conversion of lauryl alcohol and ammonia into trilaurylamine,[44] of ethanol into triethylamine with a Cu catalyst,[45] and of a mixture of cyclohexanol and ethanol into *N*-ethylcyclohexylamine in 80% selectivity.[46] A series of papers have discussed the optimal conditions for the use of ammonia in the conversion of primary aliphatic alcohols into a secondary amine,[47] the preparation of trialkylamines from these reagents using a fused iron catalyst,[48] and the amination of alicyclic and higher aliphatic alcohols.[49-52] The method uses a statistical treatment to determine the optimal conditions of pressure, temperature, and flow rate.

B. Primary and Secondary Amines

1. Formation of Secondary and Tertiary Amines

The reactions in eq 5 which result in lowered selectivity in the formation of primary amines from primary alcohols and ammonia can be used in the catalyzed synthesis of secondary and tertiary amines from reacting primary and secondary amines respectively with primary alcohols.

When aniline is treated with a suspension of sodium in 1-hexanol a 62% yield of 1-hexylphenylamine is obtained (eq 7).[53] The reaction can be extended to other

$$PhNH_2 + CH_3(CH_2)_5OH \rightarrow (CH_3(CH_2)_5)PhNH + H_2O \quad (7)$$

TABLE I. Representative Formation of Amines using Heterogeneous Catalyst Systems[a]

catalyst	alcohol	amine	product
Co, Cu	tetradecanol	ammonia	tetradecylamine
Cu, Mo	butanol	dimethylamine	*N,N*-dimethylbutylamine
Cu, Ba-Al_2O_3	dodecanol	diethylamine	*N,N*-diethyldodecylamine
Cu, W-Al_2O_3	dodecanol	dimethylamine	*N,N*-dimethyldodecylamine
Cu, Na, Cr_2O_3-SiO_2	octanol	dimethylamine	*N,N*-dimethyldodecylamine
Cu-Cr_2O_3	ethanol	dimethylamine	*N,N*-dimethylethylamine

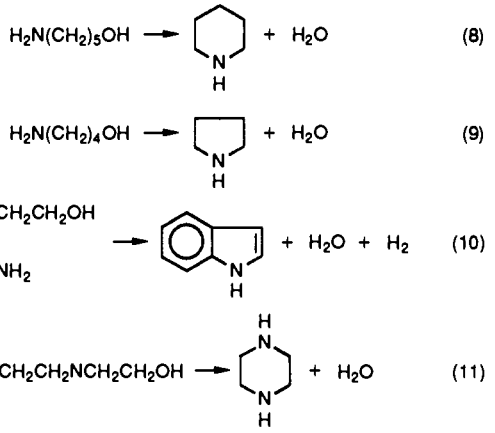
[a] Data taken from ref 1a.

TABLE II. Representative Formation of Amines using a Homogeneous Catalyst Systems[a]

catalysts	alcohol	amine	product
$RuCl_2(PPh_3)_2$	dodecanol	dimethylamine	*N,N*-dimethyldodecylamine
$RuCl_2(PPh_3)_2$	tetradecanol	diethylamine	*N,N*-diethyltetradecylamine
$RuCl_2(PPh_3)_2$	hexadecanol	dipropylamine	*N,N*-dipropylhexadecylamine
$RuCl_2(PPh_3)_2$	octadecanol	diphenylamine	*N,N*-hexyloctylamine
$RuCl_2(PPh_3)_2$	2-octanol	hexylamine	*N*-hexyloctylamine
$RuCl_2(PPh_3)_2$	2-octanol	aniline	*N,N*-phenyloctylamine

[a] Data taken from ref 69.

terminal alcohols. An alternative method of effecting the alkylation of aromatic amines with alcohols involves the use of a catalyst mixture containing the oxides of Ti, Cu, Ba, and Cr, or the phosphate salt of Sr.[54] A similar metal oxide catalyst has been used with aliphatic terminal alcohols.[55-57] A catalyst composed of copper on alumina has been used for the cyclization of terminal amino alcohols. Examples involve the selective (>90%) cyclization of $H_2N(CH_2)_5OH$ to piperidine (eq 8), $H_2N(CH_2)_4OH$ to pyrrolidine (eq 9), 2-$H_2NC_6H_4CH_2CH_2OH$ to indole (eq 10), and $H_2NCH_2CH_2NCH_2CH_2OH$ to piperazine (eq 11).[58] Changing the catalyst or the reaction temperature causes marked changes in product selectivity.[59]



These examples show that catalytic conditions are available whereby intramolecular cyclization of the amino alcohol can be induced in preference to the formation of linear polymeric material. Such cyclizations suggest that intramolecular reactions at the catalyst surface proceed faster than do bimolecular reactions with a second molecule of the amino alcohol. These amination reactions can also be catalyzed in homogeneous solution by metal complexes. Examples of such homogeneous catalysts include $RuCl_2(PPh_3)_3$,[60] $RhH(PPh_3)_4$,[60] $RuH_2(PPh_3)_4$,[61] and a complex composed of a mixture of a platinum complex and tin(II) chloride.[62] When secondary amines are used the product is a tertiary amine. The reaction can again be catalyzed under either heterogeneous or homogeneous conditions (Tables 1 and 2).[63-69] These catalyzed reactions have been extended to the amination of alkoxylated alcohols with secondary amines and morpholine.[70,71]

The complex $RuCl_2(PPh_3)_3$ can be used as a homogeneous catalyst for the reaction between ethylene glycol and amines to give 2-aminoethanol or ethylenediamine.[72] Selectivity to diamination with primary amines is favored by smaller alkyl groups on the amine, while larger substituents on the amines yield ethanolamines. This result contrasts with that found for secondary amines where diamination is always favored by this catalyst. For the case of *sec*-butylamine, where almost equal amounts of mono- and diaminated products are obtained, the selectivity can be shifted to monoamination by the addition of excess triphenylphosphine. The steric parameters of primary amines closely parallel the nucleophilicity of these amines. As the nucleophilicity parameter falls, so does the selectivity to diamination.[73] The mechanistic implications of this selectivity is discussed later in this section.

2. Alcohol–Amine Interchange Reactions

A catalyzed reaction which can result in lowered selectivity is an alcohol–amine interchange reaction which can even occur with tertiary amines. This reaction is catalyzed by metals such as Co, Ni, Fe, or Ru.[74] As an example, the reaction between $CH_3(CH_2)_{11}OH$ and $N(C_2H_5)_3$ gives primarily $CH_3(CH_2)_{11}N(C_2H_5)_2$ along with small amounts of $(CH_3(CH_2)_{11})_2NC_2H_5$ (eq 12).[75]

$$CH_3(CH_2)_{11}OH + N(C_2H_5)_3 \xrightarrow{-C_2H_5OH} CH_3(CH_2)_{11}N(C_2H_5)_2 + (CH_3(CH_2)_{11})_2NC_2H_5 \quad (12)$$

This catalyzed reaction has been extended to tertiary amines having hydroxyalkyl groups, and to the transalkylation of $N(C_2H_5)_3$ with commercially available alcohols such as tergitol 15-S-3 to yield detergent products.[76,77] An alternative use for these reactions is in the area of polymers. Thus materials suitable for reaction injection molding have been prepared from hydroxylated amines using zinc stearate as catalyst.[78] As for other reactions involving alcohols and amines, these alcohol amine interchanges are catalyzed by transition-metal complexes; examples include mixtures of $RuCl_3$ and NH_4ReO_4 with triphenylphosphine.[79]

3. Secondary Alcohols, Aldehydes, and Ketones

The secondary alcohol isopropyl alcohol has been used for the alkylation of *p*-aminocumene and aniline.[80] The reaction has been used to prepare tertiary amines, and both Ni and Pd catalysts have been employed.[81] In addition to secondary alcohols, ketones undergo condensation with ammonia in the presence of a palladium catalyst to give amines.[82] Aldehydes can also be used to prepare secondary amines from primary amines.[83] These reactions have been used to prepare a wide variety of amine products.[84,85]

C. Reaction Pathways

Although no comprehensive mechanistic study has been made of these catalyzed amine alkylation reactions with alcohols, several experimental features of the reaction provide insight into the steps involved in the reaction pathway. The molecular sieve type catalysts act as dehydrating agents for the removal of water in reaction 1.[12,14,19] These dehydration reactions apparently occur within the pores of the molecular sieve because the use of sieve catalysts with small pore sizes improves the selectivity to the formation of primary and secondary amines by excluding the larger tertiary amines.

A second class of heterogeneous catalyst used has a metal interspersed into the support. A feature of these catalysts is that they are metals which also show high activities as hydrogenation catalysts. This parallel is also reinforced by the observation that the yields of amination product from alcohols and ammonia or amines are increased if the catalyzed reaction is carried out under a pressure of hydrogen. A second role played by hydrogen is its function as a reducing agent in the generation of the catalyst. Thus a catalyst precursor can be introduced as either the metal or its oxide, since hydrogen will reduce or react with either to generate the active metal or metal hydride catalyst.

The generally accepted reaction pathway is one where the initial step involves the dehydrogenation of a primary or a secondary alcohol to an aldehyde or ketone, respectively. The aldehyde or ketone can then undergo a Schiff base condensation reaction with ammonia or an amine to give an imine intermediate, which is then catalytically hydrogenated to the final amine (Scheme 1).[86] This reaction pathway clearly defines the dehydration step as occurring in the condensation reaction between an aldehyde (or ketone) and ammonia (or amine). Support for this pathway comes from the isolation of an intermediate aldehyde product from such a catalytic reaction.[87] Further support for such a mechanism comes from deuterium labeling studies where it has been shown that the reaction rate for $CH_3(CH_2)_6CD_2OH$ is slower than that for $CH_3(CH_2)_6CH_2OH$.[86d] The effect of hydrogen pressure depends on the particular system. Although the conversion of the intermediate imine into the final amine involves the addition of hydrogen, this hydrogenation step may or may not be rate determining. Thus, whereas in some cases the reaction rate is accelerated by hydrogen pressure, the amination of 1,6-hexanediol by dimethylamine on Cu/Al_2O_3 is insensitive to hydrogen pressure.[88]

SCHEME 1

$$M + RCH_2OH \rightarrow MH_2 + RCH{=}O$$
$$RCH{=}O + R'NH_2 \rightarrow RCH{=}NR' + H_2O$$
$$RCH{=}NR' + MH_2 \rightarrow RCH_2{-}NHR' + M$$
$$\text{overall} \quad RCH_2OH + R'NH_2 \rightarrow RCH_2NHR' + H_2O$$

Similar reactions occur in the homogeneously catalyzed amination of alcohols. The commonly used catalyst is $RuCl_2(PPh_3)_3$, which is either added to the reaction mixture or prepared in situ from a mixture of triphenylphosphine and hydrated ruthenium trichloride.[69,72,89] Typically the reaction is carried out at temperatures in the region of 120 °C. The lifetime of the catalyst is shortened by its conversion into the catalytically inactive carbonyl complex $RuHCl(CO)(PPh_3)_3$.[69] This product results from the decarbonylation of the intermediate aldehyde; a reaction which is well-known in rhodium chemistry (eq 13).[90] Evidence

$$RuHCl(RCH_2CHO)L_3 \rightarrow RuHCl(CO)L_3 + RCH_3 \quad L = \text{tertiary phosphine} \tag{13}$$

for this decarbonylation step comes from the observation of small quantities of an alkane product which has one fewer carbon atoms than the parent alcohol (eq 14).

$$CH_3(CH_2)_NOH \rightarrow CH_3(CH_2)_{N-1}CH_3 + CO \tag{14}$$

The proposed pathway of the reaction shown correlates closely with that proposed in Scheme 1 for the heterogeneously catalyzed reaction. The complex $RuCl_2(PPh_3)_3$ is well-known both as a hydrogenation catalyst for multiple bonds, and as a hydrogen-transfer catalyst for interchange reactions between alcohols and ketones. The dehydration step again results from the condensation reaction between aldehyde and amine. The side reaction leading to alkane formation occurs when the decarbonylation reaction with the intermediate aldehyde occurs faster than does the condensation reaction of the amine with this aldehyde. The patterns in the heterogeneously and homogeneously catalyzed amination of alcohols with metal compounds are clearly similar, and strongly suggest that analogous mechanisms are in operation.

TABLE III. Representative Selectivities (%) in the Conversion of Ethylene Glycol into Amino Alcohols into Diamines

catalysts	amine	R_2NCH_2-CH_2OH	R_2NCH_2-CH_2NR_2
$RuCl_2(PPh_3)_3$	Morpholine	83	9
$RuCl_2(PPh_3)_3$	Pyrrolidine	79	trace
$RuCl_2(PPh_3)_3$	Me_2NH	81	4
$RuCl_2(PPh_3)_3$	Et_2NH	91	1
$RuCl_3{\cdot}xH_2O$	Morpholine	16	80
$RuCl_3{\cdot}xH_2O$	Me_2NH	11	85
$RuCl_3{\cdot}xH_2O$	Et_2NH	15	83

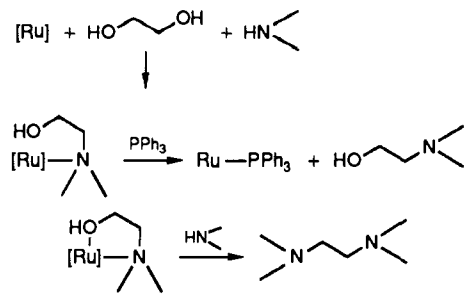
[a] Data taken from ref 72.

An interesting selectivity has been observed for catalytic aminations carried out using either $RuCl_2(PPh_3)_3$ or hydrated ruthenium chloride ($RuCl_3{\cdot}xH_2O$). In the conversion of ethylene glycol into monoamine or diamine, $RuCl_2(PPh_3)_3$ shows good selectivity for conversion into the former, and $RuCl_3{\cdot}xH_2O$ shows a similar selectivity for the latter (Table 3).[72] This difference in selectivity has been proposed as being due to relative lifetimes of the ruthenium complexes with a coordinated amino alcohol. In the absence of triphenylphosphine, the complexed amino alcohol can undergo reaction with a second amine molecule to give a diamine (Scheme 2). In the presence of triphenylphosphine, which is a very strongly coordinating ligand for ruthenium(II), displacement of the amino alcohol from the metal occurs before it can undergo further reaction.[73]

IV. Addition of N–H Bonds to Alkenes

The addition of an N–H bond to an alkene is a significant chemical transformation because it leads to the formation of a C–N bond, and therefore to the functionalization of the hydrocarbon. By changing the R

SCHEME 2



groups in amines such as RR'NH between hydrogen, alkyl, and aryl functionalities, the addition of the N–H bond to an alkene can, in principle, be used to prepare a wide range of primary, secondary, and tertiary amines (eq 15). If uncatalyzed this addition reaction is not

$$RR'NH + \text{alkene} \rightarrow \text{alkyl}NRR' \qquad (15)$$

useful from a synthetic standpoint, and it only occurs with activated alkenes.[91] Thermodynamic considerations indicate that the addition of an N–H bond to an alkene is approximately thermoneutral. This postulate, is illustrated by the addition of ammonia or diethylamine to ethylene to give ethylamine and ethyldimethylamine, respectively (eqs 16 and 17). From the

$$C_2H_4 + NH_3 \rightarrow C_2H_5NH_2 \qquad (16)$$

$$C_2H_4 + (CH_3)_2NH \rightarrow (CH_3)_2C_2H_5N \qquad (17)$$

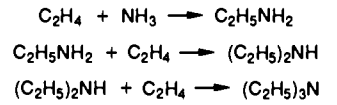
bond enthalpies given in Table 4 it can be concluded that reaction 16 is favored by approximately 8 kcal/mol, and that reaction 17 is thermoneutral.[3,92] Clearly these estimates are not exact, but they show that there is no strong enthalpic advantage to the addition or elimination of an N–H bond across a carbon–carbon bond. For alkynes the addition of ammonia or an amine is more favorable, and the reaction can be used in the preparation of imines.[93]

Little mechanistic work has been done to understand these reactions, mainly because so few systems have been discovered which are amenable for detailed mechanistic study.

A. Addition of Ammonia to an Alkene

In the absence of a catalyst, the addition of an N–H bond to an alkene is not a viable method to prepare amines. The reactions are slow, the yields are low, and multiple alkylation usually occurs to give mixtures containing primary, secondary, and tertiary amines (Scheme 3).[91,94] In some cases a transition-metal cat-

SCHEME 3

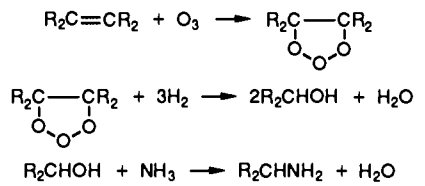


alyst can be used, but the number of examples of catalyzed aminations of alkenes are rather few.

1. Heterogeneous Catalysts

Several heterogeneous catalysts have been used for the amination of alkenes with ammonia. As an example, ethylamine has been prepared by passing a mixture of ethylene and dry ammonia over a catalyst bed containing palladium on alumina at 120 °C.[95] Nickel and rhodium catalysts have been used for the conversion of linear alkenes into amines and of cyclic alkenes into diamines.[96] This second transformation, however, involves a three-step process whereby the alkene is sequentially treated with ozone, hydrogen, and then ammonia or an amine. Since the amine products are ones which result from cleavage of the carbon–carbon double bond, the transformation can be explained by a sequence of reactions involving ozonolysis of the alkene, followed by reductive hydrogenation to the alcohol, and final condensation of the alcohol with ammonia or the amine (Scheme 4). The final step involving the ami-

SCHEME 4

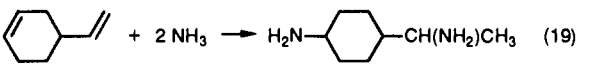


nation of the alcohol has been described in the previous section of this review.

Aluminosilicate catalysts have also been used to convert C_{2-8} alkenes and ammonia, primary and secondary amines into primary, secondary, and tertiary amines, respectively.[97] This catalyst has been used to convert propylene and ammonia into isopropylamine (eq 18). Methylamine and ethylamine have been added

$$CH_3CH{=}CH_2 + NH_3 \rightarrow CH_3CH(NH_2)CH_3 \qquad (18)$$

to 1-butene, 1-pentene, and 1-hexene, and methylamine added to 1-heptene and 1-undecene to give amines.[98] For methylamine the straight-chain amines are formed. The reaction is carried out at 135 °C in the presence a small quantity of *tert*-butyl peroxide as radical initiator, which abstracts a hydrogen from the 2-carbon of the amine. In the presence of a pentasil zeolite catalyst containing boron or germanium, ammonia reacts with 4-vinylcyclohexene by a double addition to give 4-amino-ω-methylcyclohexanemethanamine (eq 19).[99]



2. Ammonium Ion as Catalyst

Ammonium ion can be used as a catalyst for the amination of alkenes.[100] An example of such a reaction is the use of ammonium sulfate as a catalyst for the preparation of tertiary butylamine from isobutene and ammonia. The reaction is carried out at 120 °C in the presence of water. The observation that analogous reaction conditions using tertiary butanol in the reaction instead of isobutene gives tertiary butylamine, implies that at least a portion of the tertiary butylamine formed from isobutene is formed via the tertiary butanol intermediate. Thus this conversion of alkene to amine may be yet another example of a process which involves the initial hydration of the alkene, followed by amination of the intermediate alcohol. Ammonium halide catalysts have also been employed in the conversion of C_{2-8} alkenes into amines by reaction with ammonia or primary or secondary amines.[101]

3. Transition-Metal Compounds as Catalysts

Discrete transition-metal compounds have been used as homogeneous catalysts in the amination reaction

TABLE IV. Bond Dissociation Energies for C—C, C=C, N—H, and C—N[a]

Bond	$\Delta H_f°$, kcal/mol	Bond	$\Delta H_f°$, kcal/mol
H_2N—H	107.4 ± 1.1, 103.2	H_2C=CH_2	153
$(CH_3)_2N$—H	91.5 ± 2	C_2H_5—NH_2	81.6 ± 2
CH_3H_2C—H	98.2 ± 1, 98	$(CH_3)_2N$—C_2H_5	72.3 ± 2
H_3C—CH_3	85.8 ± 1, 88		

[a] Data from refs 3 and 92.

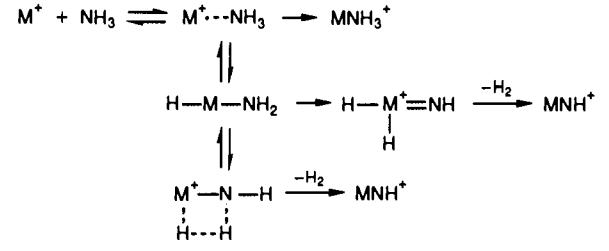
under photochemical conditions. Among the compounds used are Mo_6Cl_{12}, $Fe(CO)_5/P(OEt)_3$, and Hg.[102-104] Other photolytic procedures have involved the use of ammonium halides or semiconductor powders composed of platinum on titanium dioxide.[105-106]

In addition to a series of patents which describe the use of different zeolite preparations as catalysts for amination reactions,[107-109] amination catalysts have also been prepared by anchoring discrete transition-metal complexes onto zeolite type supports.[110] The latter method involves using silane coupling agents to "heterogenize" phosphine and phosphite complexes of the platinum group via amine or carboxylic acid group bridges. The complexes used in this attachment procedure were $RhCl(PPh_3)_3$, $RhCl_3 \cdot 3H_2O$, $[RhCl(cyclooctene)_2]_2$, $RhCl_3py_3$, $PdCl_2(PhCN)_2$, and $Pt(P(OPh)_3)_4$.

4. Gas-Phase Reactions

In gas-phase reactions involving ammonia and alkenes, homolytic reactions can be important. These reactions can involve cleavage of either N–H bonds in ammonia or C–H bonds in the alkene. A useful technique for probing such reactions is ion cyclotron resonance spectroscopy, which is a technique that can be used to study ion–molecule reactions. By using this technique it is possible to learn more about the individual reactions which can occur between metal ions and small molecules. In the gas phase, metal ions of groups III–IV (M) react with ammonia at thermal energies to generate MNH^+ via dehydrogenation. Group VI–XI metal ions (M) react to give MNH_3^+. A reaction mechanism is proposed involving initial oxidative addition of an N–H bond to the metal ion (Scheme 5).

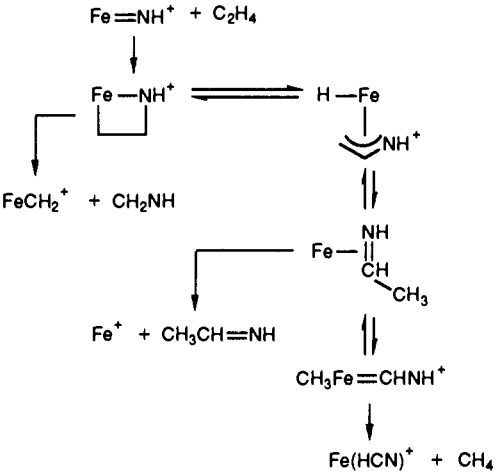
SCHEME 5



For the case of chromium, excited state Cr^+ reacts with ammonia via bond-insertion reactions to form $CrNH_2^+$ and $CrNH^+$.[111] In Scheme 5 this transformation involves the oxidative addition of ammonia to Cr^+ to give $Cr(H)NH_2^+$, which can undergo elimination of hydrogen to give $CrNH^+$. By contrast, the ion $CrNH_2^+$ is formed by hydrogen atom loss from such an intermediate.

These gas-phase studies provide useful guidelines as to the reactivity patterns which can be expected to be followed in a catalytic system. Of particular relevance to this review is the proposed pathway for the reaction of the imine cation $FeNH^+$ with ethylene. In this reaction the key step is an intramolecular nucleophilic attack by the lone electron pair on the imide ligand at the coordinated ethylene. This 2 + 2 cycloaddition reaction leads to a four-membered metallacyclic intermediate which can undergo fragmentation to give either imines or hydrogen cyanide (Scheme 6). In argon and

SCHEME 6

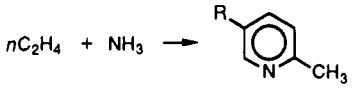


krypton matrixes, UV photolysis results in the insertion of nickel atoms into the N–H bond of ammonia. From reactions with NH_3, $^{15}NH_3$, and ND_3, the following species and isotopomers were identified: $Ni(NH_3)$, $Ni(NH_3)_2$, $HNiNH_2$, and $HNiNH_2(NH_3)$.[112] For the case of copper, the photochemical conversion between $CuNH_3$ and $HCuNH_2$ is wavelength dependent. In the reaction between Ag^+ and Cu^+ with $MeNH_2$, Me_2NH, and Me_3N, the products are the deprotonated amine ion. In general the bimolecular reaction rate is fast.[113,114] Radiation induced ion–molecule reactions in gaseous mixtures containing ethylene, propylene, 1-butene, 1-pentene, or 2-pentene, and ND_3, have been investigated by mass spectrometry.[115] Proton transfer occurs to give ND_3H^+, and also charge transfer from ND_3^+ to the olefin, and from $C_2H_4^+$ to ND_3. These observations correlate with the observations that amines can be formed from ammonia and alkenes in a silent electric discharge and by γ radiolysis from a cobalt-60 source.[116,117] As found in the reaction with gas-phase metal ions, the γ radiolysis of gaseous mixtures of ammonia and small alkenes results in the formation of hydrogen.[118] Under these conditions involving bond homolysis the range of products is frequently determined by kinetic discrimination. As an aid to better understanding the observed gas-phase chemistry it is useful to know the reaction rates. Among those known are the rate of reaction of the NH_2 radical with ethylene, propene, and 1-butene, which have ambient temperature rate constants in the region of 10^5 M^{-1} s^{-1}.[119] By comparison the rate constant for the reaction between NH_2 and acetylene is 4.4×10^4 M^{-1} s^{-1}, and for the reaction between NH_2 and alkyl radicals is of the order of 10^{10} M^{-1} s^{-1}.[120,121]

B. Formation of Heterocycles from Alkenes and Ammonia

Alkylpyridines have been prepared from alkenes and ammonia using a wide range of catalysts. An early patent describes the preparation of pyridines and alkylpyridines from a gaseous mixture of an alkene and

ammonia catalyzed by compounds of groups III–VII with atomic numbers ranging from 12 to 83. Examples are given using P_2O_5/V_2O_5 mixtures as catalyst, along with added aldehyde in the gas stream.[122] Wacker-type conditions have also been used to catalytically prepare heterocyclic compounds.[123] Wacker-type conditions involve complexing an alkene to divalent palladium in solution in order to make it susceptible to nucleophilic attack. This mode of attack results in reduction of the palladium to the zerovalent oxidation state, which is then reoxidized back in homogeneous solution to divalent palladium by an oxidant such as divalent copper. Thus the use of a mixture of ethylene and ammonia in the presence of a catalyst containing salts of palladium(II) and copper(II) gave primarily pyridines which are substituted at the 2-position (eq 20). Rhodium phthalocyanine complexes can also be used as catalysts for these reactions.[124]



$n = 3$, R = H; $n = 4$, R = C_2H_4 (20)

C. Addition of Amines to Alkenes

The lowered selectivity for the formation of amines from alkene and ammonia is due to the subsequent insertion of an N–H bond of the product amine into a second molecule of alkene. Although steric and statistical arguments favor reaction of the alkene with ammonia itself, the lower bond enthalpy of N–H in an amine may favor its reactivity with the alkene. These selectivity problems can, however, be circumvented for the formation of more substituted amines by using a primary or secondary amine as the reagent of choice in place of ammonia itself.

1. Alkali Metal Amide Catalysts

Alkali-metal amides are active homogeneous catalysts for the amination of olefins with amines, but not with ammonia. The reaction of Et_2NH with ethylene in the presence of $LiNEt_2$ gives Et_3N (eq 21).[125] At temper-

$$Et_2NH + C_2H_4 \rightarrow Et_3N \quad (21)$$

atures of 70–90 °C and pressures of 6–10 atm, the rate-determining step is the addition of the anion Et_2N^- to the olefin. The compounds $NaNEt_2$ and $KNEt_2$ are initially even more active catalysts than $LiNEt_2$, but they degrade and their catalytic activity is reduced as the reaction proceeds. At 50 °C, a series of primary and secondary amines, but not ammonia itself, add to styrene to give tertiary amines. Yields of up to 88% are obtained. A similar catalyzed addition to 1,3-butadiene gives eneamines.[126] Using a similar procedure with $LiNH_2$ as catalyst, *N,N*-diethylgeranylamine has been prepared from the addition of diethylamine to myrcene.[127]

2. Transition-Metal Compounds as Catalysts

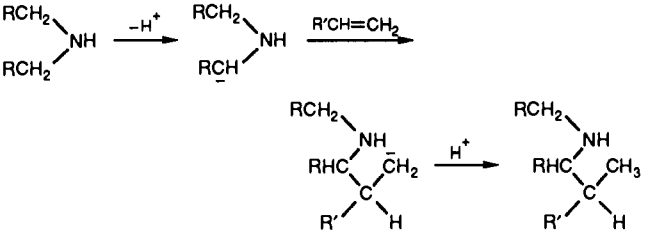
Transition-metal compounds have also been used as catalysts for the amination of alkenes. One such compound is ruthenium trichloride which has been used as a catalyst for the addition of dimethylamine to ethylene.[128] Another compound is a palladium complex of a polymeric phosphonite ester.[129] Photochemical activation has also been used for the addition of amines to olefins in the presence of a free radical initiator.[130] Low-valent transition metals such as $Fe(CO)_5$ and $Ru_3(CO)_{12}$ have also been used as catalysts for the addition of secondary amines to ethylene.[131,132] The experimental conditions, and the fact that the amine product is homologated by one carbon, supports a hydroformylation mechanism whereby the intermediate aldehyde which is formed reacts with the secondary amine to give a Schiff base, which undergoes final hydrogenation to the tertiary amine. The complex $Ru_3(CO)_{12}$ is also used as a catalyst for the amination of styrene with diethylamine. Alkenes, cycloalkenes and styrene are arylated by a combination of arylamines and *tert*-butyl nitrite in the presence of Pd(dibenzylideneacetone)$_2$ as catalyst. A mechanism is proposed involving the intermediacy of a diazonium salt as the aryl transfer reagent.[133] Aromatic amines and olefins in the presence of metallosilicates as catalysts can be used to synthesize indoles.[134]

Several other reactions have been described which show the diversity of reactions which can be obtained between amines and alkenes. One such reaction involves C-alkylation of secondary amines with alkenes. At 200 °C in the presence of $M[N(CH_2R)_2]_5$ (M = Ta, Nb), alkylamines $RCH_2NHCHRCHR'Me$ (R = H, R' = H, Me, Bu; R = Me, R' = H) are obtained from $(RCH_2)_2NH$ and $R'CH{=}CH_2$ (eq 22).[135] The reaction

$$(RCH_2)_2NH + R'CH{=}CH_2 \rightarrow RCH_2NHCHRCHR'Me \quad (22)$$

sequence likely involves carbanionic attack at the alkene, which itself may be coordinated at a high-valent tantalum center to make it more electrophilic. Regioselective attack of this carbanion at the substituted alkene carbon, followed by a final protonation step, yields the final amine product (Scheme 7). The source

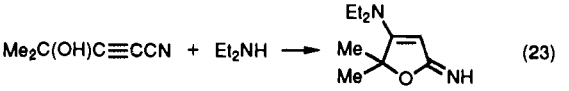
SCHEME 7



of the base is the amide ligand introduced as its metal complex.

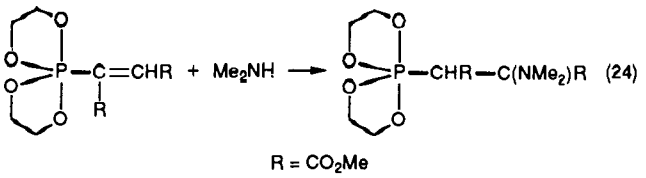
3. Noncatalyzed Reactions

Treating the cyanoacetylenic alcohol $Me_2C(OH)C{\equiv}CCN$ with diethylamine in methanol gave a mixture of compounds, of which the major component was the furan (eq 23).[136] Dimethylamine also adds to vinyl-



(23)

spirophosphoranes.[137] This reaction appears to be one of the few examples of an uncatalyzed addition of an N–H bond across an alkene. The alkene, however, is highly activated by electron-withdrawing substituents, and the reaction is carried out with secondary amines. An example using dimethylamine is shown in eq 24.



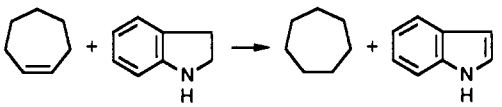
(24)

1,2-Dienes also react with secondary amines and aryl bromides in the presence of palladium acetate and a tertiary phosphine to give allylic amines; an example is shown in eq 25.[138]

$$BuCH{=}C{=}CH_2 + Et_2NH + PhBr \rightarrow BuCH{=}C(Ph)CH_2NEt_2 + HBr \quad (25)$$

4. Catalyzed Hydrogen Transfer Reactions

Hydrogen-transfer reactions between amines and alkenes are catalyzed by transition-metal compounds. These reactions result in the formation of an unsaturated amine and an alkane. In the hydrogen transfer to alkene catalyzed by $RhCl(PPh_3)_3$, the reactivity decreases in the order indoline > dioxane > cyclohexanol > isopropyl alcohol. The catalyzed reaction between cycloheptene and indoline is shown in eq 26.[139] Other

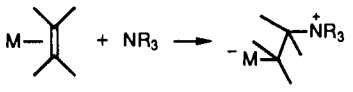


(26)

catalysts which have been used for hydrogen-transfer reactions are $RuCl_2(PPh_3)_3$, $IrCl_3{\cdot}xH_2O$, $(NH_4)_2PdCl_4$, and $RhH(PPh_3)_4$.[140] These transformations occur by insertion of the metal complex into the C–H bond of indoline. Subsequent β-hydrogen transfer in the alkyl hydride metal intermediate yields the indole and a metal dihydride. Transfer of hydrogen from this dihydride complex to the alkene completes the cycle whereby the metal complex is regenerated. In principle the reaction should be reversible, but the formation of the stable aromatic compound, indole, provides the stabilization for the reaction to proceed in the direction shown. Monoenes are efficiently hydrogenated, but 1,3- and 1,5-cyclooctadiene are reduced to cyclooctene in high selectivity. Under different catalytic conditions N–H addition to dienes occurs. Using homogeneous palladium complexes as catalysts, addition to one double bond occurs, but when $Ru_3(CO)_{12}$ or $RhH(CO)(PPh_3)_3$ are used as catalysts, double amination occurs.[141]

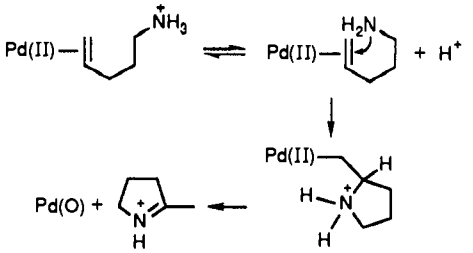
5. Reactions of Electrophilic Metal Ions

Alkenes can be aminated in the presence of electrophilic metal ions. These amination reactions are mechanistically analogous to the Wacker process, where in this case the alkene complexed to palladium(II) undergoes nucleophilic attack by water. The first step of the analogous amination reaction involves coordination of the alkene to the metal center. The second step involves nucleophilic attack at the complexed olefinic carbon by the lone electron pair of the amine nitrogen (eq 27). Subsequent steps lead to reduction of the



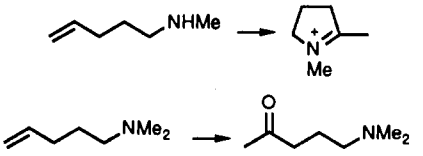
(27)

metal center, and the formation of amination products. As an example of such a reaction, primary amino alkenes of the type $CH_2{=}CH(CH_2)_nNH_2$ (n = 3, 4) cyclize to pyrrolines or piperidines under $PdCl_2/CuCl_2$ catalyzed Wacker conditions (eq 28). By contrast, amino



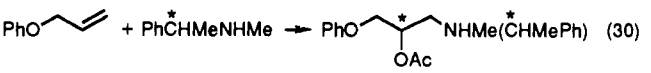
(28)

alkenes with a secondary amino group give the corresponding cyclic enamines, while tertiary amino alkenes give amino ketones (eq 29).[142] Another such electro-



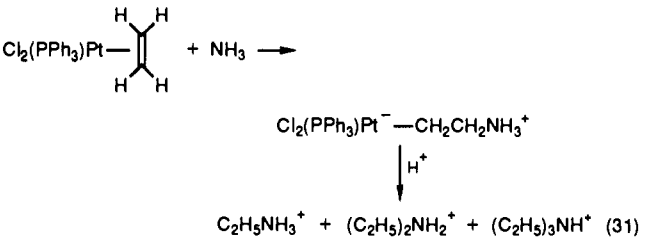
(29)

philic metal center is Hg^{2+}. Salts of mercuric acetate have been used for the reaction of dienes with anilines,[143] and for the aminomercuration of 3-alken-1-ynes.[144] Thus the reaction of MeCH=CHC≡CH with R_2NH (R_2NH = piperidine, morpholine) in the presence of mercuric acetate gave $R_2NCH(Me)CH{=}C(Me)NR_2$. Using a similar strategy with palladium(II) complexes, the compound $PhOCH_2CH(OAc)CH_2NMeCHMePh$ has been prepared from $PhOCH_2CH{=}CH_2$, and (*S*)-PhCHMeNHMe, followed by a final oxidation step in acetic acid (eq 30).[145] As support for such mechanistic



(30)

pathways, the complex *cis*-$PtCl_2(C_2H_4)PPh_3$ reacts with ammonia to give, after acid hydrolysis, $EtNH_2$, Et_2NH, and Et_3N (eq 31).[146] This reactivity pattern correlates



(31)

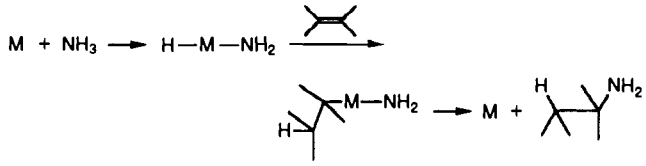
with that for isocyanide complexes, where the complexed carbon undergoes nucleophilic attack by amines to give a product with a complexed carbene (eq 32).[147]

$$cis\text{-}PtCl_2(CNR)L + R'NH_2 \rightarrow cis\text{-}PtCl_2[C(NHR)R']L \quad (32)$$

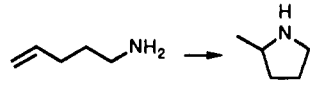
6. Catalyzed Amination via N–H Addition

An alternative approach targeted toward catalytic amination can involve a strategy involving the use of a metal center in a low oxidation state which can undergo oxidative addition of an N–H bond. Subsequent insertion of an alkene into the metal hydride formed, followed by reductive elimination of the amine from the alkyl amide intermediate, gives the desired product (Scheme 8). Even though such a scheme is conceptually simple, very few examples exist where it has been applied in practice. One of the major problems is in finding a system where the oxidative addition of an

SCHEME 8



N–H bond is a favorable process.[148] One example of catalyzed amination uses complexes of type $(cp^*_2LaH)_2$ which cause intramolecular amination resulting in the cyclization of 5-aminopent-1-ene to 2-methylpyrrolidine (eq 33). Kinetic and mechanistic evidence supports the

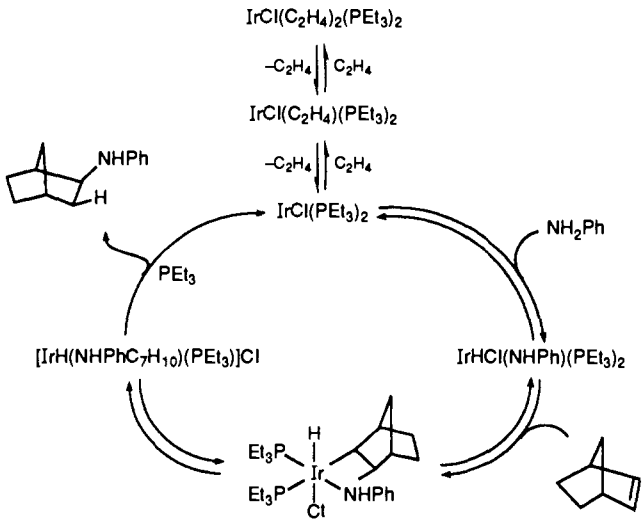


(33)

view that the limiting step is the intramolecular insertion of the olefin into the La–N bond, followed by rapid protonolysis of the La–C bond.[149] Another example of catalyzed amination uses the bimetallic complex $[IrH(\eta\text{-}NH_2)(PMe_3)_3]_2$.[150] This bimetallic complex is prepared by the addition of ammonia to $Ir(PMe_3)_4^+$, and this cationic iridium(I) complex can be used in solution as the catalyst precursor. This first successful demonstration of the amination of an alkene by a transition-metal complex catalyzed N–H activation was accomplished using aniline as the amine and norbornylene as the alkene. In the catalytic procedure, a mixture of $IrCl(C_2H_4)_2(PEt_3)_2$, $ZnCl_2$, aniline, and norbornylene was refluxed for 48 h. The product amine shown was formed in a catalytic yield of 6 turnovers

based on the iridium complex. The formation of the amine is irreversible. The proposed catalytic cycle is shown in Scheme 9. Very recently the complexes Pd-

SCHEME 9



$(SPh)_2$bipy and $Pd(SCN)_2[P(OPh)_3]_2$ have also been used as catalysts for the addition of morpholine to 1-octene, but no mechanistic details have been presented.[151]

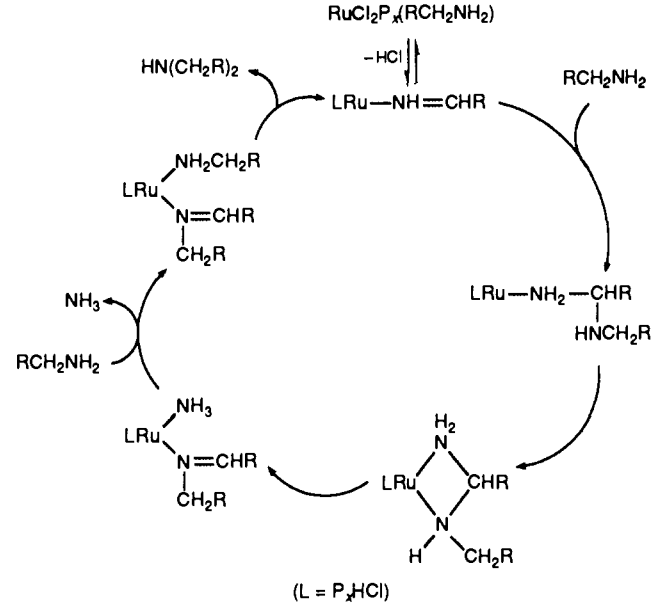
D. Amine Interchange Reactions

A problem with achieving high selectivities in these amination reactions occurs because the product amines formed can undergo interchange reactions with their precursors and with themselves. Furthermore, this problem is particularly acute because these interchange reactions are frequently catalyzed by compounds which also catalyze the reactions used to prepare the initial amines. For example, ion-exchanged bentonite (montmorillonite), an amination catalyst, also catalyzes the conversion of a primary amine into a mixture of the secondary amine and ammonia (eq 34). Under ho-

$$2RCH_2NH_2 \rightleftharpoons (RCH_2)_2NH + NH_3 \qquad (34)$$

mogeneously catalyzed conditions both $Ru_3(CO)_{12}$ and $RuCl_2(PPh_3)_3$ are also effective catalysts for these amine interchange reactions. A proposed pathway for this interchange reaction is shown in Scheme 10.[152] The

SCHEME 10



key step in this interchange reaction is the formation of an N,N′-bonded metallacycle. This reaction is critical because it is the bond-making and bond-breaking reactions leading to and from this intermediate which result in the formation of the cross products.

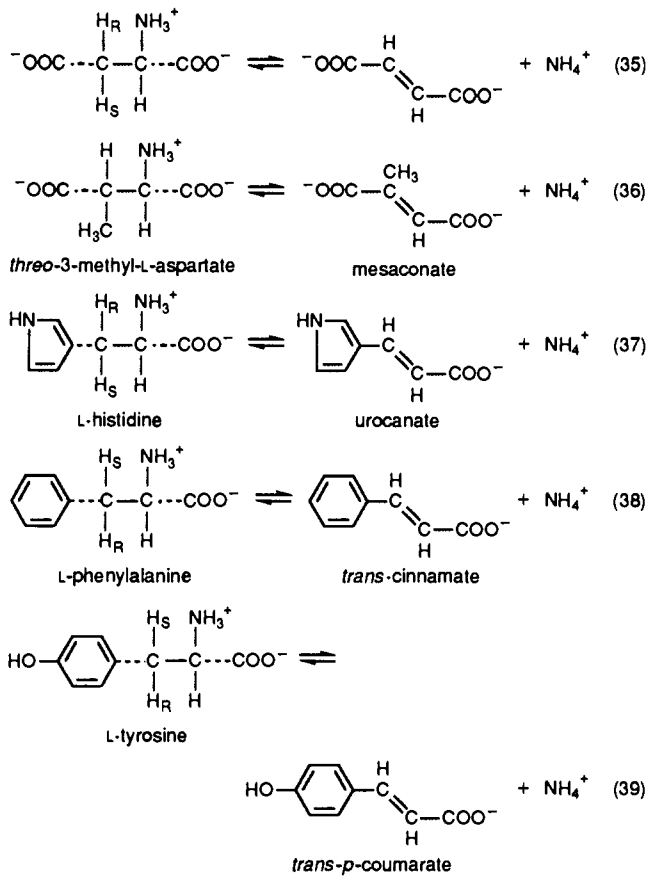
V. Enzyme-Catalyzed Addition of Ammonia to Alkenes

An early review has compared the enzymes catalyzing the elimination of ammonium ion from L-aspartate, *threo*-3-methyl-L-aspartate, L-histidine, L-tyrosine, and L-phenylalanine.[153] These enzymes are named ammonia-lyases. In each case the reaction is reversible (eq 35–39). This early review leads the reader into the early literature concerning the effects of pH and added metal ions on the enzymic reactivity as well as reviewing the early equilibrium data for these processes and presenting the evidence for a carbanionic mechanism. A later review has been published concerning aspartate ammonia-lyase, but its availability to readers is more limited.[154]

A. Isolation and Structure of the Enzymes

1. Aspartase and Fumarase

Aspartase (EC 4.3.1.1) can be obtained in high purity from *Escherichia coli* W cells grown without aeration. The early purification procedures consist of sonic extraction, streptomycin treatment, ammonium sulfate



fractionation, heat treatment, calcium phosphate gel treatment, and column chromatography on DEAE-Sephadex, hydroxylapatite, and Sepharase 6B. A later eight-step purification procedure has been detailed. The molecular weight of these purifications was found to be 193 000 by sedimentation equilibrium analysis, and four tryptophan residues were found within this unit. Polyacrylamide gel electrophoresis revealed the presence of four subunits, each having a molecular weight of 48 500.[155] The biosynthesis of aspartate ammonia lyase, induced by aspartate, is controlled by the concentration of fumarate, which itself depends on the concentration of fumarase. Fumarase remains unchanged during the induction of aspartase.[156] Aspartase of *Escherichia coli* was several-fold activated by treatment with trypsin, although no change was detected in the molecular weights of the subunits.[157] This activation leads to the formation of a rather stable activated molecule, and changes in the absorbance maxima at both 278 and 285 nm are observed.[158,159] The N-termini of both the native and the trypsin-activated enzyme are serine, but the C-terminal glutamate of the native enzyme is altered to arginine on activation. The CD spectrum of the enzyme suggests that the helical content of the activated enzyme is 5% less than that of the native enzyme, an indication that the trypsin-activated enzyme has a somewhat looser conformation than the native enzyme.[160]

Aspartase has a higher stability in immobilized *E. coli* as compared with free cells, apparently due to its binding to cellular particles or membranes within cells.[161] A kinetic study of the aspartate ammonia lyase reaction catalyzed by free and immobilized *E. coli* cells shows that the reaction rate is limited by the rate of the substrate transfer through the cell and cytoplasmic membranes.[162] In addition to the production of L-aspartic acid, aspartase can be used to prepare L-aspartic acid-^{15}N with > 99% atom% ^{15}N incorporated, and L-[1,4-$^{13}C_2$]-aspartic acid.[163]

2. Biotechnology

Numerous patents and papers have been published describing the technological details of producing amino acids by enzymic catalyzed reactions.[164-171] A biocatalyst consisting of individually covalently cross-linked and permealized cells can be used only discontinuously in a mixed reactor. By contrast a biocatalyst consisting of cell aggregates can be used under continuous conditions for up to 1 year.[172] Supports which have been used include K-carrageenan,[169] alumina impregnated by polyethylenimine,[173] and polyurethane prepolymer.[174] The optimum conditions for immobilization of *Escherichia alcalescens* cells into genu-carrageenan gel for L-aspartic acid product uses 2.5–3.0% genu-carrageenan and 15% biomass at 50–55 °C with tannin added.[175]

Other variations and developments are used which have direct implications for the development of the biotechnology for amino acid production. From a technological viewpoint, L-alanine has been produced using two sequential column reactions; a conventional column reactor containing immobilized *E. coli* cells, and a closed column reactor containing immobilized *Pseudomonas dacunhae* cells.[176] Research is also proceeding to develop new more active enzyme strains. A 2-fold increase in aspartase activity has recently been achieved by using the supernatant obtained from autolyzed bakers' yeast, and modifying the culture conditions.[177] More active strains such as EAPc-7 have now been incorporated into L-aspartic acid production.[178] The aspartase gene (*aspA*) of *E. coli* K-12 was cloned on plasmid pSC101 by selecting transformants of an *E. coli* K-12 mutant unable to assimilate glutamic acid due to lack of aspartase. The *E. coli* K-12 cells harboring these plasmids produced much more aspartase than did the control cells.[179] The runaway-replication plasmid vector pSY343 has also been used; one of the transformants gave a strain which produced approximately 60-fold more aspartase than did the control strain after 30 cell generations.[180] The physiological functions of the *E. coli* fumarases A, B, and C have been investigated using strains containing multicopy plasmids expressing each of the genes, and with single-copy fusions. Fumarase A is the citric acid cycle enzyme which is repressed by glucose and anaerobiosis, B and C are less susceptible to this repression. B is identified as the anaerobic enzyme.[181] The examination of microorganisms and soil isolates continues to produce strains of aspartase.[182]

Different techniques and methods continue to develop in the use of biotechnological methods for amino acid manufacture. Thus L-methionine, L-phenylalanine, and L-valine can be produced by the action of an acylase on the acetyl ester of the corresponding DL-amino acids in a membrane reaction. The enzymes are contained by a capillary membrane and can use NADH covalently linked to polyethylene glycol.[183] The phenylalanine analogue, 3-(1,4-cyclohexadienyl)-L-alanine, was converted to the previously unknown aminate analogue, *trans*-3-(1,4-cyclohexadienyl)acrylic acid, by phenylalanine lyase.[184] Correct alignment of the active site is apparently dependent on the space-filling properties of

the ring system; open-chain analogues that retain the γ,δ-double bond are inhibitors, not substrates. The aspartase-catalyzed production of aspartic acid has been carried out in a membrane reactor coupled with electrophoresis. The electric field was used to remove the charged aspartate molecule from the ultrafiltration membrane used as a membrane receptor.[185] In order to detect products from these enzymatic reactions, a bioenzymic electrode for the determination of aspartame has been constructed by the chemical coimmobilization of carboxypeptidase and L-aspartase on an ammonia gas sensing probe.[186]

B. Structure–Function Chemical Relationships

1. Enzyme Structures

Further genetic research on fumarase and aspartase reveals that the fumarase C structural gene comprises 1398 base pairs, and that it encodes a polypeptide of molecular weight 50 353. The fumarase C gene starts 140 base pairs downstream of the structurally unrelated fumarase A gene. The aspartase A structural gene comprises 1431 base pairs encoding a polypeptide of molecular weight 52 190. Homologies were found between the primary structures of the fumarase C and aspartase A genes and their products, suggesting close structural and evolutionary relationships.[187,188] Aspartase A of *Pseudomonas fluorescens* has four identical subunits with 472 amino acid residues. The deduced amino acid sequence is 56.3% homologous with that of the enzyme of *E. coli* W Cys-140 and Cys-430 of the *E. coli* enzyme, which has been assigned as functionally essential, are substituted by Ala-140 and Ala-431, respectively, in the *P. fluorescens* enzyme.[189] Amino acid sequence comparisons also place argininosuccinase in the same family as aspartase and fumarase.[190] The three fumarase genes belong to two classes. Fumarases A and B are thermolabile dimeric enzymes, and fumarase C is a thermostable tetrameric enzyme. Apart from a region containing a Gly-Ser-X-X-Met-X-X-Lys-X-Asn (X = any amino acid) consensus sequence, no significant homology was detected between the two classes of fumarases.[191]

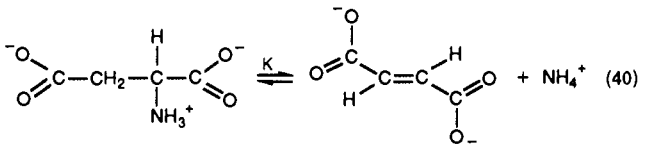
2. Thermodynamics

The thermodynamics of the conversion of aqueous L-aspartic acid to fumaric acid and ammonia (eq 35) has been investigated by both heat conduction microcalorimetry and HPLC. At 25 °C and at zero ionic strength, the following values were found: $K = 1.48 \times 10^{-3}$, $\Delta G° = 3.86$ kcal/mol, $\Delta H° = 5.86$ kcal/mol and $\Delta Cp° = -35$ cal/mol·K.[192]

C. Reaction Mechanisms

1. Effect of Metal Ions

An early mechanistic study of the aspartase catalyzed reaction was carried out at pH 7 in the presence of 1 mM Mg^{2+} ion. Product inhibition and initial velocity patterns for the forward and reverse reactions are consistent with a random mechanism in which all steps prior to the interconversion of the central complexes are in rapid equilibrium. Isotope effects for the elimination of ammonium ion from aspartate (eq 40) suggest that the rate-determining step of the reaction may be



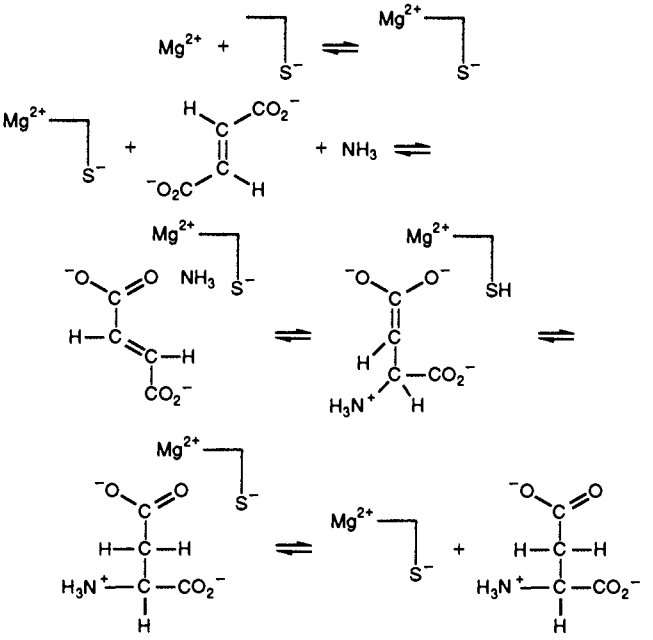
(40)

C–N breakage and imply that, as the amino acid group leaves, the resulting intermediate *may* be accompanied by considerable carbonium ion development at C-2.[193] The activity of aspartase has been probed by acetylation which changes both the catalytic and regulatory properties. At pH 7.0 a 2-fold activation was observed, but at pH 8.5 the activity was lowered. The Hill coefficient values of the substrate saturation curves were also altered under both pH conditions toward appreciable higher values. The effect of added Mg^{2+} ion also increased.[194] Kinetic data are consistent with the rapid addition of Mg^{2+} prior to aspartate, but completely random release of Mg^{2+}, NH_4^+, or fumarate. Monovalent cations such as Li^+, K^+, Cs^+, and Rb^+ are competitive against either aspartate or ammonium ion, but noncompetitive against fumarate. A primary ^2D isotope effect of approximately 1 on both $V_{max}/K_{aspartate}$ was obtained with (3*R*)-L-aspartate-3-*d*, whereas a primary ^{15}N isotope effect on $V_{max}/K_{aspartate}$ was obtained in the direction of aspartate deamination. A secondary isotope effect of V_{max} of 1.13 was obtained with L-aspartate-2-*d*. A secondary isotope effect of 0.81 on V_{max} was obtained with fumarate-d_2, whereas a value of 1.18 on V_{max} was obtained using (2*S*,3*S*)-L-aspartate-2,3-d_2. These data are consistent with a two-step mechanism with an intermediate carbanion in which C–N cleavage limits the overall rate, and the rate-limiting transition state is intermediate between the carbanion and fumarate.[195] This postulate differs from the earlier mechanism where a carbonium-type intermediate was suggested,[193] but the effect of inhibitors appears to support the carbanion postulate.

2. Cooperativity Effects

A mechanism which explains many of the features exhibited by this enzyme is shown in Scheme 11. In

SCHEME 11

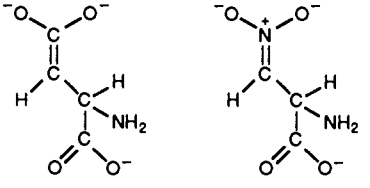


this proposed model the enzyme has a deprotonated sulfhydryl residue in close proximity to the active site. In the key step, the reversible formation of the C–N bond, the proton transfer which occurs sequentially with this step is proposed to involve the sulfhydryl residue of the enzyme. During the catalysis of the fumarate amination reaction, aspartase is markedly activated by the product L-aspartate, as well as by α-methyl-DL-aspartate, which does not serve as a substrate. Apparently, the activation is mediated by an indirect action of L-aspartate which is bound to a site distinct from the catalytic site.[196] Indeed, L-aspartase from *E. coli* has an absolute specificity for its amino acid substrate. Although aspartase is activated by metal ions, the requirement for a divalent metal ion is not specific. The binding stoichiometry corresponds to one metal ion per subunit. Paramagnetic relaxation studies show that the divalent metal ion binds at the activator site on L-aspartase and not at the enzyme active site. This activator site is believed to be remote from the active site of the enzyme because the relaxation of inhibitors that bind at the active site are not affected by paramagnetic metal ions bound at the activator site.[197] This result can be correlated with Scheme 11 if the metal ion activator bound at the carboxylate site is sufficiently remote from the carbon at C(2) and the sulfhydryl site where the proton transfer and C–N bond formation steps occur.

3. Activators and Inhibitors

Organic additives can activate the aspartase enzyme. Among such compounds are glycerol, ethylene glycol, propylene glycol, and dimethyl sulfoxide.[198] This effect has not been fully explained. The activation occurs at pH 8.5, but not at pH 7.0, where an inhibition is observed. Neither alteration of the cooperative nature of the enzyme nor subunit dissociation are associated with the activation. Two suggestions which have been offered to explain the activation are that the adducts cause subtle conformational changes within the enzyme which increases its activity, or that the adducts protect the sulfhydryl group of the enzyme against derivatization. By contrast, aspartase was competitively inhibited by *s*-2,3-dicarboxyaziridine, an antibacterial substance against *Aeromas salmonesida*.[199] Fumarase and aspartase interact more strongly with the 3-carbanions $O_2NC^-HCHXCO_2^-$ than with the parent acids $O_2NCH_2CHXCO_2H$ (X = H, OH, NH_2). This inhibition is readily understood when the proposed transition-state structure for the aspartase reaction is compared with the anion, 2-nitro-3-aminopropionate (X = NH_2) (Scheme 12). This feature manifests itself in an

SCHEME 12



inhibition of the enzyme activity, and in the relative substrate binding where the binding constants for the anions are up to 18000 times larger than for the parent acid. Indeed fumarase and aspartase bind the 3-carbanions much more tightly than their respective substrates.[200] These data suggest that the mechanisms of fumarase and aspartase reactions involve enzyme-bound 3-carbanions.

The ability to metabolize aspartate in the presence of lactate appears to be related to aspartase activity; thus the specific activity of aspartase increased during and after lactate utilization.[201]

Aspartase has a time lag during the production of aspartic acid from fumarate and ammonia. This time lag is pH dependent, being extensive above pH 8. The lag is also dependent on both substrate and M^{2+} concentrations, as well as on the degree of proteolysis of L-aspartase. These phenomenona are again consistent with a model in which there is a separate activator site for the substrate, L-aspartic acid, that is distinct from the enzyme active site. D-Aspartic acid, which does not bind at the active site, can bind at the activator site.[202]

4. Role of Sulfhydryl Groups

The role of sulfhydryl groups in aspartase from *E. coli* has been investigated. After modification of one subunit with *N*-ethylmaleimide, 85% of the original activity is lost; modification of the second sulfhydryl results in complete inactivation of the enzyme. This observation is consistent with the mechanism proposed in Scheme 11 where the sulfhydryl group is required for proton-transfer steps. This modification does not, however, lead to dissociation into subunits nor aggregation. It is concluded that the influence of the SH group modification is restricted to the active site or its vicinity of the enzyme.[203] The inactivated enzyme can usually be reactivated with sulfhydryl compounds.[204] Fumaraldehydic acid modifies one sulfhydryl group. L-Aspartate and fumarate protects the enzyme against inactivation by this compound when magnesium ions are present. This compound is therefore considered to be useful as a probe for structural differences between different enzymes since unlike *E. coli* aspartase, *P. fluorescens* aspartase is not inactivated by fumaraldehydic acid.[205]

5. Ammonia Monoxygenase

Ammonia monoxygenase of *Nitrosomonas europaea* catalyzes the oxidation of alkanes to alcohols, and alkenes to epoxides and alcohols in the presence of ammonium ion.[206] Straight-chain N-terminal alkynes all exhibit a time-dependent inhibition of ammonia oxidation without effecting hydrazine oxidation.

VI. Ammoxidation

Several reviews have been published which cover the field of ammoxidation. Ammoxidation is a process which converts a C–H bond into a C–N bond under oxidative conditions with ammonia. The primary emphasis is on the ammoxidation of propylene.[207] This reaction is an important one because it is used for the conversion of propylene into acrylonitrile on an industrial scale (eq 41). This process was developed by

$$CH_2{=}CHCH_3 + NH_3 + {}^3/_2O_2 \rightarrow CH_2{=}CHCN + 3H_2O \quad (41)$$

SOHIO, and it accounts for virtually all of the approximately 4000000 tons of acrylonitrile produced annually worldwide. The reaction proceeds via an al-

lylic oxidation process involving the abstraction of a hydrogen in an α-position to the double bond. This allylic intermediate can then be intercepted by oxygen in the catalyst lattice in the presence of ammonia to give acrylonitrile. If an olefin containing a β-hydrogen is used, loss of hydrogen from the allylic intermediate can occur at a rate faster than oxygen insertion, resulting in the formation of a diene as product (eq 42). Reviews have been published on the ammoxidation of alkanes,[208] and on the use of zeolite catalysts in ammoxidation reactions.[209]

$$CH_2{=}CHCH_2CH_3 \xrightarrow{-H} CH_2\dot{C}HCH_3 \xrightarrow{-H} CH_2{=}CHCH{=}CH_2 \quad (42)$$

A. Oxide Catalysts

Since reaction 41 is a dehydration reaction, many of the catalysts used in ammoxidation reactions are metal oxides which can readily undergo hydration reactions. Two recent examples of catalysts used for the ammoxidation of propene are either a molybdate base catalyst composed of a mixture of MoO_3 and H_3BO_3,[210] or a similar heterogeneous transition-metal catalyst comprising the metals iron, cobalt, or nickel.[211] As with all industrial catalytic processes, the engineering features are important, and by redesigning the incoming gas stream flows a 98.8% conversion of propene has been achieved with a 76.9–77.4% conversion to acrylonitrile.[212] Among the different compounds which have been added to the catalyst mixture are oxides and salts of the elements Bi, Mo, Sb, Sn, Cu, Fe, Ce, Co, Ni, Mn, Th, U, Zn, P, S, and W, and many of these catalysts have been used for both the ammoxidation of propene to acrylonitrile and of isobutene to methacrylonitrile.[213] Similarly a chromium-exchanged zeolite Y has been used as a catalyst for the conversion of 2-methyl-1,3-butadiene to 2-cyano-1,3-butadiene and of the propyne to cyanoethyne (eq 43).[214] Also, ammoxidation catalysis has been used to prepare pyridines from propylene.[215]

$$-C{\equiv}C-CH_3 \xrightarrow[[0]]{NH_3} -C{\equiv}C-CN \quad (43)$$

B. Ammoxidation of Alkanes

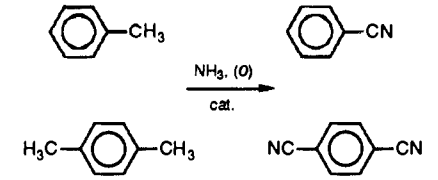
1. Aliphatics

The ammoxidation reaction can also be carried out with saturated alkanes. As for the alkenes, acrylonitrile and methacrylonitrile can be obtained from propane and isobutane, respectively (eq 44).[216] Using phosphovanadium and antimonovanadium oxide catalysts, propane has been converted to acrylonitrile in yields of up to 20%, and with a maximum selectivity of 25%.[217] The catalytic reaction is carried out at 725 K. More recently mixed metal oxide catalysts have been used to achieve a selectivity of 51.6%,[218] and an antimony–gallium catalyst has been used to achieve selectivities in the 24–34% range.[219]

$$C_3H_8 \xrightarrow[[0]]{NH_3} CH_2{=}CHCN \quad (44)$$

2. Aromatics

Alkylaromatics, as well as simple aliphatics, undergo ammoxidation. Thus benzonitrile and terephthalonitrile have been obtained from toluene and *p*-xylene, respectively (eq 45).[220] The catalyst used consists of a melt containing KCl and the chloride salt of one of the elements Cu, Mn, Co, Cr, Fe, Sb, Bi, U, and As. Oxide catalysts have also been used to prepare benzonitrile from toluene. Under ammoxidation conditions at 400 °C, toluene reacts to give 95% of benzonitrile, with 97.7% selectivity and with 97.2% toluene conversion.[221] The ammoxidation of *o*-xylene over an oxygenated vanadium–titanium catalyst gives phthalimide (eq 46).[222] The mechanism of this reaction involves the intermediate formation of *o*-toluonitrile, and the selectivity is determined both by the competition between the oxidation of the mononitrile to phthalimide and ammoxidation to phthalonitrile, and by the competition between the ammoxidation of *o*-xylene to *o*-toluonitrile and the total oxidation to carbon oxides. The kinetics of toluene ammoxidation to benzonitrile over an oxygenated vanadium–titanium catalyst have been studied.[223] The rates are independent of oxygen concentration when it was added in amounts above stoichiometric. An inhibition effect of ammonia on the overall toluene conversion was observed. A Langmuir–Hinshelwood model was proposed to represent the experimental data where it considered a competition between toluene and ammonia for the same kind of active sites. Both benzylamine and benzaldehyde were isolated as reaction intermediates, suggesting pathways involving direct attack of either oxygen or ammonia radicals on the activated methyl group of toluene. Thus this ammoxidation resembles that of propylene where the stabilized allyl and benzyl radicals facilitate the cleavage of the C–H bond.



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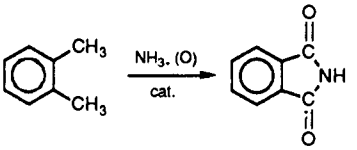

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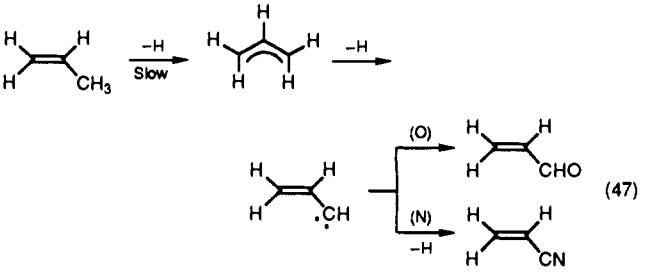
C. Reaction Mechanisms

In the mechanism for the ammoxidation of propylene the rate-determining step is the formation of an allylic intermediate formed via α-hydrogen abstraction from propylene. Abstraction of a second hydrogen can lead to an intermediate which can undergo either oxidation or ammoxidation by either O or N insertion, respectively (eq 47). In the catalytic oxidation and amm-



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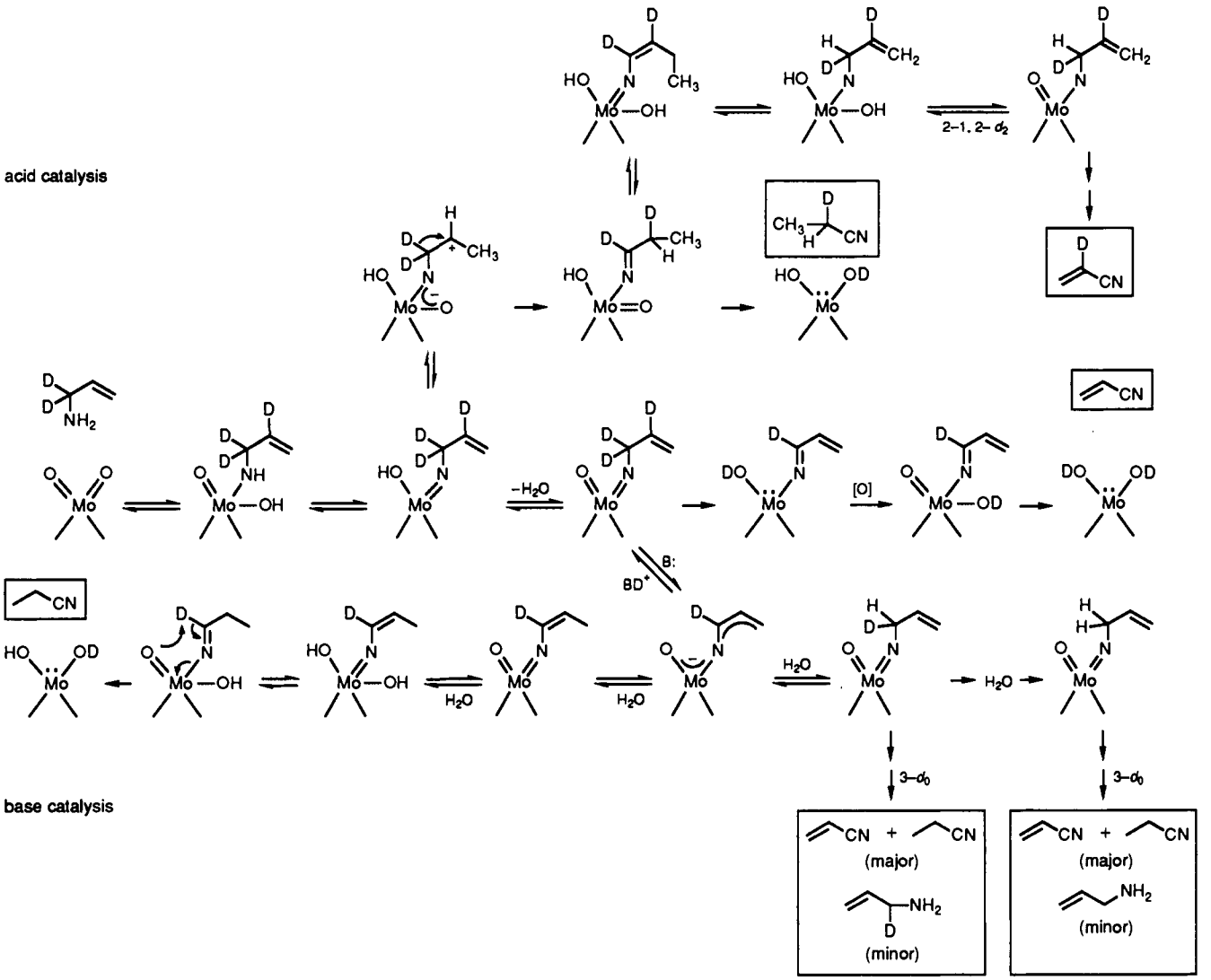
SCHEME 13

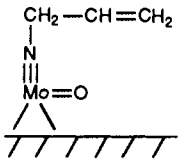


oxidation of allyl amine at 400 °C over MoO_3, Bi_2MoO_6, and $Bi_2Mo_3O_{12}$, the compounds acrylonitrile and propionitrile account for 85% of the product, along with smaller amounts of acetonitrile, propylene, diallylamine, and carbon dioxide being formed. The ammoxidation of 1,1-allylamine-d_2 gives a 95:5 d_0:α-d-acrylonitrile mixture, and a 96:4:0 α-d:d_2-propionitrile mixture, with a 88:8:4 mixture of 1,1-d_2:1-d_1:d_0 recovered allylamine. The presence of ammonia increases selectively to propionitrile at the expense of acrylonitrile. The proposed pathways for these reactions are shown in Scheme 13.[224] This scheme shows the complexity of the catalyzed ammoxidation reaction. The key intermediates all have molybdenum–nitrogen bonds. The fundamental ammoxidation process is therefore considered to involve transformations between species which have molybdenum–oxygen and molybdenum–nitrogen single and double bonds in close proximity. This study with allyl amine is of particular significance because in the ammoxidation of propylene over these catalysts, two mechanistic regions have been identified. One of these occurs under normal, high turnover conditions and corresponds to a catalytic site composed of one Mo–dioxo group. This is the site active species which is proposed to activate ammonia by formation of a Mo–diimido intermediate, which is the active N-inserting species. A key step in the formation of a Mo=NH or Mo=NR bond on the catalyst is a dehydration between ammonia or a primary amine and the molybdenum oxide, Mo=O moiety. The other regime, which is proposed to be involved at lower turnovers, is proposed to involve two Mo–dioxo or –diimido species at the active site. At this site one of the Mo species acts as an O- or N-inserting element, and the other serves as a redox element to facilitate catalyst reduction and reoxidation. In both regimes, bridging Bi–O species are proposed to serve as the α-hydrogen abstracting element to form the initial π-allylmolybdenum intermediate.[225] In a surface study of a V_2O_5/TiO_2 catalyst for the ammoxidation of toluene, the species that possesses the active sites responsible for toluene activation is believed to be a V(IV) species which is reducible to V(III) and is characterized by an IR absorption band at 940 cm^{-1}.[226]

D. Model Compounds

The proposed surface pathways have been tested using discrete metal compounds. In support of Grasselli's proposal,[224] benzyl radicals react with the complex $Cr(OSiMe_3)_2(=NBu^t)_2$ to form benzylidene-*tert*-bu-

tylamine ($PhCH{=}NBu^t$), presumably via the intermediate $Cr(OSiMe_3)_2(=NBu^t)(NCH_2(Bu^t)Ph)$.[227] This reaction supports Grasselli's proposal for the C–N bond forming step. One proposal for a step in the ammoxidation of propylene is that an allylamide molybdenum (V) surface species shown is formed. The next



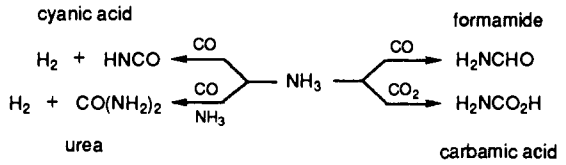
step along the route to acrylonitrile has been proposed to involve abstraction of an allylic hydrogen to form a coordinated allylideneamide group. This rate-determining hydrogen-abstraction step has also been modeled in a homogeneous system. Thus treating the complex $Cl_4(THF)W{\equiv}NCH_2CH{=}CH_2$ with tertiary butyllithium gives an allylideneamidotungsten(IV) complex (eq 48).[228]

$$Cl_4(THF)W{\equiv}NCH_2CH{=}CH_2 + t\text{-BuLi} \rightarrow Cl_3(THF)_2W{=}N{=}CH{-}CH{=}CH_2 \quad (48)$$

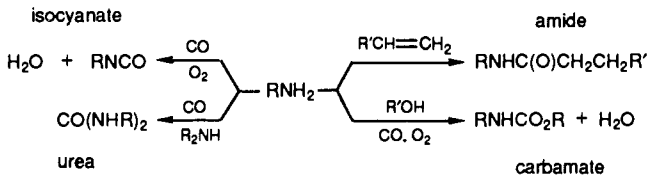
VII. Carbonylation Reactions

The reaction between amines, carbon monoxide, and other species such as an alkene can lead to a variety of carbonylated nitrogen containing products. Among these compounds are amides, ureas, carbamates, and isocyanides. Some of the transformations, which can potentially be used to prepare these nitrogen-containing compounds, are outlined in Schemes 14 and 15. For

SCHEME 14



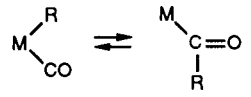
SCHEME 15



carbonylation reactions a rational catalytic scheme can frequently be devised because the individual reactions are, in many instances, reasonably well understood. The commercial importance of these reactions is high because this chemistry offers the potential of forming a wide range of useful nitrogen-containing compounds from inexpensive precursors under catalytic conditions.

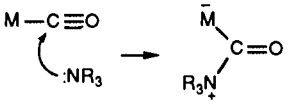
Reaction Chemistry

Some of the chemistry underlying these catalytic reactions is well understood, but in other cases further work is needed. An important reaction is the insertion of carbon monoxide into a transition-metal alkyl bond. This reaction occurs by alkyl group migration to a coordinated carbonyl ligand, and the reaction occurs with retention of configuration at the migrating carbon (eq 49). A second reaction of a complexed carbon mon-



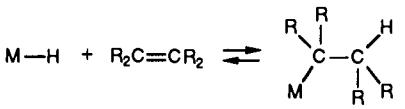
(49)

oxide is one where the coordinated carbon undergoes *external* nucleophilic attack. Such a nucleophile can be the lone electron pair on the nitrogen of ammonia or an amine (eq 50). These two individual reactions



(50)

are important ones because they lead to the formation of carbon–carbon and carbon–nitrogen bonds, respectively. The metal–alkyl (M–R) bond involved in reaction 49 can be formed by metathetical replacement reactions or by insertion of an alkene into a metal–hydrogen bond (eq 51). A reaction which is rarely ob-

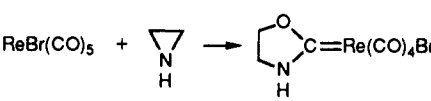


(51)

served, however, and one which can be generally discounted in any mechanistic considerations, is the insertion of carbon monoxide into a metal–hydride bond to give a metal–formyl complex.

Examples of stoichiometric reactions involving attack of a lone electron pair of an amine on the carbon of a coordinated carbonyl to give a complexed amide are shown in eqs 52 and 53.[229] These reactions between alkenes, carbon monoxide, amines, and transition-metal hydrides, and alkyls and carbonyls can be used in different combinations to give amides, amines, ureas, carbamates, isocyanates, and aromatics.

$$cpFe(CO)_3^+ + H_2N(CH_2)_2NMe_2 \rightarrow cpFe(CO)_2(CONH(CH_2)_2NMe_2) + H^+ \quad (52)$$



(53)

A. Formation of Amides

1. Amides from Alkenes

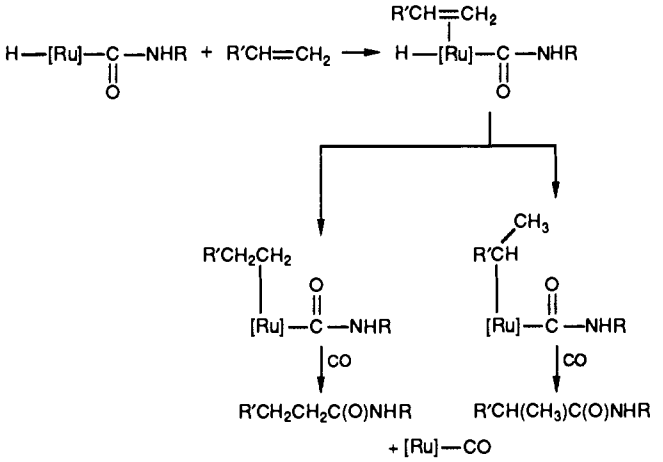
One focus of this chemistry is the catalytic formation of amides from alkenes, carbon monoxide, and ammonia. The compounds chosen as catalysts to effect these conversions are those which are commonly used as catalysts for hydroformylation reactions. As an example, carboxylic acid amides have been prepared by the reaction of olefins having 3–30 carbon atoms with CO and ammonia or amines in the presence of cobalt compounds and a pyridine base.[230] For example, when a mixture containing 1-hexene and butylamine is autoclaved under a CO pressure in the presence of cobalt carbonyl and pyridine as catalyst the product is heptenoic acid butylamide. For the case of nickel carbonyl as catalyst, butylamine, diethylamine, and diphenylamine are carbonylated by carbon monoxide to give exclusively formamide derivatives. This selectivity to amide formation follows that of cobalt and iron carbonyls, but contrasts with that of manganese carbonyl as

a catalyst, which results in the formation of ureas.[231] Ruthenium carbonyl, $Ru_3(CO)_{12}$, is also an effective catalyst. Under a pressure of CO (40 kg cm^{-2}), 1-octene ($R' = C_6H_{13}$) can be hydroaminated with benzylamine ($R = C_6H_5CH_2$) to *N*-benzylnonamide in 67% yield (eq 54). The reaction is part of a general procedure which

$$RNH_2 + R'CH{=}CH_2 + CO \rightarrow RNHC(O)CH_2CH_2R' \quad (54)$$

can be described as the hydroamination of olefins.[232] The reaction involves the intermediacy of an amide hydride ruthenium carbonyl complex which is formed by nucleophilic attack of the amine at the carbonyl ligand. Such an intermediate has been observed for the case of benzylamine. A plausible pathway for the catalytic reaction is shown in Scheme 16. The reaction

SCHEME 16



path follows two parallel sequences which result from the stereochemistry of the alkene insertion into the ruthenium–hydride intermediate to give the ruthenium alkyl. The two pathways result from the formation of both a linear and a branched alkyl complex from this insertion step. The linear alkyl complex is the most stable, but as for homogeneously catalyzed hydroformylation reactions, products resulting from the branched alkyl intermediate will also be formed. The final reductive elimination step is induced by carbon monoxide, which stabilizes the low-valent ruthenium carbonyl catalyst. The authors do not favor a pathway where an intermediate ruthenium acyl complex is formed, which can react with the amide to yield the hydroamidation product. This decision is based on the failure of the catalyst system to yield hydroesterification products when the process is carried out in the presence of sodium ethoxide in ethanol.

2. Formamides by Carbonylation of Amines

Formamides result from the insertion of carbon monoxide into an N–H bond. Thus piperidine, diethylamine, and ethanolamine are carbonylated by carbon monoxide in the presence of copper salts to give formyl derivatives. The addition of either water or acids retards the carbonylation.[233] The reaction gives copper metal or copper(I) compounds as the other product. The most likely pathway involves the formation of an intermediate copper(II) carbonyl complex which undergoes nucleophilic attack at the carbonyl carbon by the amine (eq 50). Such a pathway also explains the inhibition of the reaction by water, since this complexed carbonyl group can also be attacked by water as the nucleophile in competition with the amine. Similarly, *N*-(hydroxyalkyl)formamides can be obtained from the carbonylation of primary amino alcohols with CO in the presence of mercuric acetate or ferric chloride.[234,235] It is proposed by these authors that the role of mercuric acetate is to act as an initiator of a chain reaction,[236] and although this may be correct, the formation of elemental mercury in the reaction also supports the possibility that nucleophilic attack by an amine nucleophile at a mercury–carbonyl complex may again be involved. For the case of ferric chloride the mechanistic aspects are completely unknown, especially since the metal is recovered from the reaction as $Fe(CO)_5$. A possibility, however, is that the product $Fe(CO)_5$ is the compound from which the catalylically active species are derived. This postulate is supported by later work which has shown that $Fe(CO)_5$ does indeed catalyze the formation of formamides from a mixture of CO and either primary or secondary amines. A carbamoyl intermediate such as $Fe(CO)_4(CONR_2)^-$, formed by amide ion attack at a coordinated carbonyl, is believed to play a key role in this catalytic system.[237] Both alkali and alkaline earth metals, as well as rhodium oxide, have also been used as catalysts for the carbonylation of amines.[238,239] Cyclic amines such as pyrrolidine, piperidine, and morpholine are carbonylated in the presence of ruthenium trichloride to give the corresponding formamide.[240] Since ruthenium trichloride is readily converted to carbonyl complexes under these experimental conditions, it is likely that this reaction is a further example of amide formation by attack of an amide nucleophile at a complexed carbonyl group.

3. Amides from Syngas

Both hydrated ruthenium dioxide and $Ru_3(CO)_{12}$ are effective catalyst precursors for the conversion of mixtures of syngas (carbon monoxide and hydrogen) and ammonia to *N*-methylformamides and trimethylamine in liquid-phase reactor systems. The formation of N-methylated product is enhanced by operating at low ratios of ammonia to synthesis gas, and methanol does not appear to be a reaction intermediate. It is suggested that the formation of N-methylated products involves interception of incipient formaldehyde to form methylamines and formamides, and hydrogenation of formamides to methylated products.[241]

4. Amides from Esters

Amides have also been prepared by reacting ethers or esters with dialkylamines and carbon monoxide in the presence of a rhodium catalyst. For example, a mixture of acetamide and *N*-methylacetamides are obtained from reacting a mixture of acetic acid, methyl iodide, dimethyl ether, and ammonia in the presence of catalytic amounts of rhodium acetate.[242] In the presence of metal chlorides, ethyl acetate reacts with 1-propylamine at 65 °C to give the amide CH_3CONH-Pr-1 and ethanol (eq 55).[243] Among the metal chloride

$$CH_3CO_2Et + 1\text{-}PrNH_2 \rightarrow CH_3CONHPr\text{-}1 + EtOH \quad (55)$$

catalysts used are $AlCl_3$, $SnCl_2$, $FeCl_3$, $CuCl_2$, $RhCl_3$, and $RuCl_3$. The product yields suggest that the catalytic activity increases with increasing acidity of the metal

center. This reaction shows a strong resemblance to the metal-catalyzed formation of carbamates via the reaction of dimethyl carbonate with amines (eq 56). It is suggested that in each case the mechanism involves amide bond formation via nucleophilic attack of the amine at the carbon atom of the ester group, which is activated by oxygen coordination to the metal center.

$$(EtO)_2CO + RNH_2 \rightarrow RNHCO_2Et + EtOH \quad (56)$$

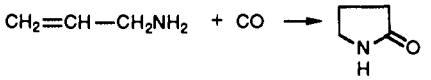
5. Amides from Allylamines

Allylamines $RCH{=}CHCH_2NR^1R^2$ (R = Me, Pr, Ph; R^1 = Me, Et, Bu; R^2 = Et, Ph, Bu, $PhCH_2$) are carbonylated with CO in the presence of low-valent palladium phosphine catalysts to give an unsaturated amide as final product (eq 57).[244] This reaction product results

$$RCH{=}CHCH_2NR^1R^2 + CO \rightarrow RCH{=}CHCH_2CONR^1R^2 \quad (57)$$

from the insertion of a carbonyl moiety into the carbon–nitrogen bond of the allylamine. The observations have been explained on the basis of an oxidative addition of the allyl amine bond across a palladium(0) center to give a π-allylic palladium(II) complex. Insertion of carbon monoxide into the palladium–carbon bond yields an acyl intermediate, which can undergo nucleophilic attack at the acyl carbon by the amine. This mechanism differs considerably from the carbonylation reactions discussed earlier in this section. The role of the metal center in these earlier reactions is to provide an electrophilic site for activation of the CO, whereas in this reaction with allylamines the metal center provides a nucleophilic site for an initial oxidative addition step. It should be noted, however, that this pathway with allylamines is proposed, but not yet proven. Carbon monoxide insertion into allylic precursors can then lead to the formation of both linear and cyclic carbonylation products.

Several rhodium-, platinum-, palladium-, and nickel-based homogeneous catalysts have been developed for the selective synthesis of γ-butyrolactam, *N*-alkyl-2-pyrrolidones, vinylacetate, and phenylacetate esters and diesters from allylic and benzylic substrates.[245] The highest yield of α-butyrolactam (eq 58) is observed with $RhCl(PPh_3)_3$. In general these formamidation reactions



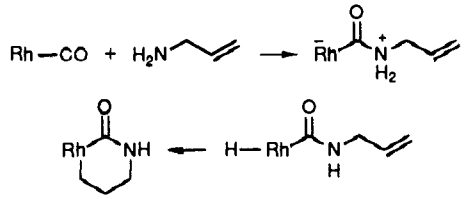
(58)

proceed readily and selectively with primary and cyclic amines having α-hydrogens. Secondary acyclic amines do not show such selectivity, and they also undergo transalkylation and condensation to give substituted ureas. Mechanistically reaction 58 can occur by a sequence of reactions which is again initiated by nucleophilic attack of the amine nitrogen at a complexed carbonyl. Proton transfer from nitrogen to rhodium, followed by insertion of the alkene into the Rh–H bond gives a metallacycle, which, upon reductive elimination, gives the α-butyrolactam (Scheme 17).

6. Solvent Effects

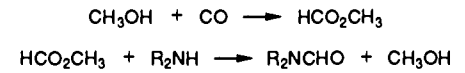
A solvent effect study on the ruthenium-catalyzed carbonylation of secondary and unreactive primary amines shows no correlation between the yield of formamide and the dielectric constant of the solvent.[246]

SCHEME 17



Alcohols are the preferred solvents. It is proposed that the enhanced selectivity and turnover with these solvents is due to the transformation of the alcohol into the formate which subsequently acylates the amine. Such a reaction combination in methanol solvent is shown in Scheme 18.

SCHEME 18



7. Double Carbonylation

Two carbon monoxide molecules are coupled in the presence of nickel bromide and secondary amines at ambient temperature to give oxamides in 82% yield.[247] The reaction is not catalytic since the nickel compound is reduced to the metal, thereby yielding a stoichiometric process (eq 59). No mechanism has been proposed, but the product composition correlates with a pathway involving nucleophilic attack by the amine at a coordinated carbonyl ligand. Catalytic processes have, however, been subsequently developed using a Wacker-type catalyst mixture composed of palladium acetate, copper acetate, and a chelating tertiary phosphine.[248]

$$NiBr_2(NHEt_2)_2 + 2NHEt_2 + 2CO \rightarrow Et_2NC(O)C(O)NEt_2 + 2NH_2Et_2^+ + Br^- + Ni \quad (59)$$

B. Formation of Amines

1. Amines from Syngas

Amines can be catalytically prepared from syngas, which is a mixture of CO and H_2, in the presence of a source of nitrogen. For example, both methylamine and dimethylamine are formed by passing mixtures of carbon monoxide, hydrogen, and nitrogen (or ammonia) over a heterogeneous catalyst. Among the catalysts used for this transformation are Hf, Zr, Ag–Zr alloy, U, Th, $ZnO–Al_2O_3$, $Fe_3O_4–Al_2O_3–BaO$, and $V_2O_5–BaO$.[249] The reaction conditions typically use temperatures in the 300–600 °C range, and the average carbon content of the amines in the product can be controlled by changing the reactant proportions or the composition of the catalyst mixtures. A plausible reaction pathway involves catalytic hydrogenation of carbon monoxide to methanol, followed by ammonolysis to the amine (eq 60). Syngas is well known as a precursor for alcohols,

$$CO + 2H_2 \rightarrow CH_3OH \xrightarrow{NH_3} CH_3NH_2 + H_2O \quad (60)$$

and the second step again emphasizes the importance of the dehydration reaction between alcohols and ammonia to give amines. If, therefore, the first step in the reaction can be tailored to give a series of steps leading to an intermediate alcohol, dehydration catalysts can be used to effect the amination reaction. Such a process requires the use of a Fisher–Tropsch catalyst. A mod-

ification of this strategy involves replacing ammonia with dimethylamine, when the products of the catalyzed reactions are now dimethylalkylamines.[250] The concept has also been extended to use isopropylamine as reactant.[251]

Homogeneous catalysts have also been employed for these types of reactions. From the reaction between olefins, synthesis gas, and ammonia in the presence of a catalyst consisting of $Co_2(CO)_8$ and PPh_3, primary amines can be prepared in high selectivity. As an example, a mixture of 1-hexene, ammonia, and syngas gives a mixture containing both C-7 and C-14 primary amines (eq 61).[252] Alternative catalysts to $Co_2(CO)_8$

$$C_4H_7CH{=}CH_2 + CO + NH_3 \rightarrow 1\text{-}C_7H_{15}NH_2 + CH_3CH(CH_3)C_4H_8NH_2 + C_4H_9CH_2CH(C_7H_{15})CH_2NH_2 \quad (61)$$

are $Fe(CO)_5$, $Ru_3(CO)_{12}$, Rh compounds, or a mixed Rh–Ru homogeneous catalyst. Under certain experimental conditions higher homologue amines can also be formed.[253] These reactions are typical of a hydroformylation sequence of reactions, where the amine is formed by reductive amination of the aldehyde product.

A somewhat different catalytic approach to synthesizing amines involves the conversion of azidoarenes into aminoarenes with CO and H_2O in the presence of rhodium trichloride (eq 62). The reaction involves the

$$ArN_3 + CO + H_2O \rightarrow ArNH_2 + CO_2 + N_2 \quad (62)$$

transfer to nitrogen of a hydrogen molecule which is formed in the catalyzed water gas shift reaction.[254] The reaction formally represents the hydrogenation of an aryl imide, presumably formed within the coordination sphere of the rhodium. The reaction does not proceed with azidoalkanes in place of azidoarenes.

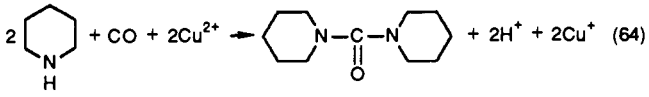
C. Formation of Ureas

1. Copper(II) Catalysts

Ureas are formed by the oxidative coupling of carbon monoxide and amines. The simplest reaction, the reaction of carbon monoxide and ammonia, is shown in eq 63. As the temperature of this gas-phase reaction

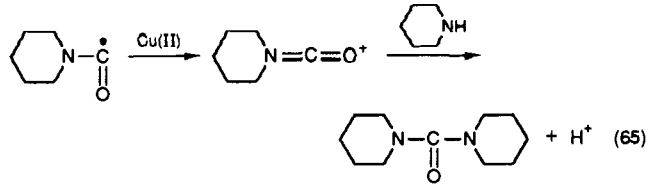
$$CO + 2NH_3 + \rightleftharpoons CO(NH_2)_2 + H_2 \quad (63)$$

is increased, the mole fraction of urea in the product increases, a result which correlates with an endothermic reaction.[255] An early report shows that carbon monoxide can be oxidized autocatalytically by amine complexes of copper(II) under mild conditions. An example of such a reaction is the conversion of a mixture of carbon monoxide and piperidine to the product urea at 25 °C and 1 atm of pressure (eq 64).[256] The system can



(64)

be made catalytic by reoxidizing Cu(I) back to Cu(II) with oxygen. Piperidinium ions do not retard the reaction. A one-electron redox mechanism is proposed whereby the formylpiperidinium radical is formed. This radical is assumed to be then rapidly oxidized by a Cu(II) complex to form an isocyanate ion, which adds to piperidine and forms the final urea (eq 65). The exceptional reactivity of piperidine and morpholine in this reaction is attributed to their high basicity and nucleophilicity and also to their rather poor coordinating ability to Cu(II).



(65)

2. Palladium(II) Catalysts

Palladium on silica has also been used as a catalyst for urea formation.[257] In this reaction the hydrogen is removed from the reaction mixture in the form of water (eq 66). This reaction has also been carried out under

$$2\ PhNH_2 + CO + \tfrac{1}{2}\ O_2 \rightarrow PhNHC(O)NHPh + H_2O \quad (66)$$

homogeneously catalyzed conditions using catalytic amounts of $PdCl_2$ or the complex $PdCl_2(amine)_2$.[258] The pathways for the formation of ureas bear a strong resemblance to those for the formation of amides. In each case, the initial carbonylation of the amine will lead to a complexed amide on the metal center. In the catalyzed synthesis of organic amides, insertion of the alkene into this metal–amide bond leads directly to the desired product. For the catalyzed synthesis of ureas, however, no alkene is present for the insertion step, and the metal amide intermediate then reacts with a second molecule of amine to give the product urea. As a variation, palladium(II) salts have been used as catalysts for the formation of ureas from the reaction of carbon monoxide with a mixture of anilines and nitrobenzenes (eq 67).[259] The catalyst used consists of a mixture of

$$ArNH_2 + ArNO_2 + 3\ CO \rightarrow (ArNH)_2CO + 2\ CO_2 \quad (67)$$

palladium acetate and triphenylphosphine. The mechanism of this reaction is unknown, but there clearly must be a stepwise reduction of the nitro group. A plausible pathway can again follow the sequence of reactions shown in eq 65, where carbonylation gives an aryl isocyanate cation. Subsequent reaction with aniline can lead to the urea.

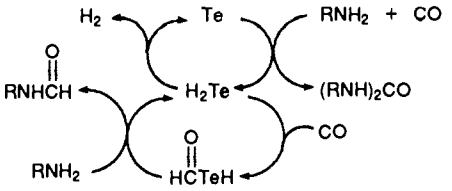
3. Selenium and Tellurium Catalysts

An alternate catalyst system employs selenium or tellurium in the synthesis of ureas from amines and carbon monoxide. In the presence of selenium and triethylamine for example, arylureas can be prepared from aromatic amines and carbon monoxide in refluxing benzene as solvent.[260] The reaction proceeds in high selectivity to give the urea and hydrogen selenide in the first stage, the latter then being reoxidized by oxygen back to elemental selenium. The overall stoichiometry of the process is shown in eq 68. When tellurium is

$$RR'NH + CO + \tfrac{1}{2}O_2 \rightarrow (RR'N)_2CO + H_2O \quad (68)$$

used as catalyst, the hydrogen telluride formed is thermally unstable, and spontaneously decomposes into hydrogen and tellurium to regenerate the catalyst.[261] In the tellurium-catalyzed carbonylation of alkylamines the selectivity is lowered, however, due to the formation of a mixture containing both the urea and the formamide. A pathway for these transformation has been suggested (Scheme 19), but the carbonylation of a Te–H

SCHEME 19



bond needs to be proven before any such pathway can be considered with confidence. The formation of formamides and hydrogen is suppressed by the addition of nitrobenzene, which is itself converted into aniline. The utility of this chemistry has been extended to the catalytic preparation of polyureas.[262]

4. Manganese Carbonyl Catalysts

Manganese carbonyl, $Mn_2(CO)_{10}$, catalyzes the reaction of 1-butylamine and cyclohexylamine with CO to give the corresponding ureas. The key steps in the reaction are outlined in Scheme 20. In this scheme,

SCHEME 20

$$Mn_2(CO)_{10} + 3RNH_2 \rightleftharpoons Mn(CO)_4(NH_2R)(CONHR) + Mn(CO)_5^- + RNH_3^+$$

$$Mn(CO)_4(NH_2R)(CONHR) + CO \rightleftharpoons Mn(CO)_5(CONHR) + RNH_2$$

$$Mn(CO)_5(CONHR) + RNH_2 \rightleftharpoons Mn(CO)_5(CONR)^- + RNH_3^+$$

$$Mn(CO)_5(CONR)^- \rightleftharpoons Mn(CO)_5^- + RNCO$$

$$RNCO + RNH_2 \rightleftharpoons CO(NHR)_2$$

$Mn_2(CO)_{10}$ reacts with the primary amine RNH_2 to give the carbamoyl complex $Mn(CO)_4(NH_2R)(CONHR)$, which is then carbonylated to give $Mn(CO)_5(CONHR)$. Subsequent deprotonation of the amide ligand by amine, followed by loss of $Mn(CO)_5^-$, leads to the formation of the isocyanate, RNCO. The urea is formed by reaction between the amine and this free isocyanate.[263]

D. Formation of Carbamates

Carbamates are salts or esters of the unknown free carbamic acid, NH_2CO_2H. This acid is formed by the reaction between ammonia and carbon dioxide. Since the free acid is unstable, the product is the salt, ammonium carbamate (eq 69). This reaction formally

$$2NH_3 + CO_2 \rightleftharpoons [NH_2CO_2][NH_4^+] \qquad (69)$$

involves the insertion of a carbon–oxygen double bond of carbon dioxide into an N–H bond of ammonia. Modifications involve using substituted amines, RNH_2, or R_2NH instead of ammonia in the reaction, or carrying out the reaction in the presence of alcohols, ROH, to give carbamic esters as the final product. With carbon dioxide as reagent, no catalysts are required to carry out these reactions.

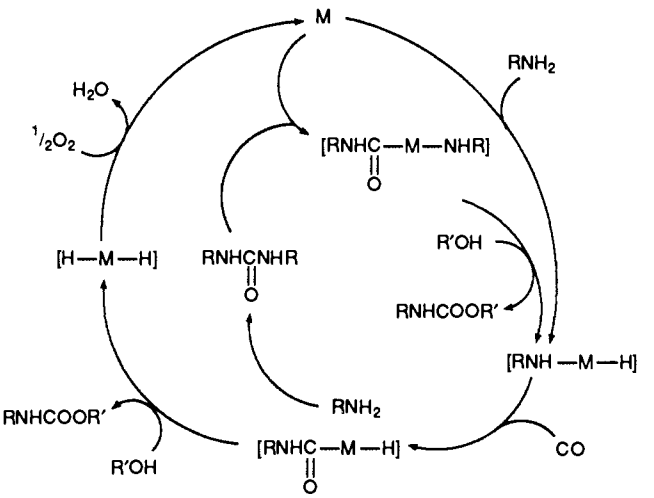
The catalytic formation of carbamates can be regarded as an extension of the earlier chemistry. The catalysts used are essentially the same as those used for the catalyzed formation of amides and ureas, except that now the reactions are carried out in the presence of oxygen and an alcohol in order to obtain a carbamate ester. The formation of carbamates can be summarized by the reaction shown in eq 70. As an example, the carbamates $RNHCO_2R'$ (R = Bu; R′ = Me, Et, Bu, 1-Pr. R = Cy, octyl; R′ = Me) have been prepared in 16–90% yield by the reaction of CO with the corresponding amines and alcohols in the presence of a catalyst consisting of selenium and triethylamine.[264]

$$RNH_2 + CO + R'OH + \tfrac{1}{2}O_2 \rightarrow RNHCO_2R' + H_2O \qquad (70)$$

1. Platinum Metal Catalysts

The combination of a platinum group metal and an alkali metal or an onium halide is also an effective catalyst system for the oxidative alkoxycarbonylation of amines by CO and oxygen to give carbamates. The catalytic effectiveness of the halide ion decreases along the series I > Br > Cl, and for the metal the order of activity is Pd ≥ Rh > Ru > Pt > Ir. The key steps in this proposed pathway is shown in Scheme 21.[265] The

SCHEME 21



key steps in this proposed pathway are the initial insertion of the metal center into an N–H bond of the amine, followed by insertion of a carbon monoxide molecule into the metal amide bond formed in the first insertion step. The carbamic ester product is formed by alcoholysis of the intermediate C-bonded amido complex. The proposed intermediacy of a urea is supported by the observation that it is almost quantitatively converted to the carbamate when it is separately added to the catalyzed reaction mixture. If further study shows that this pathway is indeed correct, it will represent one of the few cases where a catalytic cycle involves the oxidative addition of an N–H bond across a low-valent transition-metal center, and the subsequent insertion of carbon monoxide into a transition-metal amide bond. Both of these reactions are quite uncommon.[148,266]

Aromatic carbamate esters can also be prepared in high yields in the presence of $PdCl_2/CuCl_2/O_2$, the Wacker catalyst system.[267] A plausible pathway involves nucleophilic attack by the amine nitrogen at a carbonyl ligand complexed to palladium(II).[268] This step is shown in eq 71. The critical difference between

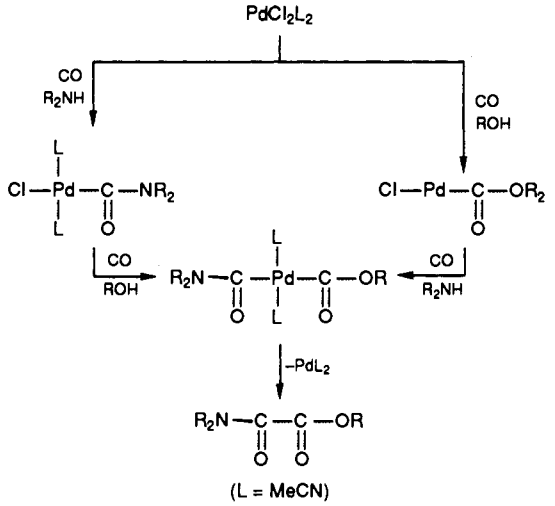
$$Pd{-}CO^+ + R_2NH \longrightarrow Pd{-}C(=O^+)NR_2 \qquad (71)$$

the mechanisms shown in Scheme 21 and eq 71 is the first step. In each case the metal center undergoes a two-electron change in this step. In Scheme 21 this step

is a two-electron oxidation, but in reaction 71 it is a two-electron reduction. The catalytic cycle is completed by a final reductive elimination step in the former case, and by a reoxidation by Cu(II) in the latter case.

Transition-metal carbonyls can also be used as catalysts for carbamate formation. At 150 °C, the carbonyls of Co, Mo, Ti, Ni, Fe, and Rh catalyze the conversion of aniline, CO, and methanol into methyl *N*-phenylcarbamate.[269] Double carbonylation yields oxamates.[270] This formation of oxamates represents the first example of a catalyzed cross double carbonylation of amines and alcohols. The Wacker-type catalyst used for this reaction is $PdCl_2(MeCN)_2$ and cuprous iodide, with the reaction being carried out in the presence of oxygen. The key step in this double carbonylation reaction is the formation of a carbon–carbon bond in a reductive elimination from an amide acyl palladium(II) intermediate (Scheme 22). Reoxidation of the zerovalent

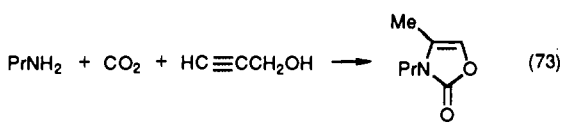
SCHEME 22



PdL_2 product in the presence of the liberated HCl will then regenerate $PdCl_2L_2$ (L = MeCN), which can take part in a second cycle of the catalyst.

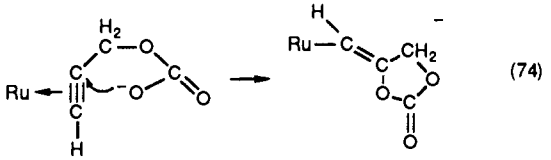
The carbonyl compound $Ru_3(CO)_{12}$ also catalyzes the formation of carbamates from secondary or primary amines with CO_2 and acetylenic alcohols or oxazolines (eqs 72 and 73).[271] The authors propose that the re-

$$Et_2NH + CO_2 + HC{\equiv}CCH_2OH \rightarrow Et_2NCO_2CH_2COMe \quad (72)$$



(73)

action pathways involves attack by carbon dioxide at propargyl alcohol to give an intermediate with the alkyne group bonded to a ruthenium center. Intramolecular cyclization of this complex is then proposed to yield a ruthenium vinyl intermediate (eq 74).



(74)

Subsequent reaction with a secondary amine such as Et_2NH gives linear product (eq 72) and with a primary amine the cyclic product (eq 73). Although this pathway is feasible, a complexed alkyne is only activated to attack by a nucleophile when the metal center is in a high-valent state. For such a mechanism to be operable, therefore, the ruthenium center cannot be in a zerovalent oxidation state, and hence the metal center must have been oxidized in some earlier stage of the reaction.

2. Copper and Cobalt Catalysts

Copper complexes themselves can act as homogeneous catalysts for the formation of carbamates. When a mixture containing aniline, carbon monoxide, ethanol, and air is heated in the presence of copper iodide a 92% yield of ethyl *N*-phenylcarbamate was formed. Dimethyl carbonate is produced as a byproduct.[272] [Bis(salicylideneamino)ethylene]cobalt(II) catalyzes the methoxycarbonylation of 1-aminoadamantane; the products are the carbamate and the urea.[273]

E. Formation of Isocyanates

Catalytic routes to isocyanates are presently being sought as a high priority. The reason for this priority is that aryl isocyanates are important compounds in the manufacture of urethane polymers, and also because they are presently synthesized on an industrial scale from phosgene, a highly toxic substance. The development of a catalytic synthesis of aryl isocyanates via a route which does not involve the use of phosgene will represent a safer method of preparing these compounds. The present thrust is to develop new catalytic routes to carbamates, compounds which can subsequently be thermally decomposed into isocyanates.[274]

Methylamine, ethylamines, and aniline can be converted to their isocyanate trimers with CO in the presence of a Wacker catalyst (eq 75). With aniline

$$PhNH_2 + CO + \tfrac{1}{2}O_2 \rightarrow PhNCO + H_2O \quad (75)$$

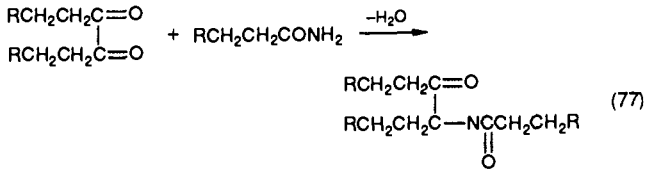
as reagent, both phenyl isocyanate and triphenyl isocyanurate, a triazinetrione trimer, are formed.[275] As a probe of such reactions, surface intermediates have been identified by IR spectroscopy on the catalyzed reaction between carbon monoxide and ammonia. On films of Rh, Ru, and Pd on Al_2O_3, SiO_2, and TiO_2, NCO was detected for all of the metals when the support was Al_2O_3 or SiO_2, but not for TiO_2. The NCO resided on the Al_2O_3 for catalysts containing this support, but on the metal when the support was SiO_2.[276] For the case of rhodium on silica, the surface species having IR bands at 2172 and 2225 cm^{-1} were identified as RhNCO and RhOCN, respectively.[277]

F. Formation of Aromatics

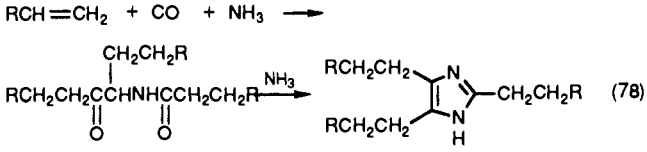
Imidazoles can be prepared from the rhodium-catalyzed reaction of 1-olefins with CO and concentrated aqueous ammonia. The reaction can be carried out in one step in 50–60% yields. The reaction is described as a two-step process with the heterocyclization occurring in the second step. The catalyst is presumed to be $RhH(CO)_3$. The pathway is proposed to involve ketonic intermediates. The first step in this transformation is clearly complex. A possible route involves the complex $RhH(CO)_3$ as a homogeneous catalyst for both the water gas shift reaction and the hydroformylation of the alkene. The water gas shift reaction (eq 76) can provide the hydrogen for the hydroformylation step. In

$$CO + H_2O \rightleftharpoons CO_2 + H_2 \quad (76)$$

the hydroformylation reaction between carbon monoxide, hydrogen, and an alkene, an intermediate is a metal acyl. This acyl intermediate, $RhCOCH_2CH_2R$, in the absence of a high concentration of hydrogen, can then couple to give the diketone $RCH_2CH_2COCOCH_2CH_2R$. In an earlier section of this review, it was shown that amides can be formed from alkenes, carbon monoxide, and ammonia under metal-catalyzed conditions. The amide formed in this particular system will be the compound $RCH_2CH_2CONH_2$. Condensation of the diketone with one molecule of this amine will yield an imine (eq 77) which, upon hydrogenation, gives the linear intermediate obtained as the intermediate in eq 78.



(77)



(78)

VIII. Summary and Conclusions

This review shows that a wide variety of compounds can be synthesized from ammonia or amines using either transition-metal compounds or enzymes as catalysts. Many of these compounds are formed from the reactions of ammonia or amines with other small molecules such as alcohols, alkenes, carbon monoxide, carbon dioxide, and oxygen. By changing the nature of the catalysts it is sometimes possible to control the selectivity of a given reaction to give the specific desired product.

These catalyzed reactions can be categorized into a small number of reaction types, many of which result in cleavage of the N–H bond. One of these reactions is the condensation reaction between alcohols and ammonia, or between alcohols and primary or secondary amines. The alcohols can be introduced directly into the reaction, or they can be generated in situ using hydroformylation conditions with alkenes and a gas mixture comprised of carbon monoxide and hydrogen. Since this condensation reaction between alcohols and amines to give higher amines involves the elimination of water, many of the catalysts used for the reaction are dehydrating agents.

The catalyzed amination of alkenes with ammonia is a reaction which cannot be achieved with high selectivity for simple unsubstituted alkenes. For the electron-poor alkene, fumarate, however, the addition of ammonia to the carbon–carbon double bond to give aspartate is catalyzed by the enzyme aspartase. The mechanism of this reaction involves cooperativity between metal ions and sulfhydryl groups at the active site. The key step in the reaction appears to involve the generation of a carbanion in the substrate.

We also show how the presence of oxygen in these reactions can be used to effect the ammoxidation of alkenes and alkanes to give nitriles. These ammoxidation processes are commercially of great importance, yet the understanding of the chemical reactions which occur at the catalyst surface is still at a rather early stage of development. The addition of small molecules other than oxygen to the reaction mixture can lead to the formation of a variety of other product compounds. Two such reagent compounds which can be added are carbon monoxide and carbon dioxide. Among the compounds which can be formed are amides, ureas, carbamates and isocyanates, all of which can potentially be obtained from using a transition-metal compound as catalyst in these reactions.

Two fundamental mechanistic types are frequently operable in reactions involving transition-metal complexes and ammonia or amines, with alkenes or carbon monoxide. The first pathway, which is plausible for an electron-rich metal center, involves an initial oxidative addition of the N–H bond to give an amide hydride. Subsequent insertion and elimination reactions with alkenes and carbon monoxide can lead to a range of nitrogen-containing products. The second pathway, which is much more commonly observed, is one which requires an electron-poor center. This latter pathway involves complexation of carbon monoxide or the alkene to this electrophilic metal center, followed by nucleophilic attack by the electron pair of ammonia or the amine at the coordinated ligand. Such a nucleophilic attack results in a two-electron reduction of the metal center. Copper salts and oxygen (Wacker conditions) present in the reaction mixture serve to reoxidize the metal back to its former high oxidation state. The coordinated ligands in these reactions are generally alkenes or carbon monoxide, and the reaction with the nitrogen nucleophile leads to the formation of a carbon–nitrogen bond.

Future work in this area will likely focus on incorporating high degrees of selectivity into these catalytic systems, and also in discovering new chemical reactions and reactivities that will present opportunities for the development of entirely different catalyst systems.

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