PREPARATION AND USE OF ALKALI METALS (Li AND Na) IN ALUMINA AND SILICA GEL AS REAGENTS IN ORGANIC SYNTHESES

By

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ABSTRACT

PREPARATION AND USE OF ALKALI METALS (Li AND Na) IN ALUMINA AND SILICA GEL AS REAGENTS IN ORGANIC SYNTHESES

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This work describes the development of alkali metals (Li and Na) encapsulated in silica and alumina gel (SG and AG), and their applications in organic syntheses. The methods elucidated involved the thermal incorporation of these metals into the pores of SG and AG, serving as solid-state reagents. The encapsulation method/approach addresses the problems associated with the high reactivity of these metals that limit their synthetic utility in research laboratories, pharmaceutical, and manufacturing industries. These problems include their sensitivity to air and moisture, pyrophoricity, difficulty in handling, non-commercial availability, and instability of some of the organoalkali metals reagents.

Herein, we describe the developments to synthesize alkali metal precursor (Li-AG) in solid form that offer safer organolithium reagents. This precursor reduces or eliminates the danger associated with the traditional handling of organolithium reagents stored in flammable organic solvents. The use of Li-AG to prepare and deliver organolithium reagents from organic halides and ethers, as needed especially for those that are commercially not available is put forward. In addition, exploration of additional applications of Na-SG and Na-AG reagents in the demethoxylation of Weinreb amides to secondary amines, and Bouveault-Blanc type reduction of amides to amines are described.

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Getting a doctoral degree in Chemistry had ever been my singular challenge in life. This was borne out of the admirations of what chemists are capable of doing in changing the universe around us. The path to this goal was quite apparently a hectic, foggy, and daring one. The challenge could have almost been impossible had it not been bolstered by the courage, inspiration, impetus and over and above all, my arduous resilience in putting together my efforts and energy to achieving this objective. Thus, translating this dream into reality could not have been achieved without the intervention of a good number of wonderful people.

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KEY TO ABBREVIATIONS

AG - Alumina gel

DSC - Differential scanning calorimetry

EtOAc - Ethylacetate

EtOH - Ethanol

HMDS - bis(trimethylsilyl)amine

HMPA - Hexamethylphosphoramide

i-PrOH - Isopropanol

$LiAlH_4$ - Lithium aluminum hydride

MeOH - Methanol

M-SG - Alkali metal in silica gel

SG - Silica gel

t-BuOH - Tertiary butanol

THF - Tetrahydrofuran

TMEDA N, N,N,N - Tetramethylethylenediamine

Chapter 1.0: The Discovery, Chemistry, and Reactions of Alkali Metals

1.1 Background

Alkali metals are well known for their high reactivity and chemical utility. The group comprises metals that have one electron in their outermost s-orbitals that proffers well characterized homologous behavior to all. These elements include lithium (Li), sodium (Na), potassium (K), rubidium (Rb), cesium (Cs), and francium (Fr). The last of the group, francium, has been less investigated since its isotopic forms are all radioactive with the longest-lived $^{223}Fr_{87}$ having a $t_{1/2}$ of 21 minutes.[1] The ns^1 valence electron configuration gives the group weak metallic bonding character, large atomic radii, and high thermal and electrical conductivity.[2] However, an amazing feature of these alkali metals observed in the past few decades, and for which current studies are on-going in our lab, is the observation that, with the exception of lithium, these metals also form the -1 oxidation state (M^-) under suitable reaction conditions.[3] These anions, known as alkalides, are often observed when crown ethers or cryptands form complexes with the cations.[4,5]

The alkali metals form compounds that are mostly ionic and water soluble. The metals themselves display high reactivity, and they are only found occurring as compounds in nature. The isolated metals are typically stored under oil to prevent their reaction with air and moisture. Lithium, sodium, and potassium are found mostly in rocks containing aluminosilicate minerals. These minerals are insoluble and under normal weathering conditions, release the alkali metal ions as soluble salts. In this soluble form, the alkali metals are washed into bodies of water.

In this chapter, some background information on the chemistries of the alkali metals is provided as a foundation for the ensuing chapters. Emphasis is placed on reactions regarding lithium, sodium, potassium, and their alloys with the goal of expanding our understanding of the potential

to explore their laboratory and industrial applications. Lastly, the research justification and aims and objectives are outlined.

1.1.1 The Discovery of Alkali Metals

The chemistry of the alkali metals has been investigated for centuries. Early in 1806 and 1807, an English chemist and physicist, Sir Humphry Davy, first isolated sodium and potassium metals by the electrolysis of molten caustic soda and potash respectively.[6] Arfvedson in 1817 identified lithium as an alkali metal in various silicate and mica minerals and named this metal after the Greek word for stone. However, Davy was the first to isolate lithium in 1818. Subsequently, the discovery of cesium (Latin name caesius for sky blue) in 1860 and rubidium (Latin name: rubidus for deep red) in 1861 by Bunsen and Kirchoff followed the development of atomic spectroscopy; with their names corresponding to the colors of their dominant spectral lines. These discoveries ushered in a huge research challenge and interest to 19th century scientists in their effort to understand the properties of these metals. Since then remarkable progress has been achieved that utilizes their reducing properties, low specific gravity, excellent heat transfer characteristics, and low vapor pressure at high temperatures. Consequently, a variety of new reactions and applications in catalysis has emerged. However, their high reactivity limits the utility of these metals in research and industrial laboratories. They are sensitive to air and moisture, and are sometimes pyrophoric, making them difficult to handle.

Lately, in the work that forms the background of this thesis research, alkali metals have been made safer by incorporating them into silica and alumina gels (M-SG and M-AG). This development has attracted the interest of researchers in Dr. Dye's group/SiGNa company, and much of the recent progress in the chemistries of the alkali metals has been focused on identification of better

alternatives to the pure elements and advances based on this underexploited encapsulation approach. For instance, Dye *et al*.,[7] reported the incorporation of sodium and lithium metals into alumina and/or silica gel as a safer handling procedure than direct use of the metals. The alkali metals have been absorbed into silica gel to form loose black powders (M-SG) that serve as strong reductants for both organic and inorganic compounds.[8–11] This development is noteworthy because while it addresses the issues of pyrophoricity and metal toxicity, the metal reducing properties are retained. Thus, the high reducing power of these metal-silica gel adducts permits their use in both batch and column-flow methods. In addition, these dry air-stable and easy-to-handle adducts have been used for hydrogen production from water.

1.2 Chemical and Physical Characteristics of Alkali Metal

The alkali metals are more like each other than any other group of elements in the periodic table. They are characterized by having electron configurations that consist of a single s orbital electron outside of a noble gas core (Table 1.1A). The gradual trend in properties of the alkali metals makes them the best example of elements in the periodic table with well-defined homologous behavior. However, limits of space and purpose confine this discussion to selected properties of these metals relevant for the reactivity of the metal in both their pure form and in silica and alumina materials.

1.2.1 Physical Properties of the Alkali Metals

Alkali metals (Li-Rb) are characterized by their soft texture and silvery appearance except for cesium, which has a golden color. All alkali metals have low melting point. Key physical properties of these metals are given in Tables 1.1A and 1.1B below.

Table 1.1A: Atomic and Related Properties of the Alkali

Metal	*Electronic configuration*	*Atomic number*	*Relative atomic mass*	*Metal radius (Å)*	*Ionization energies (KJ mol^{-1})*		*Electron affinity (KJ mol^{-1})*	*Electronegativity (Pauling scale)*
					1st	*2nd*		
Li	[He]2s^1	3	6.941	1.52	520.1	7296	59.8	0.98
Na	[Ne]3s^1	11	22.9898	1.86	495.7	4563	52.9	0.93
K	[Ar]4s^1	19	39.0983	2.27	418.7	3069	48.3	0.82
Rb	[Kr]5s^1	37	85.4678	2.48	402.9	2640	46.9	0.82
Cs	[Xe]6s^1	55	132.9054	2.65	375.6	2260	45.5	0.79

Source:[2] Encyclopedia of Inorganic Chemistry, 2006 by John Wiley & Sons, Ltd "Reproduced with permission from John Wiley & Sons"

Table 1.1B: Physical and Related Properties of the Alkali Metals

Metal	*Melting point (°C)*	*Boiling point (°C)*	*Density (g cm^{-3}, 20 °C*	*Electrical conductivity (10^4 Ω cm, 0 °C*	*Enthalpy of fusion (kJ mol^{-1})*	*Enthalpy of vaporization (kJ mol^{-1})*	*Covalent radius (Å)*	*Dissociation enthalpy of M_2 (kJ mol^{-1})*
Li	180.5	1326	0.534	11.8	2.93	148	1.34	108
Na	97.8	883	0.968	23.0	2.64	99	1.57	73
K	63.7	756	756	15.9	2.39	79	2.02	49
Rb	39.0	688	1.532	8.6	2.20	76	2.16	47
Cs	28.5	690	1.90	5.6	2.09	67	2.35	43

Source:[2] Encyclopedia of Inorganic Chemistry, 2006 by John Wiley & Sons, Ltd "Reproduced with permission from John Wiley & Sons"

These metals have low densities and high electrical conductivity.[2] Upon vaporization, each member of the group exhibits a characteristic flame color due to the ready excitation of the single

s^1 electron. Li is crimson, Na is yellow, K is violet, Rb is red–violet, and Cs is blue. The atomic radii of the alkali metals increase steadily with atomic number. These elements are the largest in their respective periods and have the lowest first ionization potentials relative to other members of the period. They form M^+ ions in the majority of compounds they form. The M^{2+} state is rarely formed because of their very high second ionization energies. The ease of formation of the M^+ ions makes bonding in alkali metal compounds ionic or significantly polarized. Lithium, the smallest and the least polarizable member of the group, displays the highest degree of covalence in its compounds.[12–14]

1.2.2 Chemical Properties of the Alkali Metals

Alkali metals are among the most reactive metals. The ns^1 valence electron common to the alkali metals makes their chemical properties very similar. They form compounds with all commonly encountered anions by losing this valence electron to the oxidants and thereby forming a uni-positive ion. The loss of the valence electron dominates the chemistry of these metals and makes them very good reducing agents. Consequently, an understanding of the chemistry of any one metal gives a general idea of the behavior of the other members.

1.2.2.1 Reactions with Hydrogen

The alkali metals react with hydrogen to form metallic hydrides (Equation 1.1); where the hydride anion acts as a pseudohalide.

$$2M + H_2 \xrightarrow{\Delta} 2MH \quad \text{..... Eq. 1.1}$$

All the hydrides adopt a face-centered cubic structure, and are used chiefly as reducing agents. The hydride anion is small and so the lattice energies of the group one metal hydrides are high. The

lattice energy decreases from LiH (where Li^+ has the smallest ionic size in the group) to RbH.[15] Evidence for the existence of H^- in these species came from the observation of a large increase in conductivity on melting, and the production of hydrogen at the anode upon electrolysis. The hydrides themselves react with water and other protic solvents to form the conjugate base in water, liberating hydrogen gas (Equation 1.2).

$$MH + H_2O \longrightarrow M^+ + \bar{O}H + H_2 \quad \text{..... Eq. 1.2}$$

1.2.2.2 Reactions with Halogens to form Halides

The alkali metals, being the most electropositive elements, form strong ionic bonds with the most electronegative nonmetals (halogens) in the periodic table (Equation 1.3). The most industrially important alkali metal halides are NaCl and KCl because of their respective uses as preservatives for meat, melting of snow ice, as plant fertilizers, and as starting materials in chemical syntheses.

$$2Na_{(s)} + Cl_{2\,(g)} \longrightarrow 2NaCl_{(s)} \quad \text{..... Eq. 1.3}$$

These metal halides are high melting, colorless crystalline solids. Their lattice energies decrease as the halogen atomic number increases, reflecting the effects of the halide ionic size and leading to variations in crystal packing arrangements. For instance, in CsCl, Cs^+ and Cl^- are comparable in size and therefore their crystal lattice is a body-centered cubic structure (bcc) with a coordination number of eight (8) for each ion. LiCl, on the other hand, is a size mismatched structure with a halide ion packing in a cubic close-packed lattice where the Li^+ occupies the octahedral holes, results in a mutual coordination number of 6.[2]

With the exception of lithium fluoride (LiF) which is only sparingly soluble in water due to its high lattice energy, all the alkali metal halide salts are soluble in water.[2] The high lattice energy for Li^+F^- is due to the electrostatic interactions between the two ions as a result of their small sizes among alkali metals and halogens.

1.2.2.3 Reactions with Oxygen and Other Chalcogens

The chalcogenides of the alkali metals are known and form compounds between elements of groups one (1) and sixteen (16). They form a variety of compounds showing varying catenation and oxidation states of the chalcogens, as well as cases where the metals exhibit formal oxidation states other than +1. The group forms an ideal example of elements influencing reaction route by their sizes and/or coordinating ability. Thus, monoxides with structures M_2O (example Li_2O, Na_2O), are the major products of burning Li and Na in air or oxygen (Equation 1.4).

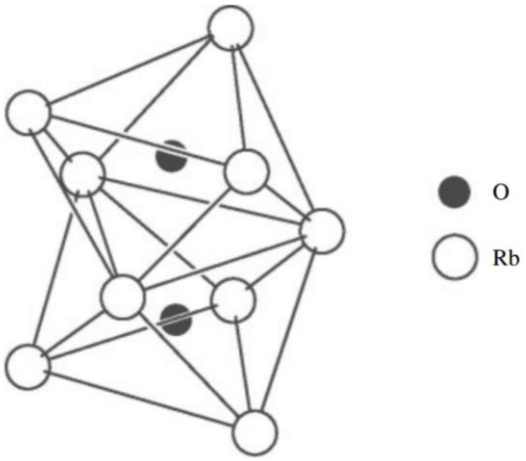
$$2M + 1/2O_2 \longrightarrow M_2O + Heat \quad \text{..... Eq. 1.4}$$

This reaction may be slow or spontaneous depending on the alkali metal involved and other factors such as temperature and water content in oxygen. For instance, sodium reacts readily with oxygen in air at room temperature to form a thick coating of the white oxide, Na_2O (equation 1.5). This reaction can ignite spontaneously if the temperature is raised to above 115ºC.

$$4Na + O_2 \xrightarrow[130 - 200\ ^\circ C]{\Delta} 2Na_2O \quad \text{..... Eq. 1.5}$$

The peroxides, M_2O_2 which contain the O_2^{2-} ion can be isolated, (examples are Na_2O_2, K_2O_2, Rb_2O_2), and the superoxides are all known.[16]

Also known are the stable sesquioxides, (M_2O_3) and the ozonides (MO_3) of the larger cations, as well as the suboxides, such as Rb_6O, Rb_9O_2, and Cs_7O. For example, Rb_9O_2 consists of two Rb_6 octahedra sharing a common face, each octahedron having a central O atom, as shown in Scheme 1.1 below.[2]



Scheme 1.1:[2] Structure of Rb_9O_2 "Reproduced with permission from John Wiley & Sons"

The alkali metal sulfides M_2S, selenides M_2Se and tellurides M_2Te are formed by the reaction of the metal in ammonia solution with sulfur and other chalcogenes.[13] They are susceptible to hydrolysis, and like H_2S, have a characteristic pungent smell after being hydrolyzed.

1.2.2.4 Reactions with Water

All alkali metals react violently with water to form the hydroxides, hydrogen gas, and heat (Equation 1.6).

$$2M + 2H_2O \longrightarrow 2MOH + H_2 + \text{Heat} \quad \text{..... Eq. 1.6}$$

In the presence of air or excess oxygen, for Na-Cs, this heat is sufficient to ignite the hydrogen gas and results in an explosion (Equation 1.7).

$$2H_2 + O_2 \longrightarrow 2H_2O \quad \text{..... Eq. 1.7}$$

1.2.2.5 Reactions with Carbon Dioxide

Alkali metals react with carbon dioxide to form the carbonates, Equation 1.8

$$2M + 2CO_2 \longrightarrow M_2CO_3 + CO \quad \text{..... Eq. 1.8}$$

This reaction, though complex, can be simplified as shown in Equations 1.9 and 1.10 below:

$$2M + CO_2 \longrightarrow M_2O + CO \quad \text{..... Eq. 1.9}$$

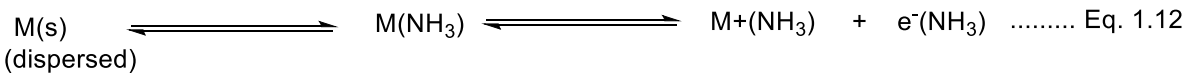
$$M_2O + CO_2 \longrightarrow M_2CO_3 + CO \quad \text{..... Eq. 1.10}$$

The resulting alkali metal carbonates can exist in a variety of hydrated forms. For example, sodium carbonate forms hydrates $Na_2CO_3(H_2O)_x$ (x = 1, 7, 10). All the carbonates undergo thermolysis (Equation 1.11).

$$M_2CO_3 \xrightarrow{\Delta} M_2O + CO_2 \quad \text{..... Eq. 1.11}$$

1.2.2.6 Reactions with Liquid Ammonia and Organic Solvents

The alkali metals are strong reducing agents when dissolved in solutions of liquid ammonia and some organic solvents such as ethers, organic amines, and hexamethylphosphoramide (HMPA). For instance, Edwards in 1982, and other groups much earlier than in the 1980s, reported that, in dilute solutions of liquid ammonia, the metals (M) ionize to give the ammonia solvated M^+ cations and electrons (Equation 1.12). The electrons occupy cavities in the liquid.[2,17,18]



..... Eq. 1.12

The cavities result from displacement of two or three ammonia molecules which occurs as a result of repulsion between the solvated electron and the electron composing these solvent molecules. This explains the lower densities, high conductivity, and paramagnetism of these solutions as compared to liquid ammonia itself. However, at higher concentrations, the solutions undergo Mott's insulator-metal transition. (Note: Mott's insulator transitions are transitions from metal, with good electrical conductivity to an insulator which is made of materials where conductivity of charge can be quickly suppress.)

1.2.2.7 Reactions with Alcohols

Alkali metals react with alcohols to form the alkali metal alkoxide and liberate hydrogen gas (Equation 1.13).

..... Eq. 1.13

The reaction rate decreases as the molecular weight of the alcohol increases. The final temperature of the reaction mixture also decreases with increasing weight ratio of alcohol to metal. This reaction is used in laboratory practice to get rid of residues of reduced alkali metals in solvent stills and related reaction glassware.

1.2.2.8 Reactions with Group 15 Elements

(Alkali metal Nitrides, Phosphides, Arsenides, Antimonides, and Bismuthides)

Alkali metals react with group fifteen (15) elements to give the nitrides, phosphides, arsenides, antimonides, and bismuthides. The most stable of these compounds is Li_3N, which forms spontaneously from the elements at room temperature (Equation 1.14).[19] It reacts with water to form the hydroxide (LiOH) and ammonia (NH_3) (Equation 1.15). The heavier nitrides were only reported recently when Fischer and M. Jansen isolated Na_3N.[20]

$$6Li + N_2 \longrightarrow 2Li_3N \quad \text{..... Eq. 1.14}$$

$$2Li_3N + 3H_2O \longrightarrow 3LiOH + NH_3 \quad \text{..... Eq. 1.15}$$

Alkali metal phosphides with varying stoichiometries have been synthesized. Examples of the lighter elements are K_3P to Rb_2P_5 to Cs_4P_6, NaP_5, Na_3P_{11}, Na_3P_{21}, Li_2P_{16}, Li_3P_{21}, Na_3Bi and NaBi.[21, 22]

1.2.2.9 Alkali Metal Carbides

Alkali metals form two types of compounds with carbon: acetylene derivatives M_2C_2, often synthesized by reaction in Equation 1.16, and graphite inclusion compounds.[2]

$$C_2H_2 + 2M \longrightarrow M_2C_2 + H_2 \quad \text{..... Eq. 1.16}$$

The stability of the carbides is attributed to stabilization of negative charge in the low-lying sp-hybridized carbon orbitals, paired with the alkali metal cations. While lithium forms only one stable carbide (Li_2C_2), sodium and potassium form polycarbides, (NaC_3, NaC_{16}, KC_3, KC_{16} or KC_9 and KC_{19}). Potassium carbide (K_2C_2), though known, is formed with difficulty. Rb and Cs form polycarbides only (MC_3 and MC_{16}).[2] The C_2 carbides react with moisture to liberate acetylene

gas.[2] Among lithiated carbides, methanides have been most widely studied due to their volatility, with spectroscopic and calculated data are available in the literature for CLi_6, CLi_3, and C_2Li_4.[2,23]

1.2.2.10 Alkali Metal Borides

The borides are those compounds comprising alkali metal and boron only. They can be prepared by directly reacting the elements, at temperature between 750 to 1200 ℃ (Equation 1.17).[24]

$$M + XB \xrightarrow[750 - 1200\ ^\circ C]{\Delta} MB_X \quad (M = Li, Na, K) \quad \text{..... Eq. 1.17}$$

The best-known examples of such compounds are the MB_6 borides, having an interconnected cubic lattice structure of octahedral B6 with the alkali metal atom at the center of each cube. An example is NaB_6.[25] No borides of potassium, and rubidium have been reported.

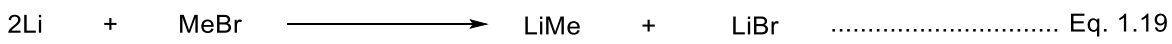
1.2.2.11 Alkali Metal Borates

The most common of this class of compounds is borax, $Na_2B_4O_7{\cdot}10H_2O$, which is prepared by boiling boric acid with sodium carbonate (Equation 1.18). It is used as an alkaline buffer, in glass manufacture, and in fire retardants. It reacts with H_2O_2 to form the perborate; $Na_2[B_2(O_2)_2(OH)_4]{\cdot}6H_2O$, which is used as a bleach in washing powders.[2,26] However, this washing powder is not so much in use anymore due to the growing use of liquid detergents.

$$4H_3BO_3 + Na_2CO_3 \longrightarrow Na_2B_4O_7 + 6H_2O + CO_2 \quad \text{..... Eq. 1.18}$$

1.2.2.12 Organometallic Compounds of Alkali Metals

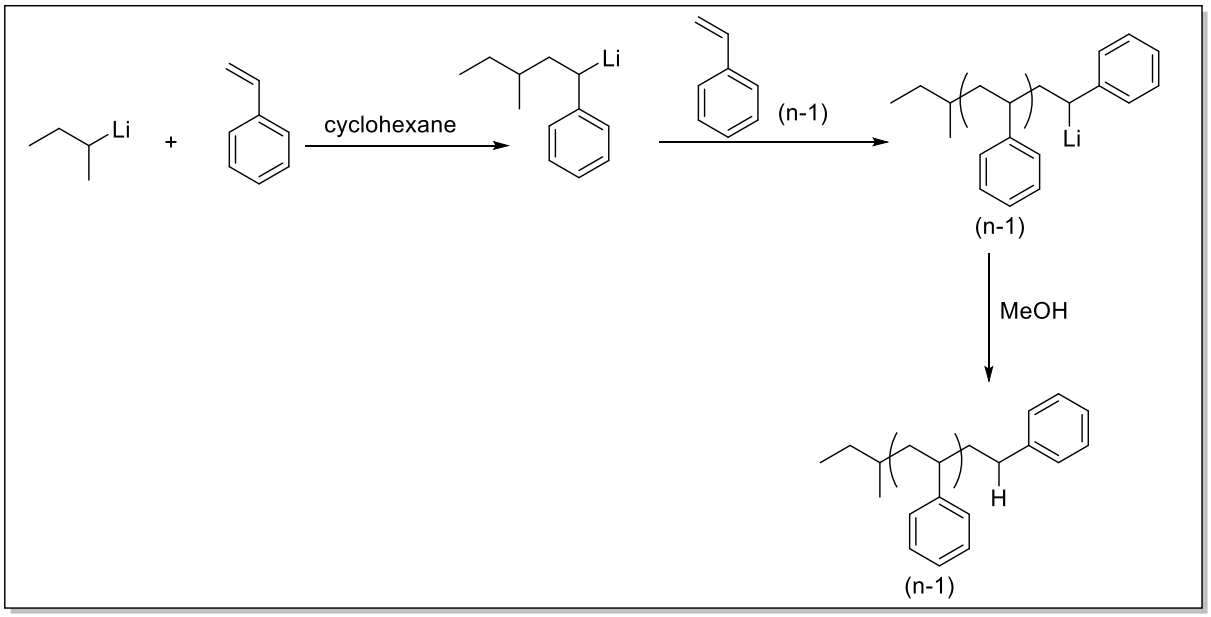
Organometallic compounds of alkali metal are compounds with an alkali metal directly bonded to a carbon atom of an organic substituent. They possess properties that differ completely from those of the metal and/or the organic substituent. The covalent organolithium compounds are by far the most stable and best-known group 1 organometallic compounds. Alkyllithium compounds, such as butyllithium, are especially significant for their uses in organic syntheses, which in turn has prompted detailed structural and spectroscopic characterization. An especially well known and characterized example is methyllithium ($LiCH_3$) (Equation 1.19).



..... Eq. 1.19

Though the carbon-lithium bond is covalent, its electron density is strongly enough polarized towards the carbon atom to make organolithium species capable of effective delivery of a carbanion. This makes organoalkali metal reagents strongly basic and nucleophilic.[27]

Organoalkali compounds are important reagents in organic synthesis. They react chiefly by nucleophilic addition or deprotonation, resulting in the transfer or introduction of organic moieties or alkali atoms to substrates. Organolithium reagents are used in industry as initiators of anionic polymerization as seen in the example shown in Scheme 1.2.[28 29]



Scheme 1.2: Initiation of anionic polymerization by organolithium reagent.[29]

These compounds have also found extensive use in metathesis (Equation 1.20) and transmetallation processes (Equation 1.21) for the synthesis of other organometallic compounds.

$$R{-}Li + R'{-}X \longrightarrow R{-}X + R'{-}Li \quad \text{..... Eq. 1.20}$$

$$R{-}M + n\text{-BuLi} \longrightarrow R{-}Li + n\text{-BuM} \quad \text{..... Eq. 1.21}$$

Note: Where X is alkyl halide and M is a metal.

1.3 Other Reduction Reactions with Aromatic Organic Compounds

Generally, alkali metals are very good electron donors, owing to the ease with which they can lose their ns^1 valence electron to form alkali metal cations. This electron is often solvated in a liquid ammonia or amine reaction medium and forms the ultimate reducing species. This makes reduction the most widely known reaction of alkali metals, and over the years, has enabled the efficient

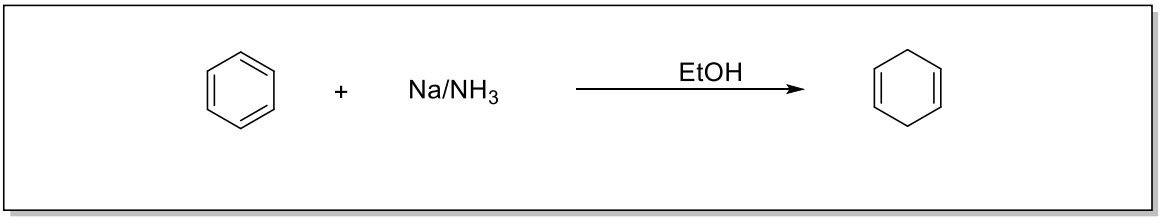
reduction of diverse organic functional groups. The alkali metals are usually employed in their pure metallic or in dissolved forms, such as in liquid ammonia.

1.3.1 Reduction of Carbon-Carbon Multiple Bonds of Aromatic Hydrocarbons

Alkali metals in liquid ammonia serves as useful reducing reagents for the conversion of aromatic compounds, into partially unsaturated six-membered rings.[30–37] This is known as the Birch reduction.[32,31] This reaction was first discovered by the Wooster group,[38] but credit was given to A. J. Birch for his significant contributions in developing the method. Most commonly, reduction of aromatic hydrocarbons has been achieved by using this method. By modifying the experimental conditions, this reduction, which involve multiple stages, can be directed to maximize the yield of a single product.[30] Generally, electrons add to the aromatic compound either individually or in pairs to form mono and dianions respectively, with sequential protonation either after the addition of each electron or both electrons. However, unlike reduction of polycyclic aromatic compounds, which undergo facile electron addition to give the radical anions or dianions in the absence of proton sources, reduction of monocyclic aromatics is often problematic. Over the years, reduction of such aromatics has been performed by conducting the reaction in the presence of proton sources such as alcohols.

The Wibaut[39] and Hückel[40] groups independently converted benzene into 1,4-cyclohexadiene by using sodium metal in liquid ammonia and ethanol. Here, the ethanol is slowly added into a solution of the aromatic compound and sodium metal in liquid ammonia after a suitable interval to afford the product (Scheme 1.3).[30,39,40] Also, Hückel in a further study, reduced fused polycyclic aromatics in a single stage. These studies found that naphthalene reacts with sodium in liquid

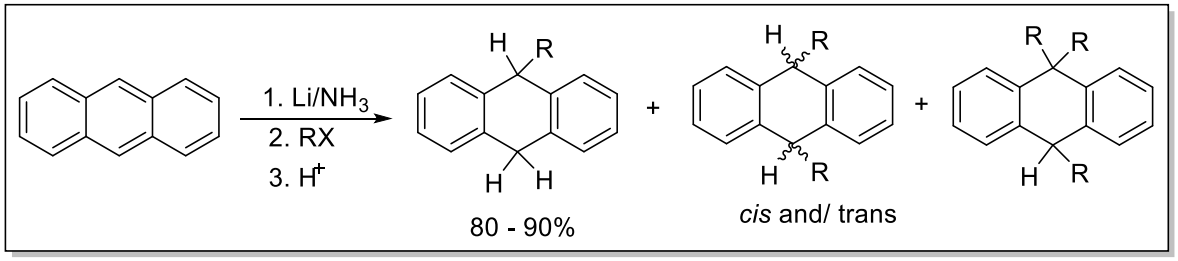
ammonia to give a red complex which undergo protonation in the presence of methanol as the proton source to give 1,4-dihydronapthanlene as the reduction product (Scheme 1.4).[41,42]



Scheme 1.3: Reduction of 1,4-cyclohexadiene using sodium in liquid ammonia.[30,39,40]

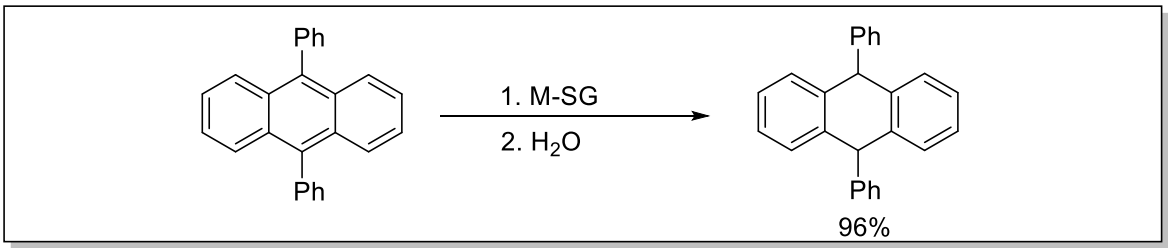
Scheme 1.4: Reduction of naphthalene using sodium in liquid ammonia.[41,42]

Reduction products can undergo further modification. For instance, alkyl groups have been introduced into the reduced product by adding alkyl halides to the metal ammonia solution of polynuclear aromatic compounds before the addition of a proton source.[43] However, the number of alkyl groups introduced varies with the reaction conditions. For example, anthracene provides mono-, di-, and trialkylated products under the reaction conditions shown in Scheme 1.5.[43,34]



Scheme 1.5: Reduction and alkylation of anthracene to form a mixture of mono-, di-, and trialkylated products.[43,34]

In 2009, our lab reported the Birch reduction of polyaromatic hydrocarbons by sodium encapsulated in silica gel (M-SG) at room temperature. This reduction is remarkable in the sense that the transformation proceeded under ammonia-free conditions in the absence of alcohol. This alcohol-free transformation afforded excellent yields with high reduction selectivity for the polyaromatics (Scheme 1.6).[8]

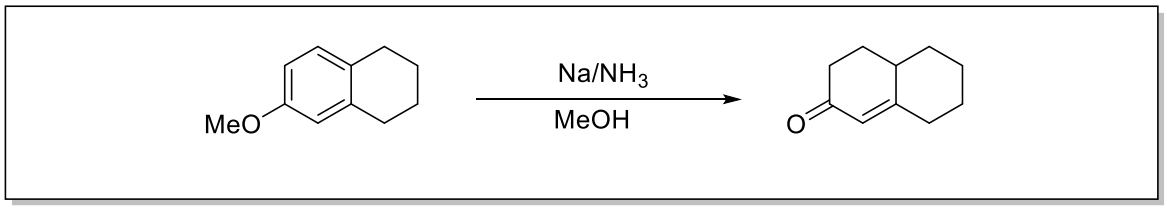


Scheme 1.6: Birch reduction of polyaromatic hydrocarbon using M-SG.[8]

1.3.2 Reduction of Carbon-Carbon Multiple Bonds of Aromatic Ethers

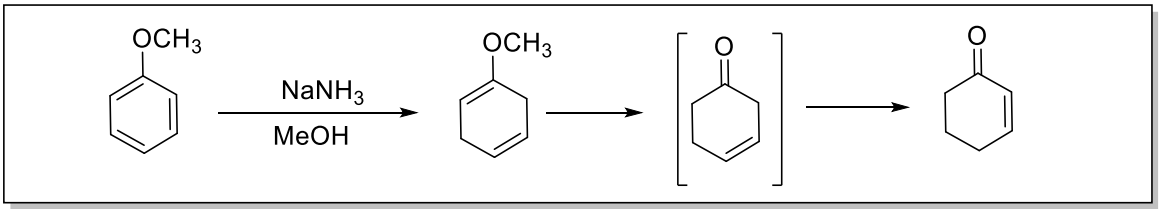
As stated earlier, alkali metal-ammonia solutions are typically a solution of metal cations and solvated electrons. They are therefore expected to effect reduction by electron addition (Equation 1.12). Based on this phenomenon, aromatic ethers have been successfully reduced to ultimately form carbonyl compounds. For example, 5-methoxytetralin has been transformed into the enone in the presence of sodium/ammonia solution, followed by the addition of methanol (Scheme 1.7).[32]

However, a limitation to this approach involved the partial or complete loss of the alkoxy group from the starting materials, especially when this group is para to an activating substituent.



Scheme 1.7: Reduction of 5-methoxytetralin using sodium in liquid ammonia.[32]

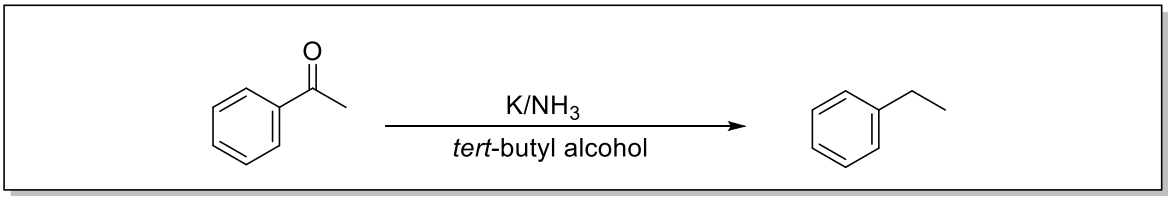
In 1938, Wooster obtained the dihydro-reduction products of anisole and its derivatives by selective aromatic double bond reduction using sodium (with methanol as the proton source) in liquid ammonia (Scheme 1.8).[44] In addition to the dihydro-reduction product, which was obtained as a mixture with some unreacted starting material, the demethylated product (i.e. phenol) was obtained as a minor product. The presence of the dihydro-derivatives was proven upon treatment of the product mixture with hot dilute mineral acid to afford the α, β-unsaturated ketones. In a similar reaction, 3-methylanisole afforded 3-methyl- Δ^2-cyclohexenone.



Scheme 1.8: Reduction of anisole using sodium in liquid ammonia.[44]

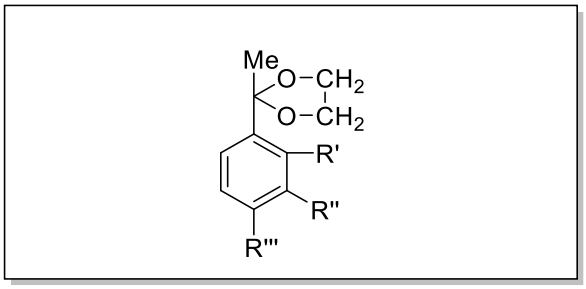
1.3.3 Reduction of Carbon-Carbon Multiple Bonds of Aromatic Carbonyls

In metal-ammonia reduction of aromatic ketones, the site of reduction is either at the aromatic nucleus (Birch type reduction) or at the carbonyl carbon.[45,46] For instance, reduction of acetophenone with potassium/ammonia in the presence of tert-butyl alcohol gave ethylbenzene or its nuclear reduction product depending on the reaction condition, Scheme 1.9 presents the formation of ethylbenzene.[47]



Scheme 1.9: Reduction of an aromatic ketone using potassium in liquid ammonia.[47]

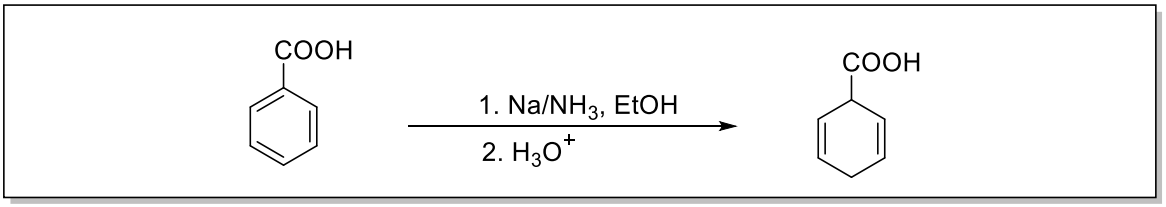
This reaction proceeds by formation of potassium enolate which can be prepared by a simple metathesis in liquid ammonia between acetophenone and the potassium salt of a very weak acid (such as tert-butanol). The tert-butyl alcohol acts as proton source in the subsequent reduction with potassium. Further, to reduce the aromatic ring without reduction of the carbonyl, some protection is required. For instance, in addition to other known methods for obtaining aromatic reduction product of substituted carbonyls, Birch and Robinson, in an unpublished report in the early 1940s, postulated that 2-acetylcyclohex-2-enone can be obtained from the Birch reduction of a suitable aromatic carbonyl precursor. Compounds of this nature are suitable for this purpose because they possess the appropriate substituent bearing an oxygen functionality ortho to it. In this configuration, the sodium-liquid ammonia-alcohol reagent is prevented from attacking the carbonyl group in the resulting equilibrium. Also, in the reduction of acetophenone to obtain a Birch type product, the carbonyl group can be protected using cyclic ethylene ketals/dioxolanes (structure below, Scheme 1.10).[47]



Scheme 1.10: Cyclic ethylene ketal.[47]

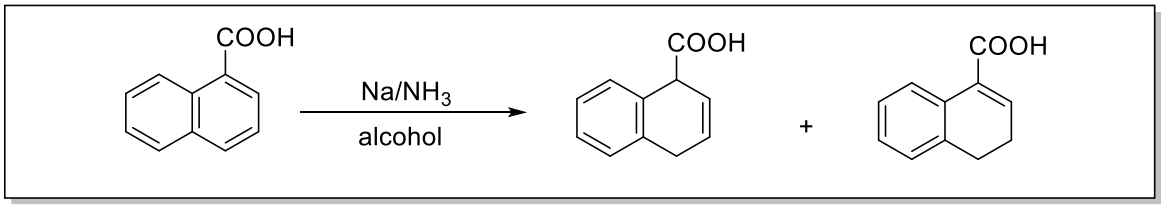
1.3.4 Reduction of Carbon-Carbon Multiple Bonds of Aromatic Carboxylic Acids

Birch reduction of aromatic carboxylic acids has been particularly useful not only for the reduction of carboxylic acids but also for the synthesis of 1,4-cyclohexadiene derivatives. The reaction is often complex and at some stages, may involve the isomerization and/or reduction of products that are prone to further reduction under given reaction conditions. This problem was overcome in 1978, when Rabideau *et al.*, improved on the reduction technique by introducing an inverse quenching technique which minimized the effect of the excess alkali metal used.[48] This technique has been successfully applied to the synthesis of 1,4-dihydro-1-naphthoic acid from 1-naphthoic acid.[49] While the Birch reduction of benzoic acids mostly gives high yields of the diene acid, 1,4-dihydrobenzoic acid (Scheme 1.11),[34,50] the reaction with polynuclear or polycyclic aromatic carboxylic acids is often complicated[51] because of challenges due to subsequent isomerization and or overreduction.



Scheme 1.11: Birch reduction of benzoic acids using sodium in liquid ammonia.[34,50]

However, reduction is easy when the carboxyl group is located on a carbon of high electron density in the parent hydrocarbon.[50] For example, reduction of 1-naphthoic acid gives a mixture of 1,4-dihydro- and 3,4-dihydro-naphthoic acid in the presence of an alcohol, with 3,4-dihydro-naphthoic acid as the major product. But with ammonium chloride as the proton source, 1,4-dihydro-1-naphthoic acid becomes the exclusive product.(Scheme 1.12).[49,52]



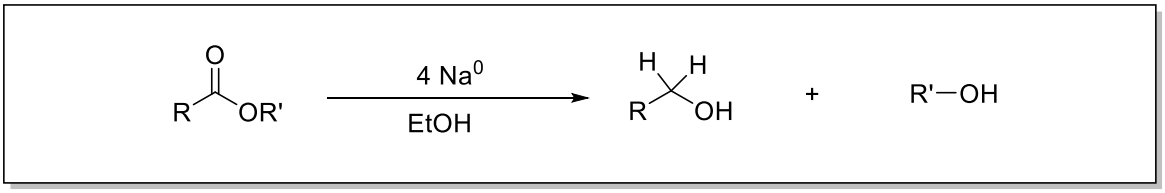
Scheme 1.12: Reduction of 1-naphthoic acid using sodium in liquid ammonia.[49]

1.3.5 Reduction of Carbon-Carbon Multiple Bonds of Aromatic Esters

The Bouveault-Blanc reduction (Scheme 1.13)[53–55] is one of the techniques for the reduction of esters. However, dangers associated with the handling of alkali metals and the harsh reaction conditions employed posed some limitations on the utility of the technique. Alternative approaches involving the use of metal hydrides such as lithium aluminium hydride and sodium borohydride have been used lately while progress in devising techniques that can make alkali metals stable and safe were ongoing in some laboratories.

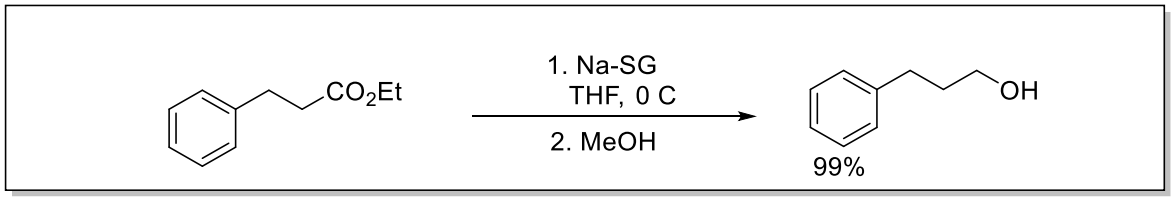
As with modern metal hydride reduction method, the Bouveault-Blanc reductions have been applied at industrial scales, but have been limited by the possible foaming and/or fires that may result from their use. Today, the classical Bouveault-Blanc reduction has been modified, using techniques developed by the Dye group, such as the work of Bodnar and colleagues at SiGNa Inc,[56] have reported improved version that afforded better yields of primary alcohols from the

corresponding aliphatic esters. As a result, alkali metals and proton sources should be able to effect reduction of esters to alcohols on an industrial scale using milder reaction conditions and faster reaction rates.



Scheme 1.13: Bouveault-Blanc reduction of an ester to alcohol.[53–55]

As a major effort of the Dye group, alkali metals have been encapsulated into nanostructured porous oxides to reduce the dangers associated with their handling while retaining their reducing power.[7] In silica gel, sodium or sodium-potassium alloys (Na-SG, Na_2K-SG, and K_2Na-SG) are free-flowing solid powders that have been successfully used in a number of important transformations including Birch reduction[8] and desulfonation[10] under ambient conditions. For instance, Bodnar *et al.*,[56] in their efforts to perfect the Bouveault-Blanc approach for the reduction of esters, used sodium encapsulated in silica gel (Na-SG), together with methanol as the proton source. The free-flowing Na-SG powder is non-pyrophoric, effecting complete conversion in times as short as 5 minutes (Scheme 1.14), with significantly simpler workups than are required for more conventional lithium aluminum hydride reductions.[56]



Scheme 1.14: An improved Bouveault-Blanc reduction of ester to alcohol.[56]

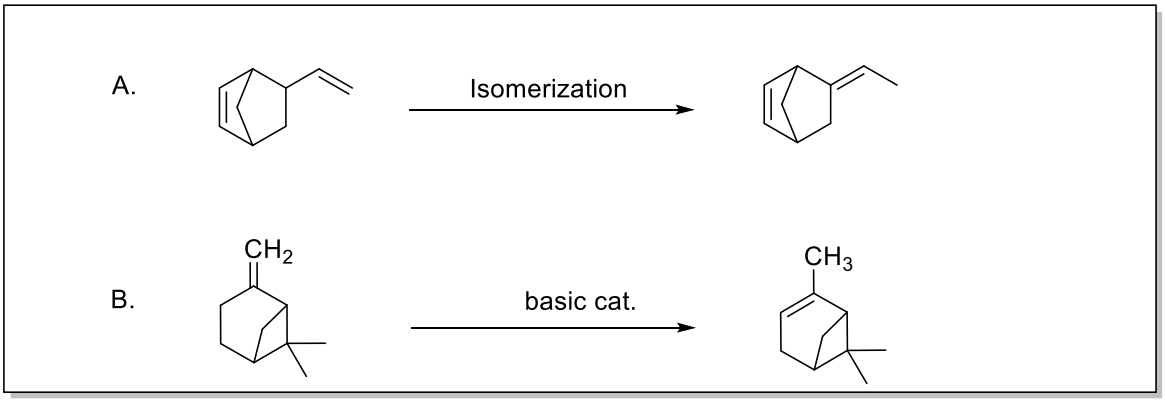
Contrary to the aliphatic esters, conversion of aromatic esters under dissolving metal conditions can be demanding due to the potential competition between reduction of the carbonyl and that of the aromatic nucleus. In the reduction of esters to primary alcohols, the substrate is either dissolved in alcohol followed by the rapid addition to a mixture containing sodium metal in an inert solvent. In either case, complete conversion of the ester is achieved when the sodium metal and alcohol are mixed quickly.

1.4 Catalytic Reactions

The majority of industrially relevant chemical processes involve catalysis. Alkali metals are well known as effective promoters of important industrial processes or reactions. For instance, alkali metals have been used extensively as catalysts to accelerate steam gasification of carbon or coal into syngas.[57–62] Unlike the conventional transition metals which do not promote such gasification processes alone, alkali metals do, enhancing throughputs, and lowering reaction temperatures. The most effective catalysts are generally the alkali metal carbonates.

Another important industrial role of alkali metal catalysts is in the manufacture of ammonia used as fertilizers and industrial feedstocks.[63] The rate of ammonia synthesis over ruthenium catalysts was found to increase significantly when the former was employed as a promoter.[64–68] However, the catalytic activity was found to increase with decrease in the ionization potential of the alkali metal in the order Na < K < Cs.[64] The promoter action is due to a charge transfer from the alkali metal to the transition metal catalyst, which raises the electron density at the transition metal, leading to a favorable state for the reductive activation of nitrogen.

Also, sodium-coated metal oxide catalysts (such as Al_2O_3, SiO_2, MgO, and TiO_2) and sodium-potassium alloy have been used for the isomerization of the double bond of 5-vinyl-2-norbornene (VND) to 5-ethylidene-2-norbornene (ENB), (Scheme 1.15A)[69–71] Alkali superbases are also known to be effective for such transformations.[72–76] One such reaction is the isomerization of beta-pinene to alpha-pinene by potassium superbase on γ-alumina surface (Scheme 1.15B).[72]



Scheme 1.15: Examples of catalytic reactions using alkali metal.[70–72]

1.5 Applications in Organometallic and Inorganic Synthesis

Since alkali metals are highly sensitive to air and moisture, they must be handled in inert atmospheres. Thus, organoalkali metal compounds must also be synthesized and handled under similar conditions.[77] Organolithium compounds have been more widely used than the other organoalkali compounds. In 1917, organolithium compounds were first synthesized by Schlenk and Holtz[78] and since then they have been extensively used in carbon-carbon bond formation and also as precursors for the preparation of other organometallic reagents.

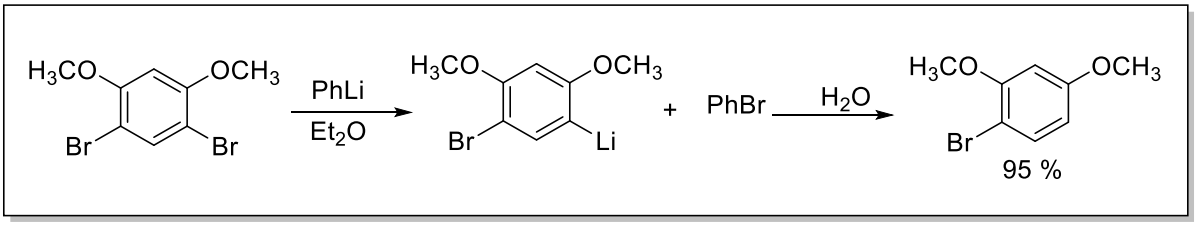
1.5.1 Preparation of Organolithium Reagents

Organolithium reagents are compounds with an organic group bonded to a lithium atom. They are well known for their reactivity and have long been reagents of choice for synthesis in organic chemistry. As noted earlier, Lithium (Li) is much more electropositive than carbon, so that a Li-C bond has most of its charge density on the carbon atom, effectively making it a carbanion. This polarization enables organolithium reagents to act as a powerful bases and nucleophiles.[6]

In general, these reagents are prepared in four major ways; lithium-halogen exchange,[1,6,8,9], direct metalation via deprotonation,[1,10] transmetalation, [1,6] and reaction of metallic lithium with organic halides.[1,8]

1.5.1.1 Lithium-Halogen Exchange

Lithium-halogen exchange was first described by Wittig *et al.* in 1938.[79] The initial report involved the treatment of 4,6-dibromo-1,3-dimethoxybenzene with phenyllithium in diethyl ether, resulting in the formation of 4-bromo-1,3-dimethoxybenzene in 95% yield (Scheme 1.16)



Scheme 1.16: Lithium-halogen exchange[79]

Basically, the organic halide R-X interacts with the organolithium reagent R'-Li by metathesis, exchanging the lithium and halogen atoms to produce a new organolithium reagent (Equation 1.22)

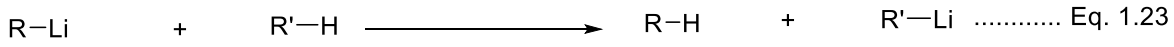
$$R{-}Li + R'{-}X \rightleftharpoons R{-}X + R'{-}Li \quad \text{..... Eq. 1.22}$$

The process is a reversible reaction, and the equilibrium favors the forward direction if the newly formed organolithium reagent (R`Li) is a weaker base than the starting organolithium (RLi). In other words, the reaction proceeds in the direction that forms the most stable organolithium reagent or the one derived from the more acidic organic compound. The method is most suitable for exchanges between C_{sp}^3-Li (stronger base) and C_{sp}^2-X to give the weaker base C_{sp}^2-Li alkenyllithium and C_{sp}^3-X.[80–82] Lithium-halogen exchange is also favorable for the formation of vinyl-,[83,84,] cyclopropyl-,[85–87] and aryllithium[82–84,88–91] by treatment of the corresponding organic halide with a more reactive alkyllithium.

Formation of organolithium reagents by halogen-metal exchange is a fast reaction, and is often carried out at – 60 ℃ to - 20 ℃.

1.5.1.2 Direct Metalation via Deprotonation

Direct metalation, commonly referred to as lithium-hydrogen exchange or simply lithiation, involves proton abstraction to form a new organolithium reagent (Equation 1.23).

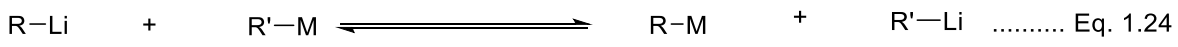


..... Eq. 1.23

In general, the position of lithiation is determined by the relative acidity of the available hydrogen and the directing effect of substituent groups.[82] Benzylic and allylic hydrogens are relatively reactive toward lithiation because of the resonance stabilization of the resulting anions. Lithiation may also be promoted by appropriately positioned heteroatomic substituents.[92] Also, the Scocum,[73] Khaldi[74], and Collum[75] groups have independently demonstrated that lithiation can be accelerated by adding tertiary amines, such as N,N,N,N-tetramethylethylenediamine (TMEDA).[93–95]

1.5.1.3 Lithium-Metal Exchange (Transmetalation)

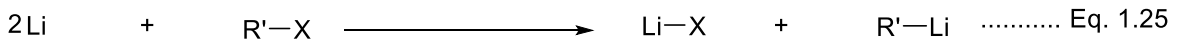
This method is commonly used for preparation of allylic, benzylic, and propargylic organolithium reagents that are difficult to synthesize by other methods. Generally, two organometallic compounds interact, one of which is an organolithium. The most common exchange occurs between organotin and alkyllithium reagents. The reaction proceeds in the direction that associates the more electropositive metal with the more acidic carbon (Equation 1.24).[82]



..... Eq. 1.24

1.5.1.4 Reaction of Metallic Lithium with Organic Halides

Most organolithium reagents can be prepared by reaction of an organic halide with lithium metal (Equation 1.25). This method has been traditionally used to synthesize alkyl, aryl, and alkenyllithium reagents.



..... Eq. 1.25

In some cases, finely divided lithium powder is used directly alone or with a catalytic amount of an aromatic hydrocarbon, such as naphthalene, 4,4′-di-tert-butylbiphenyl (DTBB), or N,N-dimethylaniline (DMA) has been used as catalyst.[96–98]

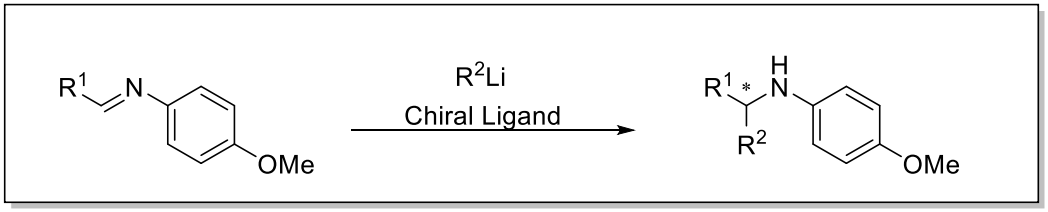
1.5.2 Application of Organolithium Compounds in Organic Synthesis

Organolithium compounds are among the most frequently used reagents in organic synthesis because of their properties as strong bases,[3] powerful nucleophiles,[3] efficient reducing agents, and effective catalysts for initiating anionic polymerizations.[4,5] They are generally used in carbon-

carbon and carbon-heteroatom bond formation processes such as alkylation, additions to carbon-heteroatom double bonds, opening of epoxides, and conjugate additions.

1.5.2.1 Addition to Carbon-Nitrogen Multiple Bonds

Addition of organolithium reagents to C=N bonds of imines and their derivatives is well-known, but this addition over the years has been limited by the poor electrophilicity of the imine carbon atom. Recently however, the use of stoichiometric or catalytic amount of a chiral ligand/catalyst has been developed, resulting in the synthesis of optically active amines.[99–103] This strategy is important because the chiral ligand can be recovered and reused without change in its activity. The optically active amines are important intermediates in organic synthesis and are used in production of pharmaceutically useful compounds. In 1990, Tomioka *et al.*, first reported the stoichiometric and catalytic asymmetric 1,2-addition of organolithium reagents to *N*-aryl imines, mediated by an external ligand (Scheme 1.17).[104]

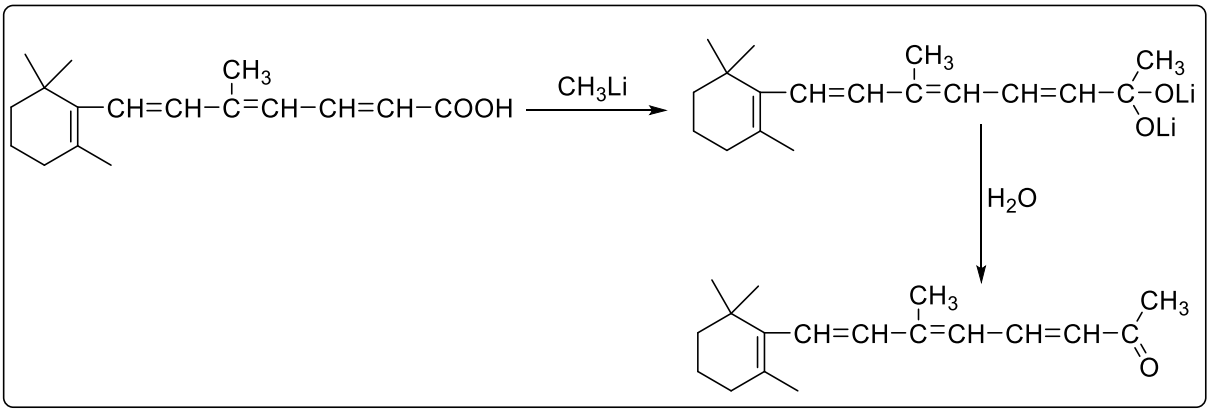


Scheme 1.17: Addition of organolithium reagents to carbon-nitrogen multiple bond.[104]

1.5.2.2 Addition to Aldehydes, Ketones, and Carboxylic Acid

Nucleophilic addition of organolithium reagents to carbonyl compounds is one of the fundamental carbon-carbon bond-forming reactions in organic synthesis. These reagents afford 1,2-addition products on reaction with aldehydes and ketones to give alcohols.

The reaction of carboxylic acids and organolithium reagents constitutes a direct preparative route for the synthesis of ketones. The chemical utility of this method dates as far back as 1933, when Gilman and Van Ess[105] showed that carbonation of phenyllithium formed benzophenone in 70% yield. Preparation of methyl ketone by direct reaction of methyllithium with carboxylic acids has been of great use in synthetic organic chemistry.[106,107] For instance, vitamin A has been prepared by reaction of methyllithium with *β*-ionylidenecrotonic acid to yield the intermediate ketone on hydrolysis, (Scheme 1.18).[108, 109]

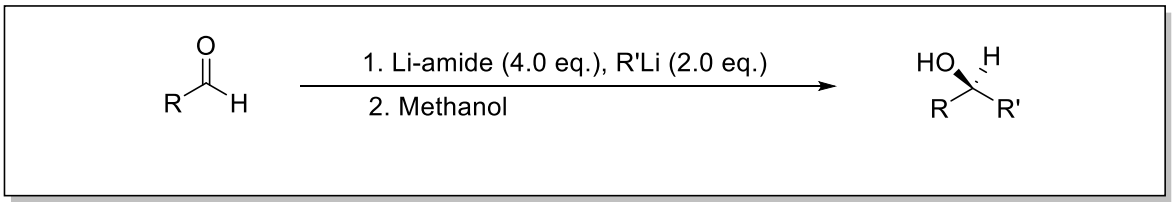


Scheme 1.18: Addition of organolithium reagent to carboxylic acid.[108, 109]

Although the reaction of organolithium reagents with carboxylic acids serves as a procedure for the synthesis of ketones, poor yields are usually reported for *α*, *β*-unsaturated carboxylic acids. Mixtures of the ketone, and the acid resulting from double deprotonation of the starting material as well as a small amount of the conjugate addition product are obtained.[110]

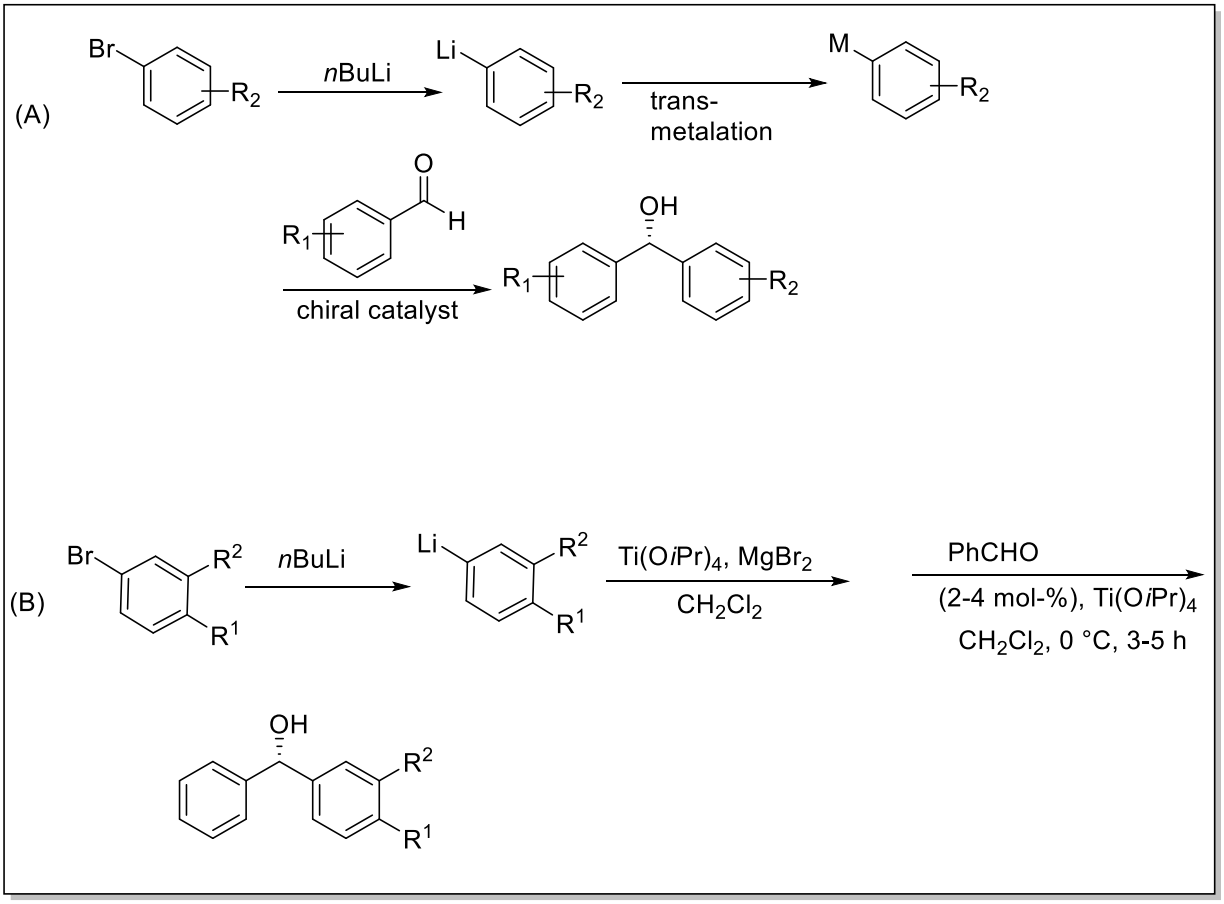
Enantioselective addition of organolithium reagents to aldehydes and ketones is of great interest in the pharmaceutical industries.[111,112] They are the reagent of choice because of their reactivity, ready availability, and low cost.[113,114] However, in addition to their strong basicity, their high reactivity also limits their applications in enantioselective catalysis[115–118] because it leads to loss

of chemo-, regio-, and enantioselectivity.[119] Measures to decrease such loss involve the addition of stoichiometric amount of chiral ligand, or catalyst, conducting the reaction at low temperature, (Scheme 1.19)[120–124] and/or applying strategies to lessen the reactivity through transmetalation.



Scheme 1.19: Enantioselective 1,2-addition of organolithium reagents to aldehyde mediated by chiral lithium amide.[124]

Similarly, alkyllithium has been transmetalated to less reactive species in the presence of a catalytic amount of a ligand for subsequent enantioselective reactions. For instance, Nakagawa and Salvi's have independently reported the transmetalation of aryllithium to organozinc[125] and organomagnesium[126] compounds for subsequent addition to aldehydes in the presence of N,N,N,N-tetraethylethylethylenediamine (TMEDA) or titanium tetraisopropoxide respectively (Scheme 1.20).[126]

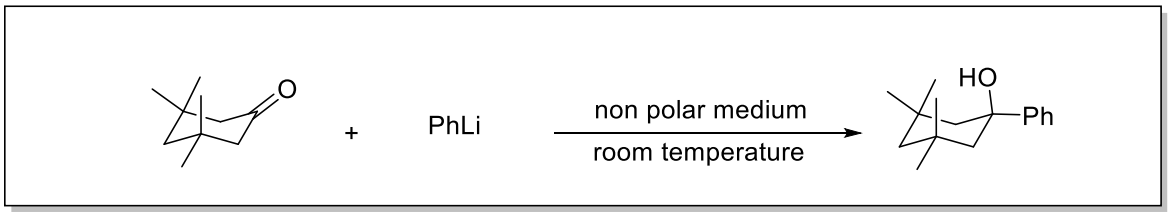


Scheme 1.20: Catalytic enantioselective arylation of aldehyde through transmetalation.[126]

Also, Harrison-Marchand *et al.*, in 2011 reported the first substoichiometric use of a chiral ligand for the enantioselective addition of methyllithium to o-tolualdehyde.[122]

Addition of organolithium reagents to hindered and or enolizable ketones sometimes was slow or was accompanied by competing side reactions. However, this difficulty has been lately addressed with the development of methods that either reduce the basicity or increase the nucleophilicity of the organolithium complex, through transmetalation. For instance, Lecomte *et al.*, have demonstrated the efficient addition of phenyllithium to hindered and or enolizable ketones using low-polar media (toluene or toluene-diethyl ether medium).[127] Thus this strategy serves as a cheap

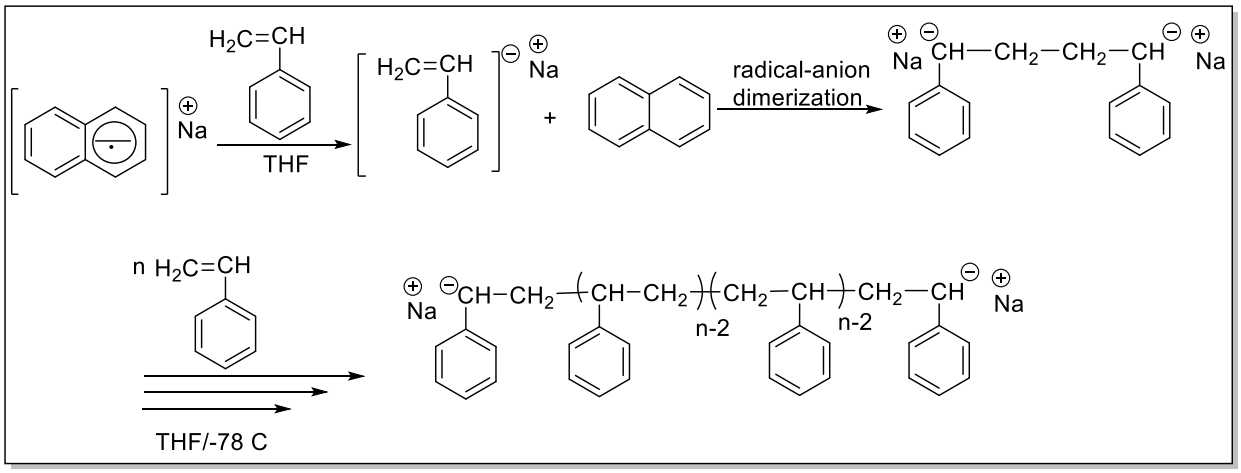
and easy way of improving the low reactivity of six membered ring hindered ketones towards phenyllithium (Scheme 1.21).[127] Also in 2003, this group improved on their earlier protocol by the introduction of aryllithium (phenyllithium), and alkyllithium (*n*-butyl-, and t*ert*-butyllithium), in both polar and non-polar solvent at various temperatures,[128] resulting in the desired alcoholic products in high yield.



Scheme 1.21: Addition of phenyllithium to a hindered ketone by the use of non-polar media.[127]

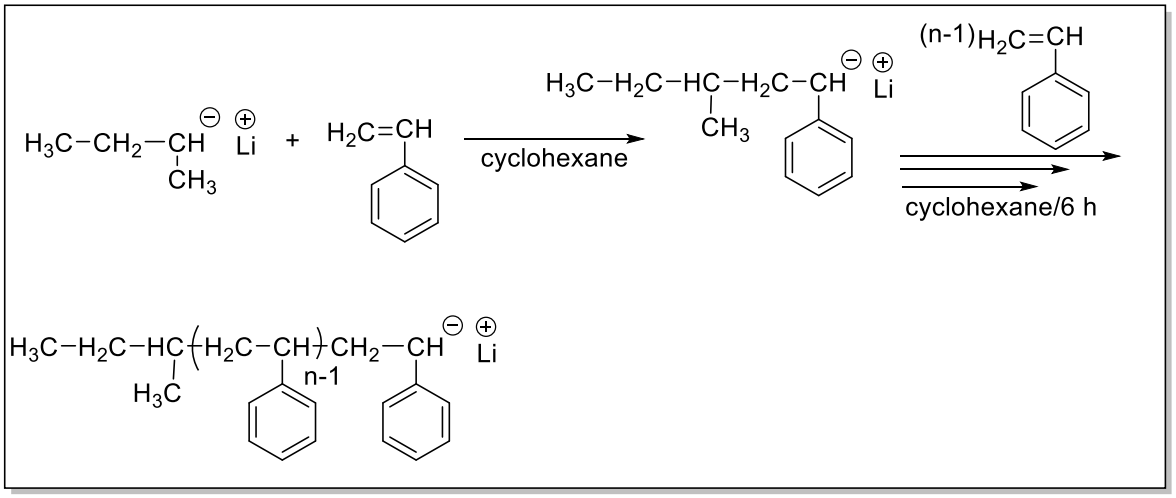
1.5.3 Initiation of Polymerization

The use of alkali metals for anionic polymerization of dienes can be traced back to around 1910-1911 in a patent by Mathews *et al.*, and Harries.[129,130] They both described the use of sodium and potassium, with the possibility of using lithium, as initiators in isoprene polymerization. In the late 1920s, Ziegler *et al.*,[131–133] published results of their research on the addition polymerization of butadiene, isoprene, piperylene, and 2,3-dimethyl-butadiene in polar solvents using alkali metals, (particularly lithium and organolithium reagents, as catalysts). The demonstration of anionic polymerization of styrene was first demonstrated by Michael Szware, who used sodium naphthalenide as an initiator in tetrahydrofuran (THF).[134,135] He suggested that the initiation occurred via an electron transfer from the naphthalenide radical anion to styrene monomer, resulting in the formation of styryl radical anion, which dimerized to form a dianion (Scheme 1.22). The formation of the styryl anion was confirmed by the change in color, from green color of the radical anion when in contact with styrene to red.[136,137]



Scheme 1.22: Anionic polymerization of styrene using sodium naphthalenide as an initiator.[134]

In addition, organolithium reagents, such as alkyllithium have been used extensively as initiators of anionic polymerization reactions. For instance, stereoregular polymerization of isoprene was achieved using alkylithium, resulting in 93-95% yield of a *cis*-1,4-addition polymer.[138] Also, *n*-butyllithium[139] and *sec*-butyllithium[140] has been used in the polymerization of styrene with benzene as the polymerization medium, or in cyclohexane (Scheme 1.23).[141,142]



Scheme 1.23: Anionic polymerization of styrene using butyllithium.[141,142]

1.6 Summary

This chapter outlines the discovery of alkali metals, their physical and chemical properties, and their conventional modes of reactivity in both laboratories and industries. Special emphasis is placed on MSU-based developments of the chemistry of these metals, and on the need to address major drawbacks, (mainly the sensitivity to air and moisture of these metals and their organic compounds) where highlighted and discussed.

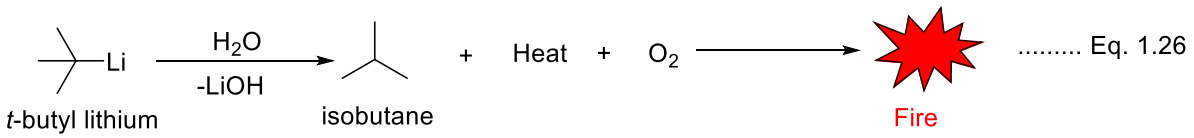
1.7 Research Justification and Aims

In organic chemistry, researchers are always searching for new methods to synthesize new and complex molecules. Organometallic reagents have continued to be pivotal in this direction due to their high basicity, nucleophilicity, reduction potential, and for some other reactions.[143] These properties are responsible for their spreading application as chemical building blocks in both pharmaceutical and manufacturing industries.

The organolithiums, for example, have long been reagents of choice for synthesis in organic chemistry. They are generally used in carbon-carbon and carbon-heteroatom bond forming processes including alkylation, additions to carbon-heteroatom double bonds, opening of epoxides, and conjugate addition reactions, to name but a few.

However, some of these organoalkali species, although effective in conventional synthesis, may be unstable or commercially unavailable. In addition, some organolithium compounds are so reactive that they can spontaneously ignite in the presence of air and moisture. For instance, *t*-butyllithium, though commercially available and widely used, reacts with air and moisture to form

lithium hydroxide and isobutane, a flammable gas (Equation 1.26). This process also releases an enormous amount of heat, enough to ignite fuels, such as the above isobutane or organic solvents.



..... Eq. 1.26

Many chemicals are dangerous in one way or the other, but the organoalkali compounds deserve special attention because their high reactivity seriously impacts their safe use, handling, and storage especially for laboratory-scale occasional use. Traditional methods to moderate their pyrophoricity and handling often involve storage of these reagents in solutions of hydrocarbons or ethers, which themselves are very volatile and flammable. However, these steps are still far from addressing the above issues. In 2009, a 23-year-old graduate student at UCLA attempted to transfer a syringe of 1.6 M *t*-BuLi (in pentane) into a round-bottomed flask. The reagent accidentally spilled on her body and ignited, causing serious burns that led to her death.[144]

In this regard, the desire to address the issues of pyrophoricity, stability, shelf life, handling and use of the organoalkali reagents and the need to develop safer organoalkali precursors without exposure to air or moisture remains an important research challenge. In an attempt to address these problems, work has been on-going in our labs and some success has already been achieved in making non-pyrophoric alkali metal reagents for use in both small and large scale syntheses. Developments are also on-going in our lab to produce solid alkali metal materials to enable safer formation of organolithium reagents. These developments yield powerful reducing reagent that are readily packaged and shipped with extended shelf lives of years.

In this regard, the over-arching aim of the present work is to form a lithium alumina composite that is non-pyrophoric (if handled with care), amenable to indefinite storage without loss of

reactivity, and usable as needed to prepare and react organolithium reagents of choice without exposure to air. In addition, applications of Na-SG and Na-AG reagents are to be explored.

From this goal, my specific research objectives were:

1. Preparation of lithium alumina gel – metallic lithium absorbed into porous alumina with mild heating that can enable its solvent-free storage and delivery for use in synthetic transformations, in both batch and column flow reactor systems.
2. Preparation of organolithium alumina gel – Developing a procedure for the reaction between lithium alumina gel with organic halides (or other organic compounds) to generate organolithium alumina gel, in a form that is readily available for use in chemical synthesis or other chemical processes.
3. Applications of Na-SG and Na-AG reagents in the N-O bond cleavage of Weinreb amides and in Bouveault-Blanc type reduction of amides to amines.

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Chapter 2:0 Li-AG: Preparation, Properties, and it Use as Precursor to Generate Organolithium Reagents

2.1 Background

Alkali metals are powerful reducing agents and are usually utilized in either the pure metallic forms, as alloys, as amalgams, or in solutions of liquid ammonia. Their organic compounds, especially organolithium species, are strong bases, potent nucleophiles, and effective catalysts for various chemical transformations, such as anionic polymerization.[4,5,91] However, the high reactivity of the unmodified metals poses serious challenges to their use in both small and large scale applications.

In the past decade, our research group, in collaboration with the Dye group, has focused on the development of strategies that enable the alkali metals/alloys (lithium, sodium, and sodium/potassium alloys) to retain their chemical reactivity while encapsulated in an inert inorganic support.[7,10,145,146] This encapsulation is envisioned to reduce the dangers associated with their handling and storage. Porous inorganic supports, typically oxide minerals, are used extensively in catalysis due to their high surface areas and thermal, chemical, and mechanical stability.[147] Oxide supports, such as alumina, silica, and zeolites, usually have surface hydroxyl groups that can be modified or functionalized chemically or used without any changes prior to attachment to a catalyst or used as a support. Recently, our laboratory has successfully encapsulated sodium metal alone and sodium/potassium alloys into the pores of nano-structured silica and alumina gels (SG and AG) to give free-flowing black powders that are non-pyrophoric and stable in dry air.[8,148] Extensive research and development are also ongoing in our lab to encapsulate lithium metal in the pores of high surface area aluminas, described herein as alumina gels. These solid free-flowing powders, used in situ, could serve as safer precursors for preparation

of organolithium and lithium amide reagents. This chapter therefore focuses mainly on the preparation of organolithium precursors that have lithium metal encapsulated in γ-alumina gel.

2.2 Aluminum Oxide for the Synthesis of Li-AG

In preparing lithium alumina gel, the appropriate aluminum oxide (Al_2O_3, alumina) is an important component. Aluminum (Al) is the third most abundant element in the Earth's crust. Its most common oxidation state is +3 which combines with oxygen to form aluminum oxide (Al_2O_3),[149,150] commonly referred to as alumina, which possesses strong ionic bonding that gives rise to its desirable material characteristics. It can exist in several crystalline phases or polymorphs (*α, γ, η, δ, κ, χ...*)[149,151] Of all the polymorphs, the *α, γ,* and *θ,* are the most important and commonly used phases. The *α* phase is the most thermodynamically stable, up to its melting point of 2051 °C but *γ,* and *θ,* are metastable, and are frequently used as catalysts and supports.

2.2.1 Structure of Aluminum Oxide

The different crystal phases or polymorphs of alumina are divided into two main categories based on the structural arrangement of the oxygen anions.[149,152,153] These structures can have either face-centered cubic (fcc) or hexagonal close-packed (hcp) lattices. The structures with oxygen based on the face-centered cubic (fcc) lattice are the γ (spinel), η (cubic), θ (monoclinic), and δ (tetragonal or orthorhombic) phases, whereas those with oxygen based on the hexagonal close-packing (hcp) lattice include the α (trigonal), κ (orthorhombic), and χ (hexagonal) phases. Studies on the structures of some of these different phases are yet to be reported. However, the structure of α-Al_2O_3, the most stable form so far, consists of an hcp sublattice of oxygen anions with trigonal symmetry, with 2/3 of the octahedral interstices filled with aluminum cations in an ordered array

(Figure 2.1).[154] Although this simplified model describes the general nature of the ion packing, it is somewhat misleading because it does not reflect the true trigonal symmetry of the crystal.

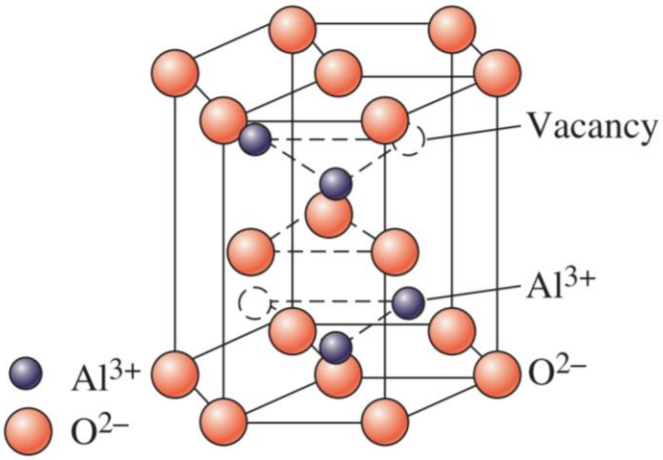


Figure 2.1: Structure of α- Al_2O_3 [154]

Source: Askeland, D. R., Fulay, P. P., Wright, W. J. The Science and Engineering of Materials 6th ed. Chapter 3 – Atomic and Ionic Arrangements pp. 90.

On the other hand, the commonly accepted structural model of γ-Al_2O_3 is related to that of a defect spinel, and it is assumed to contain 32 oxygen ions in an approximately close packed arrangement of a cubic lattice. To satisfy Al_2O_3 stoichiometry, 64/3 aluminum cations are distributed over 16 octahedral (~75 %) and 8 tetrahedral (~25 %) sites (Figure 2.2).[152] In this structure also, 8/3 of the aluminum vacancies are assumed to be randomly distributed over the tetrahedral sites, so that the cation sublattice is partially disordered as compared to an ideal spinel.[149]

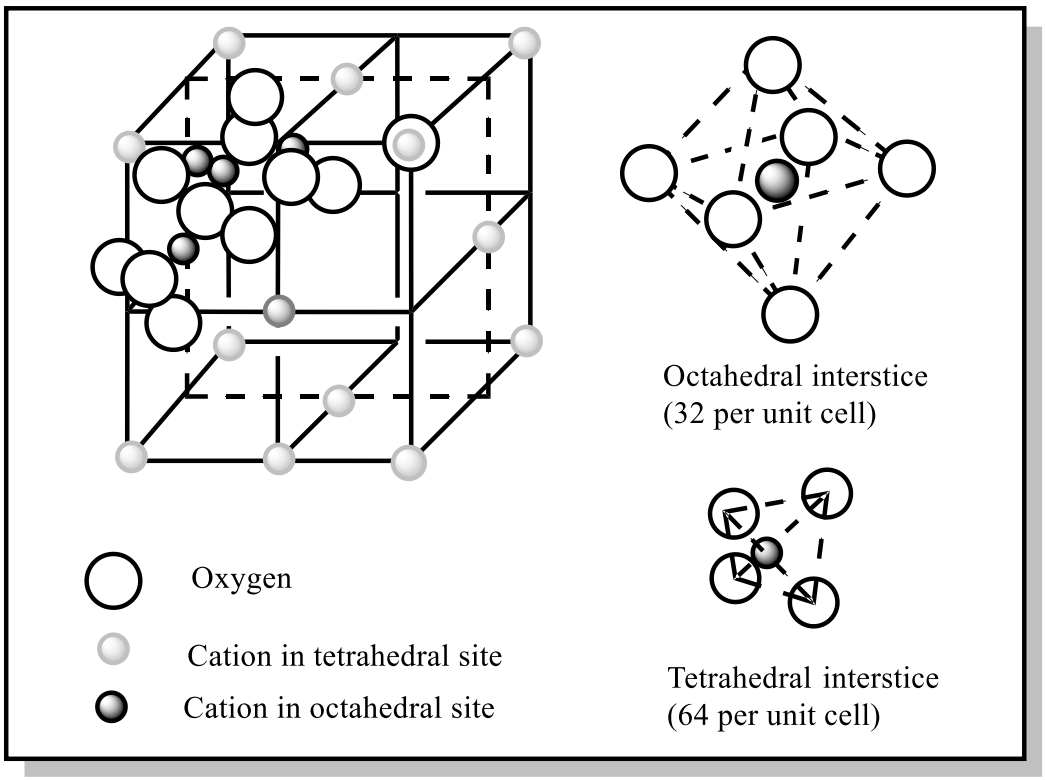


Figure 2.2: Structure of γ-Al_2O_3 [152]

2.2.2 Alumina as a Support

The use of alumina as inorganic support in catalysis dates as far back as the 1940s,[155–164] and perhaps, γ-alumina (γ - Al_2O_3) is the most important in these applications.[165] This is due mainly to it unique properties which include its surface area, pore size distribution (textural properties), pore volume, and its acid-base properties.[166]

The surface of alumina contains hydroxyl groups and physisorbed water when exposed to air and moisture. While the physisorbed surface water can be removed by heating to around 250 °C, removal of hydroxyl groups at the surface requires much higher temperatures, about 600 °C. However, when γ-alumina is heated above 750 °C it is converted to the δ form. The various transformations of alumina hydroxide are outlined in Figure 2.3.[153]

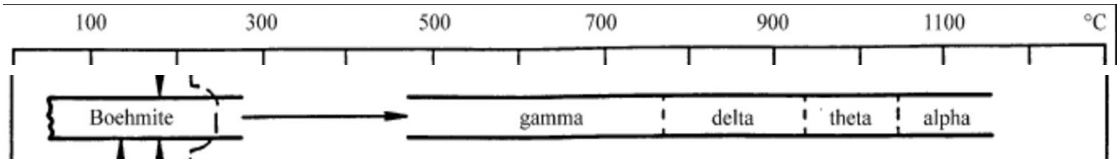


Figure 2.3: Thermal transformation sequence of aluminum hydroxides.[153]
Source: Wefers, K.; Misra, C. Oxides and Hydroxides of Alumium; Alcoa Laboratories, 1987, pp. 47

2.3 Generating Organolithium Reagents from Li-AG

Alkali metals, other than Li, have been encapsulated in silica and or alumina gel and used for the synthesis of organic molecules.[10,8,148,11] However, many traditional techniques in organic synthesis involve the use of organolithium compounds. Their applications as building blocks in the pharmaceutical and other manufacturing industries have enabled the efficient construction of diverse new compounds.[91,28,114,139,143,167–169] However, the major drawbacks associated with their utility are handling difficulties, storage, stability, and their non-availability.[170,171,] The few that are commercially available are often stored in organic solvents that are highly flammable.

Organolithium reagents can be prepared in four major ways, as mentioned, and discussed in chapter 1. The most popularly used routes involve lithium-halogen exchange,[82,84,90,172,173] transmetalation,[82,84,172,174] direct metalation via deprotonation,[82,84,175] and reaction of metallic lithium with organic halides.[82,84] These methods often entail competing side reactions, such as Wurtz Coupling,[82] β-elimination,[82,88] and electron transfer processes. Although organolithium reagents made in these ways are effective, and specific procedures are well-developed, their instability requires their immediate use after preparation.

Recently, our laboratory has developed a new method for the preparation and application of a stable, free-flowing, non-pyrophoric organolithium precursor with the lithium metal in the pores of alumina gel (Li-AG).[146] Li-AG can be used to generate a wide variety of organolithium reagents,

followed by their immediate use in nucleophilic addition reactions. Prior to this development, our laboratory had reported the synthesis of sodium incorporated in silica (Na-SG) and alumna gels (Na-AG) and their effective chemical applications in organic syntheses.[7,145,8] As with these reagents, Li-AG is a free-flowing powder that can be easily packaged under an inert atmosphere, shipped, and stored with an indefinite shelf life that preserves its reactivity and synthetic utility. It is even stable for a limited time in dry air.

Li-AG can form a variety of organolithium reagents in THF by reaction of nanoscale lithium particles (within the pores of alumina gel) with organic halides, or by cleavage of the C-O bond in unsaturated ethers to form the corresponding organolithium reagent. Following the formation of the organolithium solution in a closed system, reaction with a suitable electrophile can be carried out without opening the system. This is advantageous because organic halides themselves can be toxic,[176–178,179] carcinogenic,[177,179–181] and lachrymatory.[182,183] The formation of the desired organolithium intermediate can be verified by its reaction with either of two electrophiles, benzophenone and benzaldehyde, or upon quenching with water. Since the main objective of this research was to demonstrate the use of Li-AG to form a variety of organolithium reagents in a closed system, no extensive studies were made with other electrophiles.

2.4 Experimental Section

2.4.1 Development of Li-AG

In the formation of lithium alumina gel (Li-AG), *γ*-alumina gels purchased from Davison Catalysts, (with an average pore size of 190 Å) and from US Research Nanomaterials Inc. (with an average pore size of 50 Å) were used since they have high surface areas, well-defined pore size distributions and pore volumes.[165] The purchased *γ*-alumina was a three-dimensional cross-linked

network of crystalline structure with irregular pores. The alumina gel was calcined at 200-600 °C to remove the hydroxyl groups. It should be noted however that, the Davison alumina gel is no longer commercially available.

2.4.1.1 Calcination of Alumina Gel (AG)

The purchased γ-alumina gel (AG) typically contains adsorbed materials such as water and air, which can be removed by calcination. During calcination, about 50 g of AG is placed in a porcelain tray and heated in a closed oven at 200 °C for 6 hours and then at 600 °C overnight (12-14 hours). Next, the AG is cooled while covered with aluminum foil to minimize the absorption of moisture. After a few hours, when it is cool enough to be held with a glove (Bel-Art H13201-10001 heat resistant), the AG is transferred into a container in the He-filled glove box (VAC model M040-1).

2.4.1.2 General Method for the Preparation of Li-AG

Li-AG can be prepared with various percentages of Li by weight (such as 25, 20, 10, and 7) based on the average pore volume of the alumina gel. In a He-filled glove box, the surface of lithium metal is cut away to remove any lithium oxide surface coating that might be present. For example, the preparation of 25% Li-AG is as follow; 10 g of clean lithium metal is weighed and cut into smaller pieces (about half cm to one mm). Next, 30 g of the calcined AG is weighed and mixed with the 10 g of lithium. The mixture is placed in a rotary steel Parr reactor (Parr Instruments Company, model 452 HC, item T-316033004 29118) and sealed with a Teflon gasket. This steel reactor is taken out of the He glove box and placed in a rotary oven (at 60 rpm) set at 185 °C for 6 hours and then at 200 °C overnight (12-14 hours). The heat is turned off and the reaction is allowed to cool down to room temperature while rotating for few hours. It is then transferred back into the

He-filled glove box and opened, to give approximately 40 g of free-flowing black powder of Li-AG. The resulting black powder contains approximately 25 % Li, which is further analyzed by using the H_2 evolution method.

2.4.2 Characterization of Li-AG

2.4.2.1 Scanning Electron Microscopy (SEM) Analysis

SEM studies on JEOL JSM 6610LV, JEOL 7500F and JEOL 6400V instruments were used to image both the AG and Li-AG. These samples were mounted onto an aluminum stub with carbon paste and then dried under vacuum for few hours. Secondary electron imaging was used to obtain the images. Energy-Dispersive X-Ray (EDX) coupled with JEOL 6400V SEM was used to show the crystalline nature of the sample.

2.4.2.2 Differential Scanning Calorimetry (DSC) Analysis

DSC studies on a Model Q-200 (made by TA instruments) were used to measure weighed samples of Li-AG (approximately 5 mg) placed in a hermetically-sealed aluminum pans (sealed inside the He-filled glove box). This instrument was used to determine the particle size distribution and the presence or absence of any un-incorporated Li metal particles.

2.4.2.3 H_2 Evolution Analysis to Estimate the Amount of Li in Li-AG

In a He-filled glove box, ~1 g of Li-AG is weighed and placed in a dry 50 mL round bottom flask equipped with a greased vacuum stopper. It is then evacuated via a rough pump that has a connection valve within the glove box. The flask is taken out and connected to a vacuum line (with a known volume up to the shut-off valve) and pumped down to about 10^{-4} torr. The closed part of

the vacuum line is connected to another flask (1000 mL), 5 mL of degassed water is added to the evacuated sample flask with a syringe, and the flask is allowed to cool down to room temperature. The pressure of the resulting H_2 gas in the known volume is measured with a digital pressure gauge (Cecomp electronics, model no. ARM760B-5). From the known total volume of the closed system, the pressure of the H_2 (corrected for the vapor pressure of water), and the temperature, the molar quantity of H_2 is determined from the ideal gas equation (PV = nRT), based on the equation below;

$$2\ Li + 2\ H_2O \longrightarrow 2\ LiOH + H_2$$

From this, the amount of Li in the Li-AG sample is calculated, with an estimated error of ± 2%.

2.4.2.4 Nuclear Magnetic Resonance Spectroscopy (NMR)

Prior to solid state NMR studies, the Li-AG sample was added to a quartz MAS NMR tube in the He-filled glove box, sealed with heat-shrink tubing and then taken out, and flame-sealed with the sample portion kept cold with liquid nitrogen. All solid-state NMR experiments were run at ambient temperature on a Varian Infinity-Plus NMR spectrometer equipped with a 6 mm (0.236 in.) magic angle (MAS) broadband probe operating at 155.35 MHz for ^{7}Li. A standard one-pulse sequence with ^{1}H decoupling during acquisition was used for all experiments. The ^{7}Li pulse width was 4 μs, the pulse delay was 100 ms, and the acquisition time was 41 ms.

2.4.3 Procedure for Initial Optimization of Reaction Conditions Using 4-Bromotoluene and 4-Chlorotoluene

In a helium-filled glove box, a sample containing 5 mmol equivalents of Li-AG was added to a round bottom flask, equipped with a glass-coated magnetic stirrer and rubber septum. This closed

system was then taken out of the glove box, while it was purged with argon, 1 mmol of 4-bromotoluene/4-chlorotoluene dissolved in 10 ml of anhydrous THF was injected. The resulting mixture was stirred at -78 °C (dry ice-isopropanol bath) for 3 hours. Then with a glass syringe and needle, aliquots of the reaction mixture were removed and quenched with water at 15-minute intervals for the first hour, followed by 30-minute intervals for the second hour, with a final one-hour interval. The quenched samples were then prepared for quantitative analysis by GC/MS with an internal standard (dodecane) at fix concentration of 5 mM. The GC/MS results from the time course experiment were then plotted against the calibration curves generated for 4-bromotoluene/4-chlorotoluene and toluene. This information enabled us to determine the time at which all the starting material had been consumed and converted to product (toluene).

2.4.4 Procedure for Generating Organolithium Reagent from Organic Halides

In a helium-filled glove box, Li-AG, (usually containing 5 mmol of Li) was added to a modified round- bottom flask (Figure 2.4) containing a glass-coated magnetic stirrer and a rubber septum. This flask was connected to a 3-neck flask via a joint packed with glass wool. After removal from the glove box, 1 mmol of the organic halide dissolved in 5 mL of anhydrous THF was injected through the septum with a continuous flow of argon. The resulting mixture was stirred at -78 °C for the desired time (30-150 minutes) followed by filtration through a glass wool plug into the 3-neck flask. After solvent removal by vacuum evaporation, the solid lithium alkyl was washed with two 1 mL portions of anhydrous THF. This was followed by the addition of 0.5 mmol of the electrophile (benzophenone or benzaldehyde) dissolved in 5 mL of anhydrous THF. The reaction mixture was left with continuous stirring until all the electrophile was consumed, after which the reaction was stopped by a deionized water quench (~1 mL). The mixture was then extracted with

ethyl acetate and the organic layer was concentrated under reduced pressure with a rotary evaporator. The crude product was purified via silica gel column chromatography.

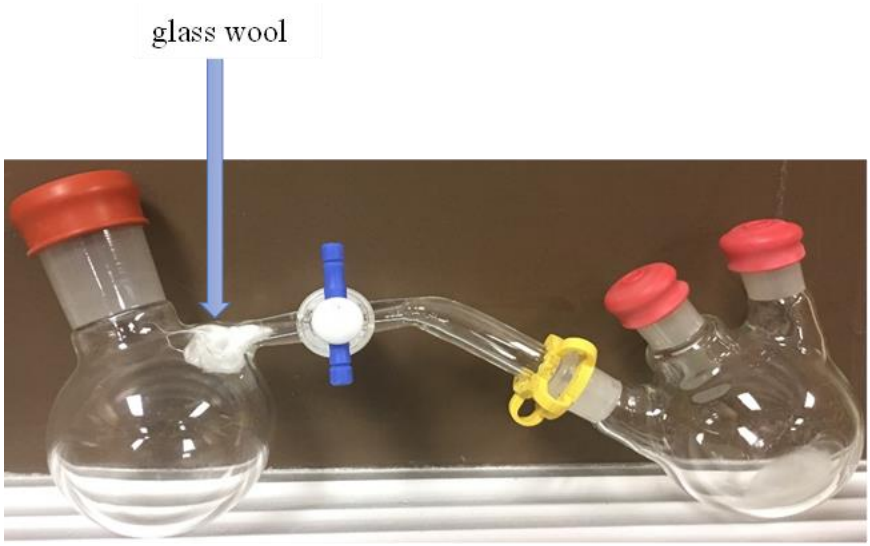


Figure 2.4: Sketch of modified round- bottom flask

2.4.5 Procedure for Generating Organolithium Reagent from Organic Ethers

In a helium-filled glove box, Li-AG, (usually containing 5 mmol of Li) was added to a modified round-bottom flask (Figure 2.4) containing a glass-coated magnetic stirrer and a rubber septum. This flask was connected to a 3-neck flask via a joint packed with glass wool. After removal from the glove box, 1 mL of the organic ether dissolved in 5 mL of anhydrous THF was injected through the septum with a continuous flow of argon. The resulting mixture was stirred at 0 °C for the desired time (30-150 minutes) followed by filtration through the glass wool plug into the 3-neck flask. After solvent removal by vacuum evaporation, the solid lithium alkyl was washed with two 1 mL portions of anhydrous THF. This was followed by the addition of 0.5 mmol of the electrophile (benzophenone or benzaldehyde) dissolved in 5 mL of anhydrous THF. The reaction mixture was left with continuous stirring until all the electrophile was consumed, after which the reaction was stopped by a deionized water quench (~1 mL). The mixture was then extracted with

ethyl acetate and the organic layer was concentrated under reduced pressure with a rotary evaporator. The crude product was purified via silica gel column chromatography.

2.5 Results and Discussion

2.5.1 Characterization of Li-AG

SEM images (Figure 2.5) show interconnected nanocrystalline nature of γ-alumina (purchased from Davison Catalysts, with average pore sizes of 190 Å) at two different magnifications.

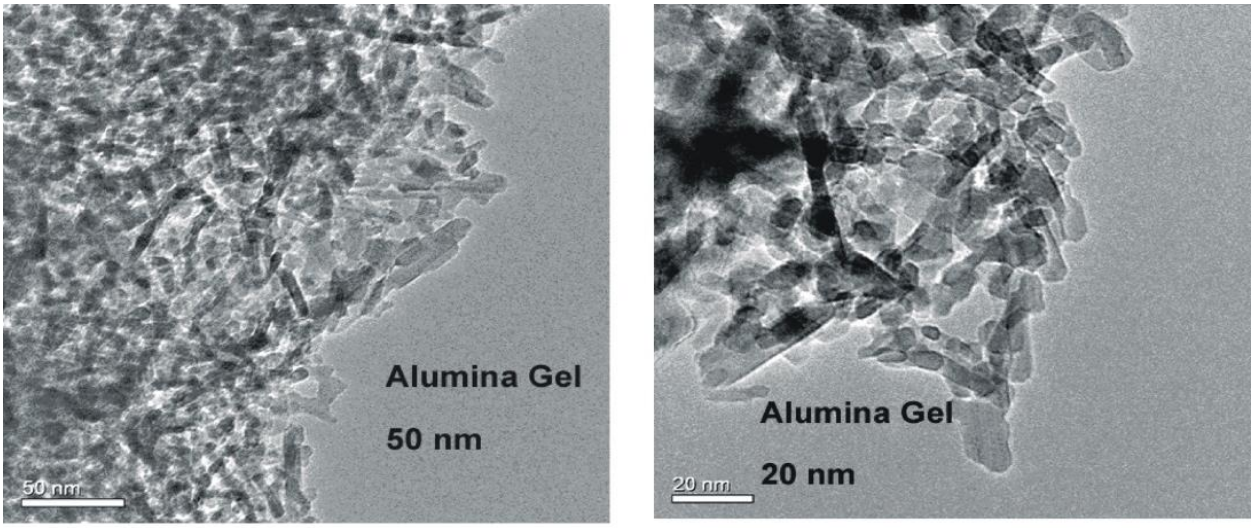


Figure 2.5: Scanning electron microscopy (SEM) of γ-alumina gel

Both qualitative and quantitative information about physical and chemical changes that involve endothermic and exothermic processes can be obtained by using DSC. This instrument measures the temperatures and heat flows associated with transitions in materials as a function of time and temperature. Figure 2.6 and 2.7 shows both the melting endotherm and the enthalpy of melting (ΔH_{melt}) compared with the bulk Li metal. An endotherm of lithium at 160 °C from Figure 6 indicate that Li-AG is non-pyrophoric and within the pores of AG. If this endotherm shows at the melting point of Li (180.50 °C), (as occurred in some samples) it would indicate the presence of

metallic Li on the surface of the AG, which can lead to pyrophoric behavior. In addition, the width of the endotherm reflects the size and distribution of the particles within the pores. Comparing the DSC of Figure 2.6 and 2.7 below, the shift and broadening of Figure 2.7 indicates smaller average particles size, and a considerable spread in particle size distribution as a result of the smaller pore sizes of AG (50 Å) compared with those of AG, 190 Å (Figure 2.6). The lowering of the melting point shows that particles are small and the spread of this endotherm illustrate the distribution of particles sizes. ΔH_{melt} from Figure 2.6 and 2.7 (1.2% and 2.8% respectively) are reduced compared to the bulk metal. These decrease in both the melting endotherm and the enthalpy of melting is thought to be associated with decrease in the percent present as metal distributions into small sites, and or the effect of particle size on the enthalpy of melting.[184] Also, changes in ΔH_{melt} could be used to estimate the fraction of metal remaining in the pores after heat treatment compared with that initially present.

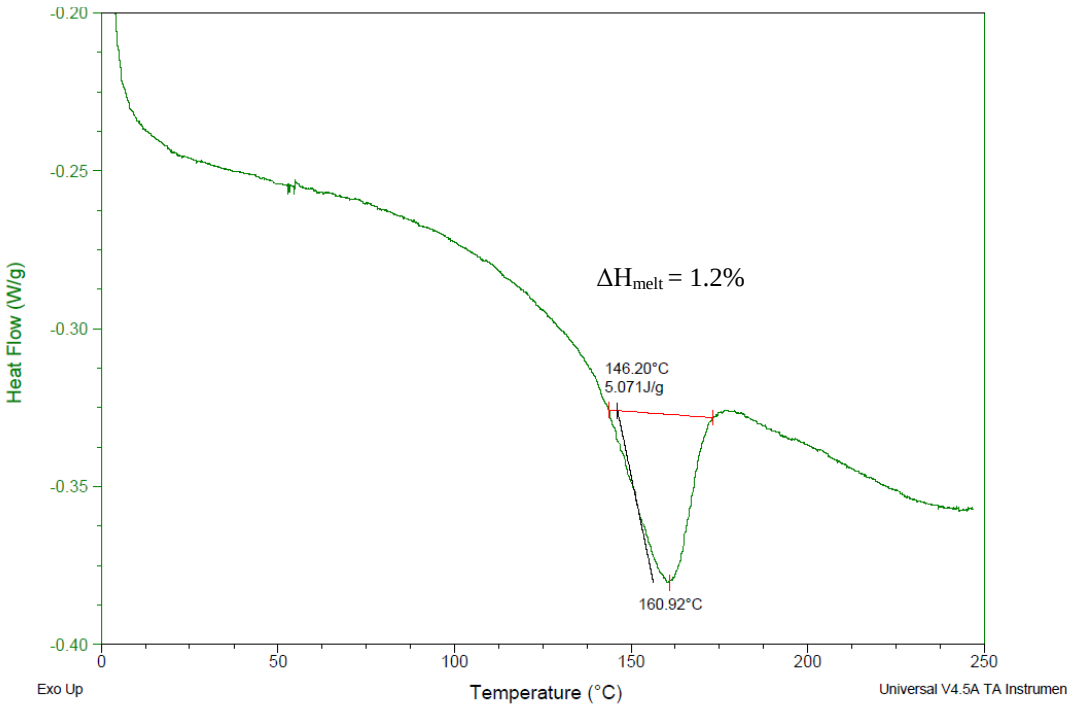


Figure 2.6: Differential Scanning Calorimetry (DSC) thermogram of Li-AG (AG 190 Å)

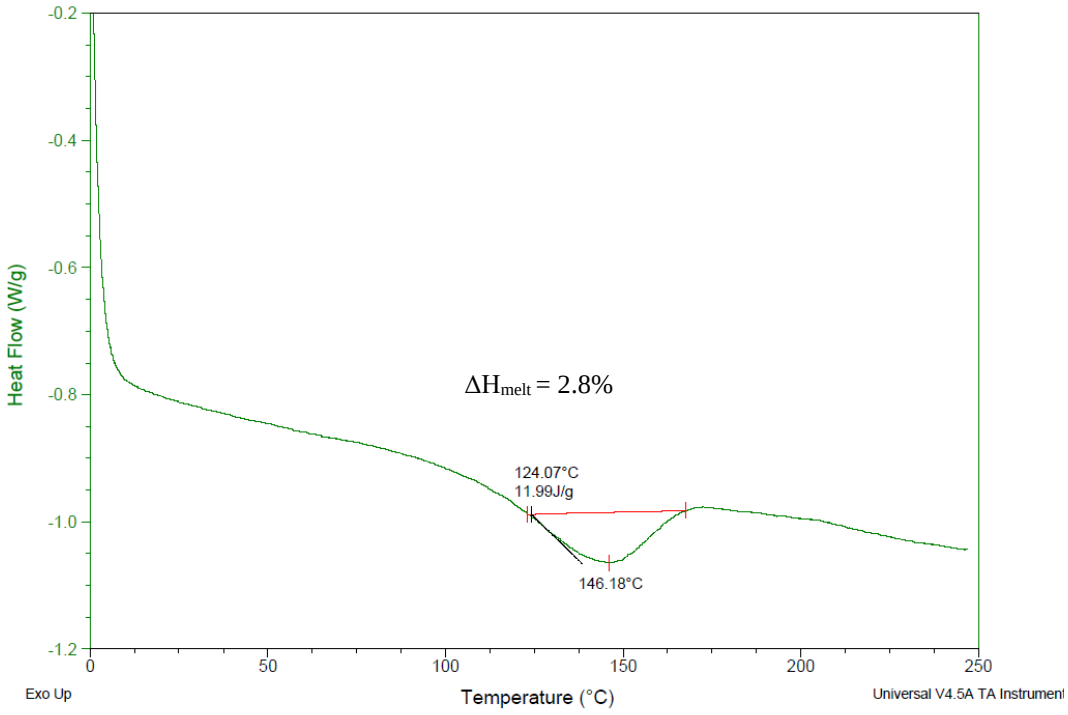


Figure 2.7: Differential Scanning Calorimetry (DSC) thermogram of Li-AG (AG 50 Å)

The MAS solid-state ^{7}Li NMR Figure 2.8 (performed by Prof. James L. Dye), shows Li^0 and a small amount of Li^+ which indicate that Li ionized to some extent or has undergone a reaction, probably with residual Al-OH groups or moisture. The relative intensity of Li^0 (257 ppm) and Li^+ (near zero) may also be temperature dependent or depends on the percent of metal loading, which can vary from batch to batch, and the average pore size of the AG.[145,184,185]

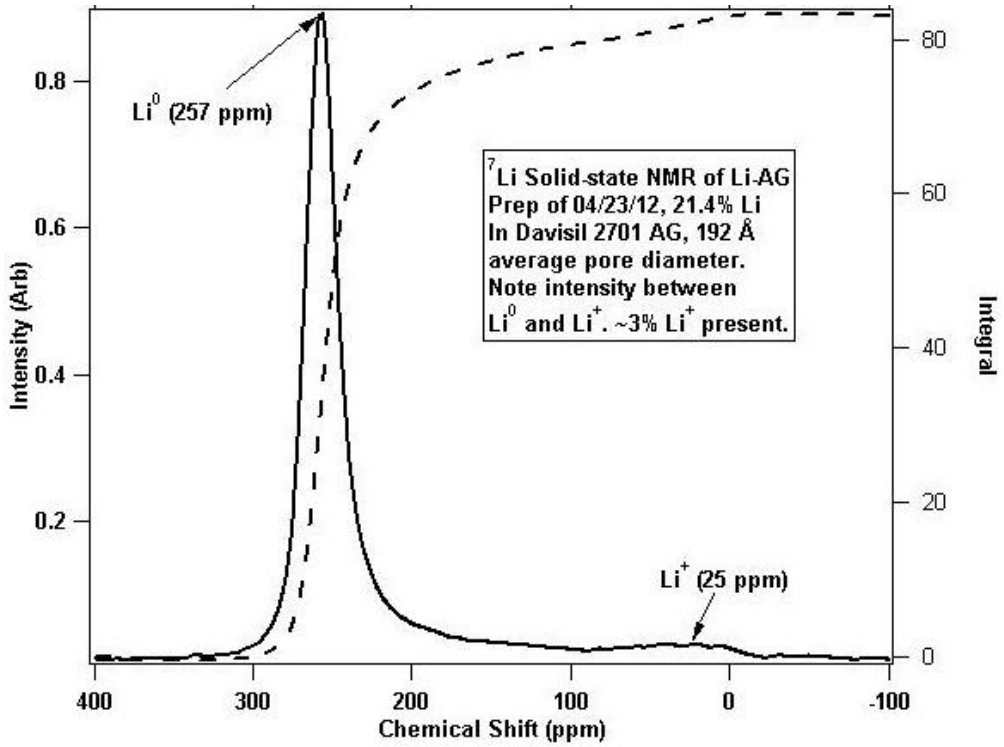
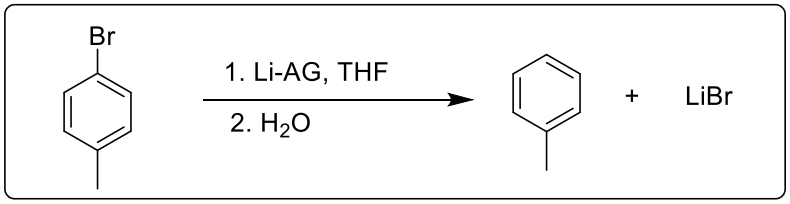


Figure 2.7: Solid-state Nuclear magnetic resonance spectroscopy (NMR) of Li-AG

2.5.2 Preliminary Optimization of Pore Size, Loading, and Temperature

Our initial efforts of the Li-AG precursor to form organolithium reagents utilized 4-bromotoluene, bromobenzene, and 4-chlorotoluene as substrates under various reaction conditions. These substrates were chosen because of their ease of analysis by GC/MS. The results of the transformations are summarized in Table 2.1 and Scheme 2.1, and representative time-courses are

shown in Figure 2.9. In an effort to optimize the conditions used to form an organolithium by reacting Li-AG with an organic halide, we used alumina gel (AG) with different pore sizes (190 and 50 Å) and with different loadings of lithium metal (20 and 7% Li) (Figure 2.9).



Scheme 2.1: Preliminary optimization of 4-bromotoluene

Table 2.1: Preliminary optimization of pore size, loading, and temperature

Entry	Pore Size (Å)	Loading (wt.% Li)	Li-AG (equiv.)	Time (min)	Temperature (°C)	% Conversion to Product
1	190	20	5	120	-78	98
2	190	7	5	90	-78	97[a]
3	50	20	5	90	-78	98
4	50	9	5	45	-78	98
5	190	7	10	30	-78	98
6	190	7	5	30	0	60[b]
7	190	7	5	30	-15	80[b]
8	190	7	5	150	-78	97[c]

Note: Except for entries 6,7, & 8, the yield is based on the GC-MS conversion of 1 millimolar equivalent of 4-bromotoluene to product in 10 ml of THF, at -78 °C. [a] Two determinations (with ±2%), [b] bromobenzene. The balance for entries 6&7 is biphenyl, produced by a Wurtz reaction. [c] 4-chlorotoluene.

The results show that complete conversion of 4-bromotoluene to toluene via the intermediate formation of 4-tolyl-lithium can be achieved at -78 °C. Although higher temperatures accelerated the reaction, the competing Wurtz reaction to give the biphenyl also occurred, as shown in entries

6 and 7 (36 and 18 % biphenyl respectively, Table 2.1). The dependence of the rate on pore size and loading is in agreement with the general behavior previously seen in organic reductions with alkali metals in silica gel.[21-23] The particles of lithium in fully filled 190 Å diameter pores contain about 43,000 lithium atoms, whereas only about 2,000 are in the surface layer. Thus, saturation of the surface with organic substrate and/or product molecules that exchange slowly would slow down the conversion. Lighter loading (7% Li) or smaller pore sizes (50 Å) presumably would lead to smaller particle sizes and therefore greater lithium surface area. The shift and broadening of DSC traces show that there is considerable spread in particle sizes even in nominally filled pores (Figure 2.6 and 2.7), in agreement with results reported earlier by Dye *et al.*[7,145,148] It is important to note that decreasing the percent Li loading (by mass) requires an increase in the overall amount of Li-AG needed for complete reaction. The general effects described here are also evident from the growth curves of Figure 2.9.

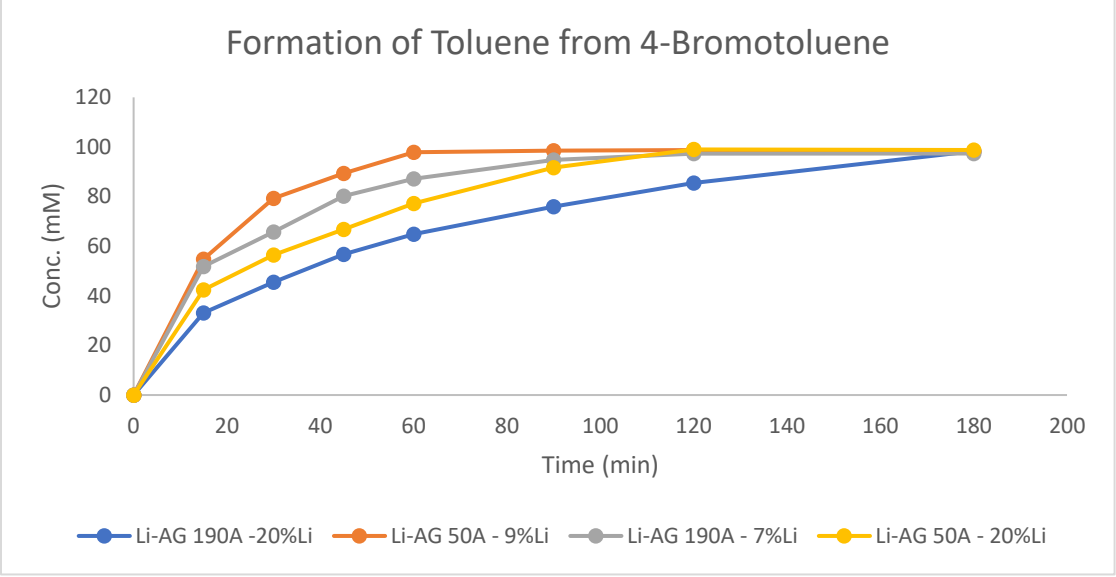


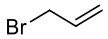
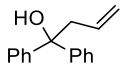
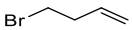
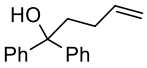
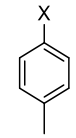
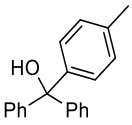
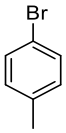
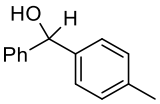
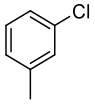
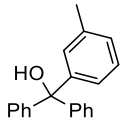
Figure 2.8: Effects of pore size and percent loading on the rate of formation of toluene upon aqueous quenching of the lithium-toluene adduct.

2.5.3 Substrate Scope

2.5.3.1 Reaction of Li-AG with Organic Halides

A variety of oganolithium reagents were formed by the reaction of Li-AG with organic halides and their structures were verified by their subsequent nucleophilic addition to benzophenone and/or benzaldehyde. Because of its low cost and ready availability, the 190 Å pore size AG was used with a 7% loading and a total of 5 equivalents of Li (Table 2.1, Entry 2). Table 2.2 shows the results obtained from this AG with various halides.

Table 2.2: Formation of organolithium reagents in 90 minutes at -78 °C by reaction of Li-AG precursor with organic halides

Entry	Halide	Electrophile	Product	Isolated Yield ±2
1				91
2				88
3				80[a] 79[b]
4				85[a] 80[b]
5				90
6				96
7				82[b]

[a] Isolated yield from Br, [b] isolated yield from Cl and formation of organolithium at 150 minutes.

Alkenyllithiums, (entries 1 and 2) are not stable enough to be stored and therefore are not commercially available. Thus, they need to be prepared shortly before use. The literature preparation of allyllithium by direct reaction of metallic lithium with allyl halides in ethyl ether solution gives a very low yield because of significant formation of the biallyl coupling

byproduct.[186] Allyllithium can be effectively prepared in high yield by lithium-tin transmetalation (between phenyllithium and allyltriphenyltin, phenyllithium and tetraallyltin),[187,188] but this requires long reaction time (overnight) at low temperatures. In contrast, the present process yields alkenyllithium (entries 1 and 2), with good isolated yields of the target alcohols (91% and 88% respectively), demonstrating that efficient formation of alkenyllithium occurs prior to nucleophilic addition to benzophenone in 90 minutes.

Changing from alkenyl halides to aryl halides also afforded the desired alcohol product in 80 - 96 % yield (entries 3–7) as demonstrated by trapping with two different electrophiles (benzaldehyde and benzophenone). Although both entries 3 and 4 gave comparable yields, the aryl chloride took longer (150 minutes) than the aryl bromide (90 minutes) to form the corresponding organolithium as determined from time course experiments (Table 2.1, entries 8 and 2), prior to the addition of benzophenone. This is not surprising, aryl bromides also undergo halogen-metal exchange, and reaction with metallic lithium much more readily than the chlorides.[88]

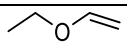
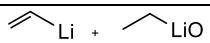
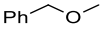
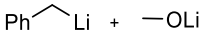
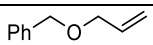
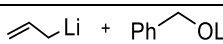
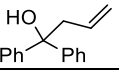
When the electrophile was changed to benzaldehyde (entries 5 and 6), the products were obtained in yields of 90% and 96% respectively, compared to the reduced yields observed in entries 3 (80%) and 4 (85%). This is expected because of the higher reactivity of aldehydes compared to the more sterically hindered ketone substrates. It is noteworthy that, except for the chloride analogs, all the organolithium intermediates were formed in 90 minutes before the subsequent addition of the electrophile. This route is obviously faster than the typical reaction of metallic lithium with organic halides,[189] which usually takes overnight. However, additives strategies have been developed to accelerate such reactions.[92,97,190–194]

2.5.3.2 Reaction of Li-AG with Organic Ethers

In the 1950s, organolithium reagents were, in some cases, prepared by the cleavage of ethers with lithium metal.[195] Later, Bachki *et al.* prepared alkyllithium reagents by lithiation of alkyl aryl ethers.[196] However, their method involved the use of excess lithium powder and catalytic amounts of 4,4'-di-tert-butylbiphenyl (DTBB, 5%), in THF.

Because of the toxic and carcinogenic nature of organic halides used to prepare the organolithium compounds described in Table 2, we decided to explore their formation by cleavage of the C-O bonds of ethers with Li-AG. The results are given in Table 2.3.

Table 2.3: Formation of organolithium reagents in 90 minutes at 0 °C by the reaction of Li-AG precursor with organic ethers

Entry	Ether	Intermediates	Product	Isolated Yield
1				83
2				71
3				62[a]

[a]10% benzyl alcohol byproduct.

Vinyllithium is an important non-commercially available precursor for C–C bond formation. This reagent was first synthesized in good yield by Seyferth *et al.*, through transmetalation.[188,174,197] Even though other techniques have been used that involve the direct metalation of ethylene with lithium,[198] and lithium-halogen exchange,[83] these procedures have been limited by poor purity of isolated products, solvent requirements and low yields. Here, vinyllithium has been prepared via the cleavage of ethyl vinyl ether, (Table 2.3, entry 1), as verified by nucleophilic addition to benzophenone, to give 83 % isolated yield of the alcohol product. The cleavage of the ethyl vinyl ether provides a safer and easier route for preparing vinyllithium. As with allyllithium,

benzyllithium is a challenging reagent to prepare. Protocols reported in the literature[176] so far result in significant amounts of Wurtz coupling to form bibenzyl as a major product, producing only trace amounts of benzyllithium. This is not surprising, since benzyllithium, once formed, reacts rapidly with excess benzyl halide to yield bibenzyl. The first direct synthesis involved reaction between lithium ribbon and benzyl chloride, using dioxane as the solvent.[199] In 1958, Gilman *et al.* first reported the preparation of this organolithium by cleavage of benzyl methyl ether in THF by running the reaction at a temperature range of -5 to -15 °C, in up to 83% yield, determined by double-titration.[200,201] This method was further improved to form benzyllithium in higher yields using a solvent mixture of diethyl ether-THF.[202] By using Li-AG, we were able to prepare benzyllithium from benzyl methyl ether in 71% yield at -78 °C as shown in Table 2.3, entry 2. In addition, allyllithium was prepared from ((allyloxy)methyl)benzene in a reasonable yield **(**entry 3**)**. Thus, the methods described here, which involve dispersion of lithium in alumina, provide enhanced reactivity of the metal with few side reactions.

2.6 Summary

This chapter shows the first use of Li-AG as a solid-state precursor for in situ generation of organolithium reagents on demand. The precursor was prepared as a non-pyrophoric free-flowing powder, which can be stored for extended periods and used to produce a variety of organolithium reagents. This has the potential to replace commercial pyrophoric reagents that are stored in flammable organic solvents, especially for laboratory scale applications. Li-AG provides a larger effective surface area than pieces of lithium metal, decreasing the reaction time for the generation of organolithium reagents from organic halides and ethers. Although excess Li-AG (5 equivalent)

has been required for these reactions to be completed in a reasonable time, that restriction is not a barrier for small-scale syntheses and could probably be modified by further studies.

2.7 Future Directions

Application of Li-AG as a precursor in generating organolithium should be extended to various reactions that use traditional organolithium reagents. Among others, mention must be made for the examination of this technique on the following reactions:

Conversion of Weinreb amides to ketones, otherwise known as the Weinreb ketone synthesis. The Weinreb substrate can be easily synthesized from acid chlorides, followed by treatment with organolithium reagents. This organolithium can be generated by the reaction of an organic halide/ether with Li-AG precursor to give an alcohol. The main advantage of this approach is the stability of the metal-chelated intermediate that prevents over-addition as seen with other functionalities.

The conversion of epoxides to alcohols. Traditional technique used involve the of organolithium reagents. Use of the Li-AG could likely replace traditional approach making it worthwhile explorable. Epoxides which are highly reactive due to ring strain can undergo nucleophilic reaction with organolithium reagents generated using Li-AG to form alcohols.

Li-AG could also be applied in the formation of lithium amides by direct reaction with the corresponding amides. This area of research was explored by a former lab member (Partha Nandi), by reacting Li-AG with dimethyl amine, diisopropylamine, and bis(trimethylsilyl)amine or HMDS instead of using metallic lithium. The result obtained was in the order of dimethyl amine >

bis(trimethylsilyl)amine > diisopropylamine. However, more substrate needs to be explored to be able to make a comparison of metallic lithium and lithium in AG.

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Disclaimer

I hereby declare that in this chapter of my thesis, part of the original work has already been published.[1]

Further, I have acknowledged all sources used are cited in the reference section.

Chapter 3.0: Reductive N-O Cleavage of Weinreb Amides by Sodium in Alumina and Silica Gels: Synthetic and Mechanistic Studies

3.1 Background

Weinreb amides (WAs) have played key roles in many organic syntheses.[2] Their main value is as acylating agents for various organometallic reagents, giving direct access to useful ketones and aldehydes without overalkylation.[3–5] Complementing this functionality, their stability makes Weinreb amides especially useful as intermediates in exploration and scale-up for pharmaceutical production.[6,7,8]

A less-exploited use of WAs is as N-protected species which can undergo N–O cleavage and functionalization leading to secondary and tertiary amides and amines.[9] Weinreb amides, after N–O bond cleavage, have been catalytically derivatized with alkynes[10] and with olefins[11] in both intermolecular and intramolecular annulative processes.[12]

Various reagents have been used to effect reductive cleavage of the N–O bonds in Weinreb amides. These include samarium diiodide,[13–15], sodium amalgam,[16] lithium powder,[17] organic 'super electron donors',[18] and $RuCl_3$/Zn-Cu/alcohols.[19]

Recently, alkali metals, usually employed as finely divided dispersions in an inert hydrocarbon, are simple and potent reducing agents, but their use is often limited due to their pyrophoricity and the need to remove the dispersant before or after the reaction. sodium metal trapped in the nanoscale pores of alumina gel (Na-AG) or silica gel (Na-SG)[20] are commercially available free-

flowing powders that are powerful reductants and are non-pyrophoric in dry air.[21,22,23] Other advantages are that many of their reductions can be run under ambient conditions and that the environmentally benign spent reducing agent can be removed by simple filtration. Hence, this chapter focuses on the use of Na-AG and Na-SG to reduce a range of Weinreb amides. The chemoselectivity of the method, and some mechanistic studies are discussed.

3.2 Silicon Dioxide for the Synthesis of Na-AG and Na-SG

Silicon (Si) is the second most abundant element in the Earth's crust but very rarely occurs as the pure free element in nature. However, it commonly exists in various forms of silicon dioxide (silica) and silicate. Si is a metalloid, allowing for many forms of covalent bond. Like carbon, it typically forms four bonds; however, it can accept additional electrons and form five or six bonds sometimes in silicate compounds.

3.2.1 Structure of Silicon Dioxide

The structure of silica (SiO_2) varies; in general, it forms three-dimensional networks of corner linked SiO_4 tetrahedral (with one silicon surrounded by four oxygen atoms) in most of its physical states. The large number of different structures that the linkage may take leads to many different forms of SiO_2. The linkage can be random, leading to an amorphous structure, where some oxygen atoms are bonded to only one silicon atom (non-bridging atoms) in e.g., opals, and glass. In the crystal form, all or most of the oxygen atoms are bonded to two silicon atoms in such a way that the tetrahedra are joined at a corner, forming bridging atoms; this pattern results in a regular crystalline structure (example quartz, tridymite, cristobalite), Figure 3.1.[24]

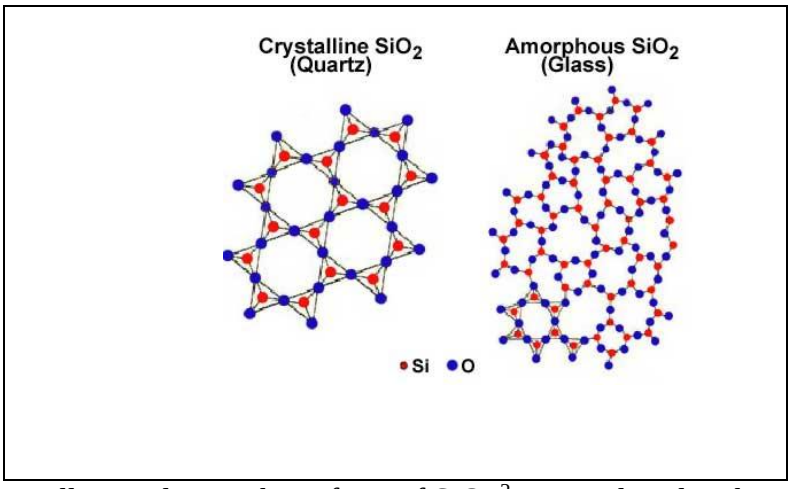


Figure 3.1: Crystalline and amorphous form of SiO_2.[2] "Reproduced with permission from Nondestructive Testing (NDT) Resource Center and Center for Nondestructive Evaluation (NDE), Iowa State University."

Although the Si-O bond lengths and distances may vary from amorphous to crystalline, a typical bond length of a Si-O bond is 0.162 nm and the normal distance between oxygen ions is 0.262 nm, Figure 3.2.[25] The Si-Si distance (depending on the particular form of SiO_2) is about 0.31 nm. The bond angle Si-O-Si is about 145°, but can vary from about 100° to 170° with very little change in bond energy.[6] However, in formation of Na-SG, the amorphous or "gel" form of silica is used due to its high surface area, thermal stability, and chemical stability.

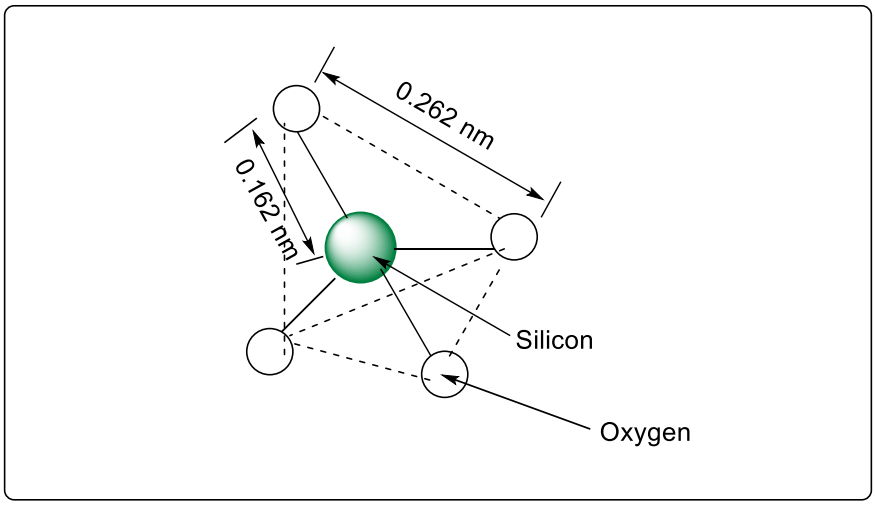


Figure 3.2: Bond length and geometry of SiO_2 [25]

3.2.2 Silicon Dioxide (Silica Gel) as a Support

Silica has been in use as an inorganic support since the late 1970s.[26–29] Its amorphous nature combined with its high surface area in the range of 100–1000 m^2/g makes it suitable for use as a support. Due to its high surface area and pore volume, silica is not only used as support but also for drying and purification of gas and organic products. In 2005, the Dye group reported the absorption of alkali metal into silica gel and its use as reducing agents.[22]

3.3 Experimental Section

3.3.1 Development of Na-SG and Na-AG

In the formation of sodium alumina and silica gel (Na-AG and Na-SG), γ-alumina gel purchased from Davison Catalysts, (with an average pores size of 190 Å) and silica gel from Davisil (with an average pore size of 150 Å), were used. These purchased materials are composed of a three-dimensional cross-linked network of crystalline (alumina) and amorphous (silica) structure with irregular pores, which are calcined to remove the hydroxyl groups.

3.3.1.1 Calcination of Silica and Alumina Gel

The purchased γ-alumina (AG) and silica gel typically contain adsorbed materials such as water and air, which can be removed by calcination. During calcination, about 50-100 g of AG/SG is placed in a porcelain tray and heated in a closed oven at 200-250 °C for 4-6 hours and then 600 °C overnight (12-14 hours). Next, the AG/SG is covered with aluminum foil while cooling to minimize the absorption of moisture. After a few hours, when it is cool enough to be held with a

glove (Bel-Art H13201-10001 heat resistant), the AG/SG is then transferred into a container in the He-filled glove box (VAC model M040-1).

3.3.1.2 General Method for the Preparation of Na-SG and Na-AG

Na-AG and Na-SG can be prepared in various percentages of Na by weight (such as 25, 20, 10, and 7) based on the average pore volume. In a He filled-glove box, the surface of sodium metal is cut away to remove any oxide surface coating that might be present. For example, the preparation of 25% Na-SG and or Na-SG is as follows; 10 g of clean sodium is weighed and cut into smaller pieces. Next, 30 g of the calcined AG/SG is weighed and mixed with the 10 g of sodium. The mixture is placed in a rotary steel Parr reactor (from Parr Instruments Company, model 452 HC, item T-316033004 29118) and sealed with a Teflon gasket. This steel reactor is taken out of the He-filled glove box and placed in a rotary oven (at 60 rpm) set at 100 °C for 6 hours and then at 165 °C overnight (12-14 hours). The heat is turned off and the assembly is allowed to cool down to room temperature while rotating for a few hours. It is then transferred back into the He-filled glove box and opened, to give approximately 40 g of free-flowing black powder of Na-SG/Na-AG. The resulting black powder contains approximately 25 % Na, which is further analyzed using the H_2 evolution method.

3.3.2 Characterization of Na-SG and Na-AG

3.3.2.1 Scanning Electron Microscopy (SEM)Analysis

SEM studies on JEOL JSM 6610LV, JEOL 7500F and JEOL 6400V instruments were used to image both the AG and SG. These samples were mounted onto an aluminum stub with carbon

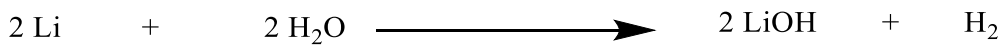
paste and then dried under vacuum for a few hours. Secondary electron imaging was used to obtain the images. Energy-Dispersive X-Ray (EDX) coupled with JEOL 6400V SEM was used to show the crystalline nature of AG and the amorphous nature of silica.

3.3.2.2 Differential Scanning Calorimetry(DSC) Analysis

DSC studies on Instrument Model Q-200 (made by TA instruments) were used to measure weighed samples of Na-SG and Na-AG (approximately 5 mg) placed in a hermetically-sealed aluminum pan (sealed inside the He-filled box). This instrument was used to determine particle size distribution and the presence or absence of any un-incorporated Na metal particles.

3.3.2.3 H_2 Evolution Analysis for Estimating the Amount of Li in Na-SG and Na-AG

In a He-filled glove box, ~1 g of Na-AG/Na-SG is weighed and placed in a dry 50 mL round bottom flask equipped with a greased vacuum stopper. It is then evacuated via a rough pump that has a connection valve within the glove box. The flask is taken out and connected to a vacuum line (with a known volume up to the shut-off valve) and pumped down to about 10^{-4} torr. The closed part of the vacuum line is connected to another flask (1000 mL), 0.5 mL of degassed water is added to the evacuated sample flask with a syringe, and the flask is allowed to cool down to room temperature. The pressure of the resulting H_2 gas in the known volume of the vacuum system is measured with a digital pressure gauge (Cecomp Electronics, model no. ARM760B-5). From the known total volume of the closed system, the pressure of the H_2 (corrected for vapor pressure of water), and the temperature, the molar quantity of H_2 is determined from the ideal gas equation (PV = nRT), based on the equation below;



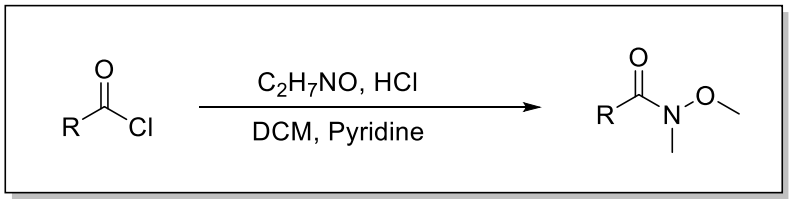
From this, the exact amount of Na in Na-AG and Na-SG is calculated, with an estimated error of ± 2%.

3.3.2.4 Nuclear Magnetic Resonance Spectroscopy (NMR)

Prior to solid state NMR studies, the Na-AG and Na-SG samples were sealed in the He-filled glove box using a 5 mm diameter quartz MAS NMR tube, sealed with heat-shrink tubing and then taken out, and flame-sealed with the sample portion kept cold with liquid nitrogen. All solid-state experiments were run at ambient temperature on a Varian Infinity-Plus NMR spectrometer equipped with a 6 mm (0.236 in.) magic angle (MAS) broadband probe operating at 105.74 MHz for ^{23}Na. A standard one-pulse sequence with ^{1}H decoupling during acquisition was used for all experiments. The ^{23}Na pulse width was 3 μs, the pulse delay was 100 ms, and the acquisition time was 2.05 ms.

3.3.3 Procedure for Weinreb Amide (WA) Synthesis Prior to Reduction

Weinreb amides are easily synthesized from the corresponding carboxylic acid or acid chloride forms.[30,31] All WA were synthesized from their acid chloride counterparts (Scheme 3.1).

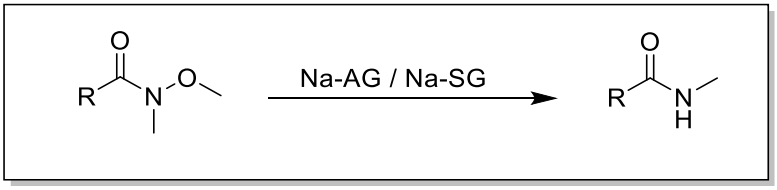


Scheme 3.1: Synthesis of Weinreb amide

In a 50 mL round bottom flask, equipped with a magnetic stir bar and a septum, air was displaced with a continuous nitrogen flow. Then, in approximately 10 mL of dichloromethane, 1 mmol of the appropriate acyl chloride and 1.1 mmol of N,O-dimethylhydroxylamine hydrochloride were dissolved and injected into the flask using a syringe. The reaction mixture was cooled to 0 °C, followed by the addition of 2.2 mmol of pyridine. The resulting mixture was stirred at ambient temperature for an hour. This mixture was then partitioned between brine and a 1:1 mixture of ether and dichloromethane to separate the organic layer from the aqueous layer via separation funnel. The organic layer was dried with sodium sulfate, and filtered into an oven dried round bottom flask, using a Buchner funnel under vacuum. The solvent of the organic layer was then removed, using a rotary evaporator, to isolate the amide product which was pure and no further purification was done. Structures were characterized by ^{1}H NMR.

3.3.4 Procedure for Weinreb Amide (WA) Reduction

In a helium-filled glove box, the desired number of equivalents of Na-AG or Na-SG was added to a round bottom flask, along with a glass-coated stir bar, and the flask was sealed with a septum. This closed system was then taken out of the glove box, continuously purged with nitrogen, followed by injection of the pure synthesized WA dissolved in anhydrous THF (Scheme 3.2). The resulting mixture was stirred for the time specified. After completion of the reaction, the mixture was then partitioned using ethyl acetate and brine. The organic layer was concentrated under reduced pressure using a rotary evaporator. ^{1}H NMR of the crude product was taken to check for reaction extent/completion and to identify the products obtained. Crude product was fractionated and purified by column chromatography on silica gel to afford the desired product and byproducts.



Scheme 3.2: Reduction of Weinreb Amide

3.4 Results and Discussions

3.4.1 Characterization of Na-SG and Na-AG

SEM images (Figure 3.3 and 3.4) show the crystallinity of γ-alumina and the amorphous nature of silica gel (purchased from Davison Catalyst) at two different magnifications (for both AG and SG). The AG shows interconnected nanocrystals of γ-alumina, while SG shows interconnected SiO_2 amorphous nanoparticles with diameters comparable to those of the interparticle pores.

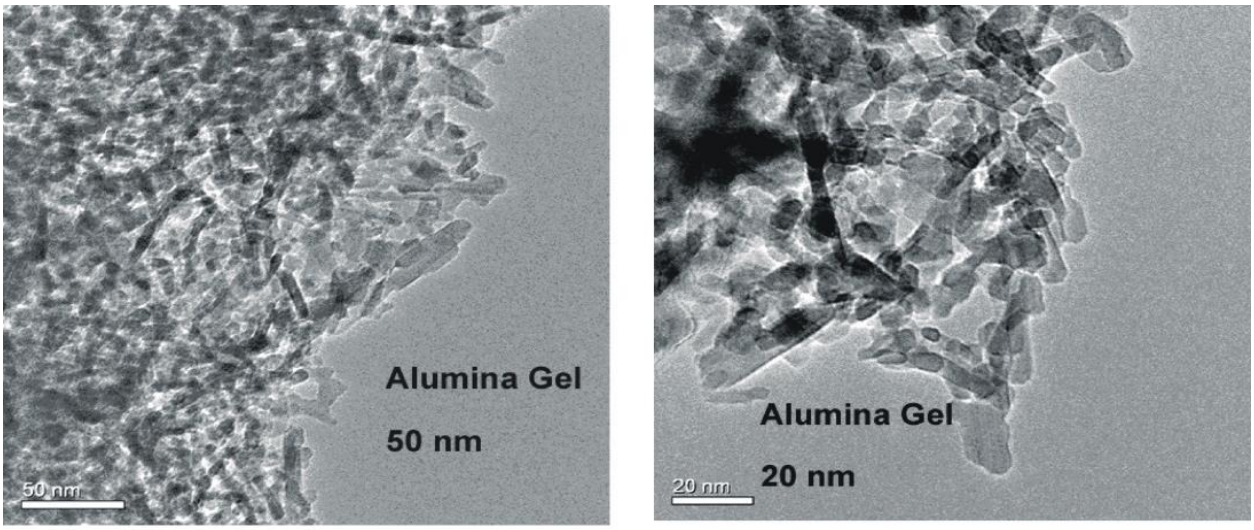


Figure 3.3: Scanning electron microscopy (SEM) of γ-alumina gel (AG)

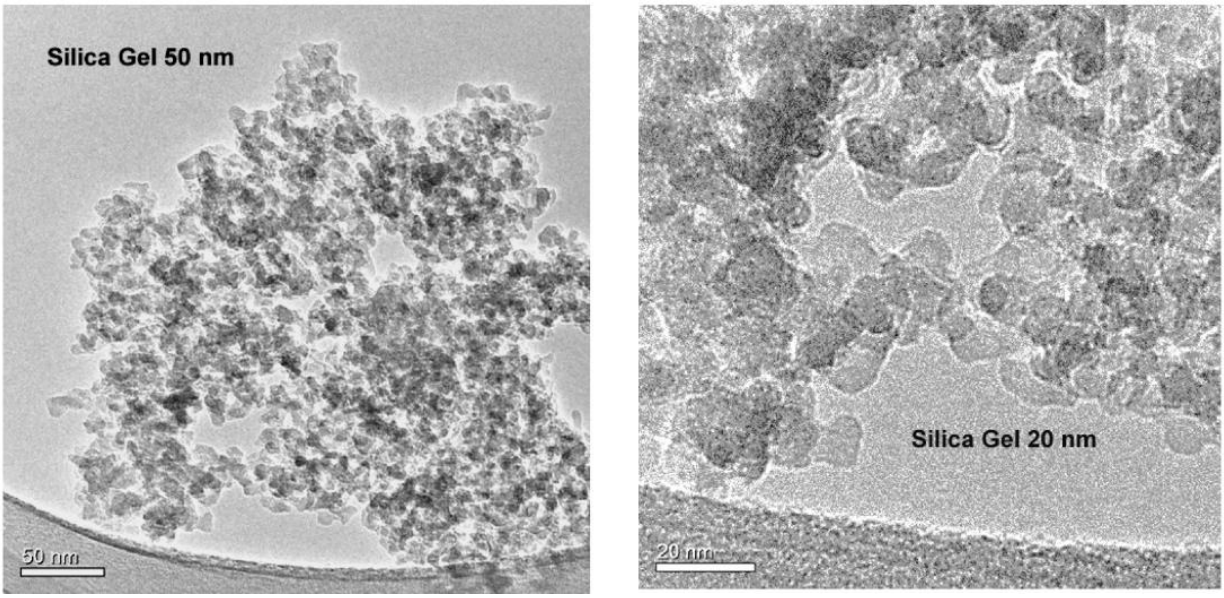


Figure 3.4: Scanning electron microscopy (SEM) of silica gel (SG)

Both qualitative and quantitative information about physical and chemical changes that involve endothermic and exothermic processes of a catalyst can be obtained by using DSC. This instrument measures the temperatures and heat flows associated with transitions in materials as a function of time and temperature. Figure 3.5 and 3.6 shows the melting endotherms of sodium at 82 °C and 76 °C, with ΔH_{melt} (compared with the bulk metal) reduced to 17.7% and 26.4% respectively. These endotherms indicate that Na-AG/Na-SG is non-pyrophoric and the sodium metal is within the pores of AG. If these endotherms had shown a peak at the melting point of Na (97.7 °C), (as occurred in some samples) it would indicate the presence of metallic Na on the surface of the AG, which can lead to pyrophoric behavior. Also, lowering of the melting point shows that the particles are small and the spread of these endotherms reflect the distribution of particle sizes. In addition, these decrease is said to be associated with decrease in the percent present as metal distributions into small sites, and or the effect of particle size on the enthalpy of melting.[20] Changes in ΔH_{melt} could be used to estimate the fraction of metal remaining in the pores after heat treatment compared with that initially present.

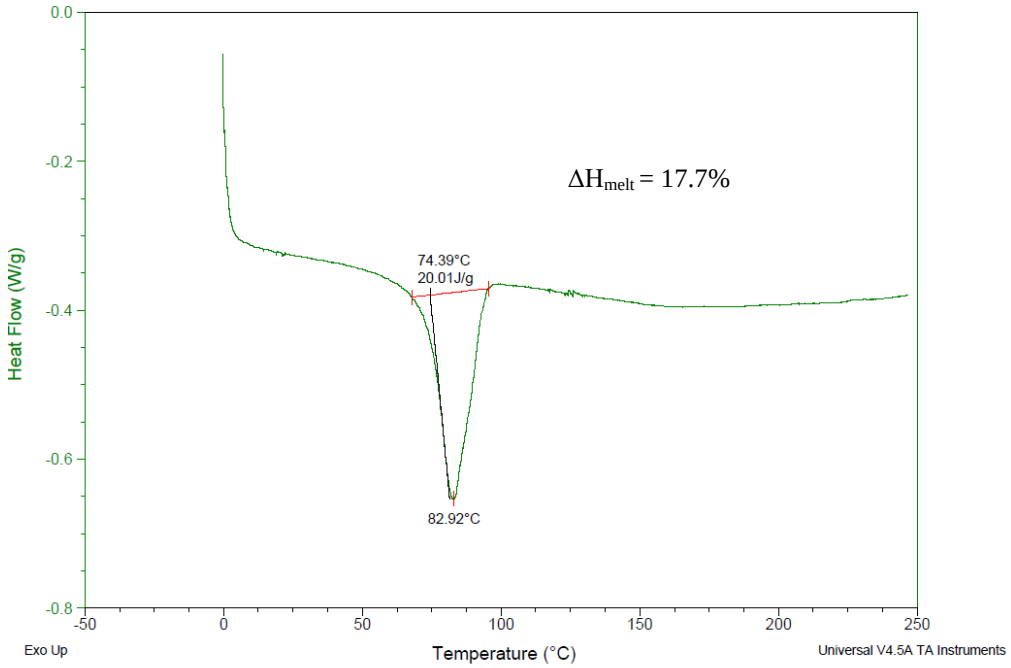


Figure 3.5: Differential Scanning Calorimetry (DSC) thermogram of Na-AG (AG 190 Å)

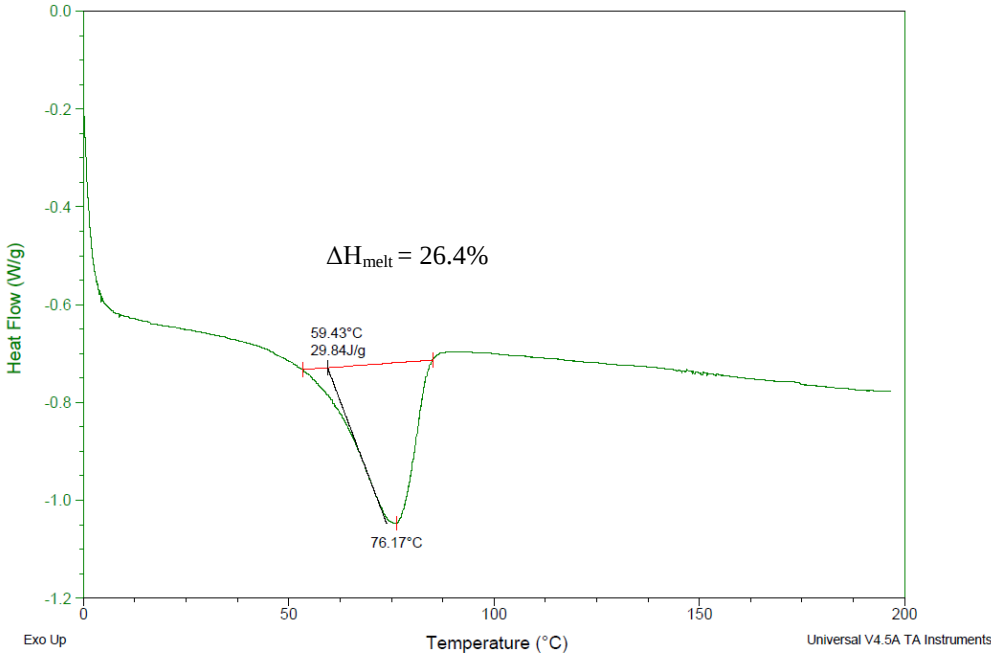


Figure 3.6: Differential Scanning Calorimetry (DSC) thermogram of Na-SG (SG 150 Å)

The MAS solid-state ^{23}Na NMR of a sample of Na in AG (Figure 3.7, performed by Prof. James L. Dye), shows both Na^0 and Na^+. This indicates that Na is ionized to some extent or has undergone a reaction, probably with residual Si-OH groups or moisture.[20] The relative intensity of Na^0 (1069 ppm) and Na^+ (near zero) maybe temperature dependent.[20,21] The difference between Na in AG (which occurs only in pores or on particle surfaces) and Na in SG which can occupy pores and surface sites, but is also present as highly mobile Na^+SG^- pairs, in which the electron of Na is transferred to an oxygen of Si. The details of this process is not known but it clearly appears, but not with Na-AG. This probably results from the amorphous nature of SG as indicated in Figure 3.4 (contrast with Figure 3.3 for AG).

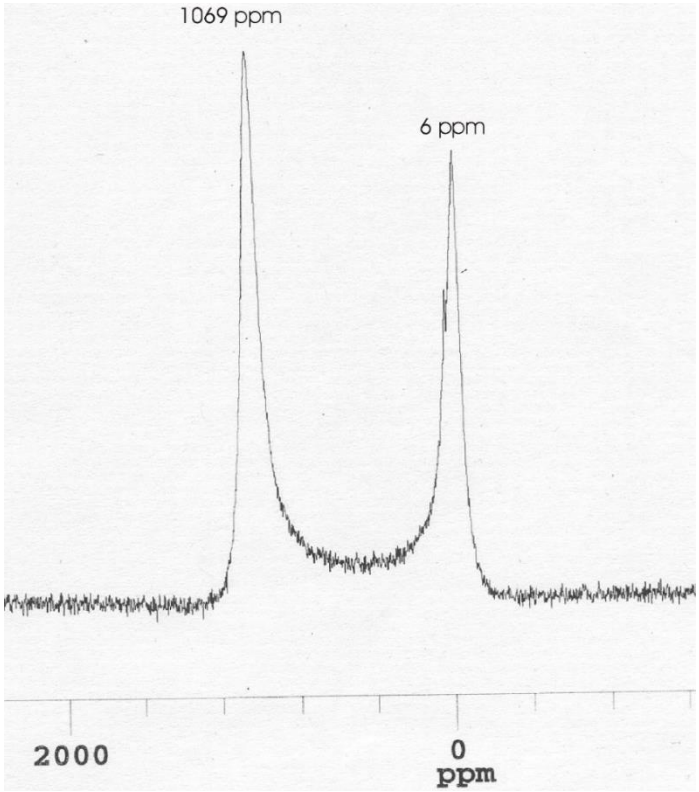


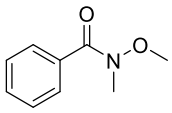
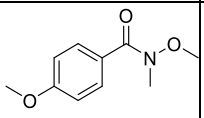
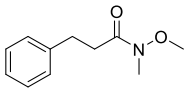
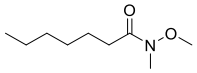
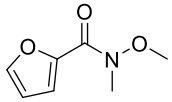
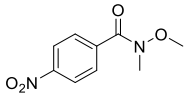
Figure 3.7: Solid-state Nuclear magnetic resonance spectroscopy (NMR) of a sample of Na-AG which shows both Na^0 and Na^+.

3.4.2 Substrate Scope

3.4.3 Reduction of Weinreb Amides (WA)

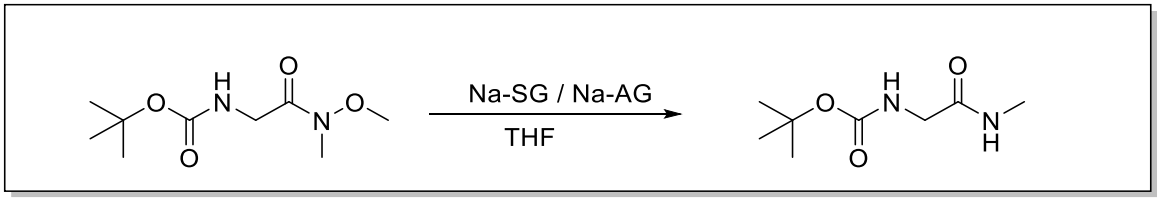
Table 3.1 lists reductions effected by Na-AG and Na-SG on a group of aromatic and aliphatic WA. Reaction times and conditions listed were optimized by TLC monitoring. For example, two and three equivalents (counted as electron pairs—i.e. 4 and 6 mol of Na/mol substrate) did not fully convert all of substrate **1** to product within a reasonable time (4 h) so the number of Na-AG equivalents was increased to speed the reaction to completion. Isolated yields were determined by the mass of the purified product. For the isolated yields shown, Na-AG was used as the reducing agent since it proved more difficult to quantitatively recover the products from silica gel. However, ^{1}H NMR spectra showed that both reagents achieved similar extents of reactant conversion and product purities under similar conditions.

Table 3.1: N-O bond cleavage by Na-SG and Na-AG

Substrate	Na-SG		Na-AG		
	Equiv.	Time (hrs.)	Equiv.	Time (hrs.)	Isolated Yield[a] (%)
 1	4	2	5	2	91
 2	4	2	5	2	96
 3	3.5	2	4	2	75
 4	5	3	4	2	68
 5	6	4	6	4	78
 6	5	2	5	4	57

[a] Isolated yield is based on mass of purified product obtained from Na-AG.

To explore reactions of WA substrates of higher functionality, we examined the *t*BOC-protected WA of glycine, *t*-butyl(2-(methoxy (methyl)amino)-2-oxoethyl)carbamate (Scheme 3.3). This WA was cleanly reduced with 2 equivalents of Na-AG in two hours (80% crude yield by ^{1}H NMR). However, product purification was stymied by degradation during chromatographic workup.



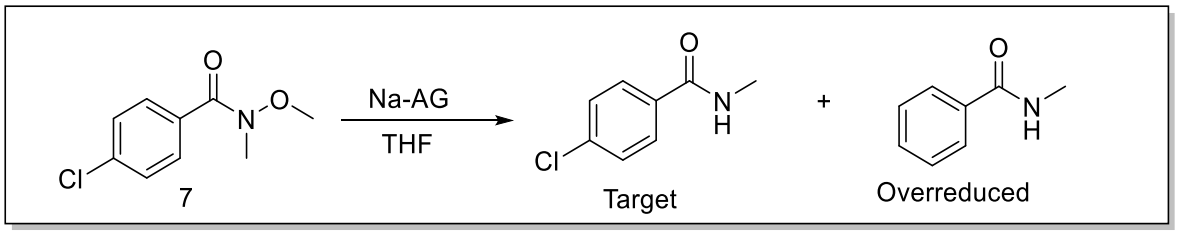
Scheme 3.3: t-BOC-protected WA reduction

Overall, these reactions, run under ambient conditions, are comparable in simplicity to the procedures used for analogous reactions using reagents such as SmI_2/THF (typically at -78 °C) or Li/4,4'-di-t-Butylbiphenyl (-78 °C or ambient temperature).

3.4.4 Mechanistic Studies and Over-reduction

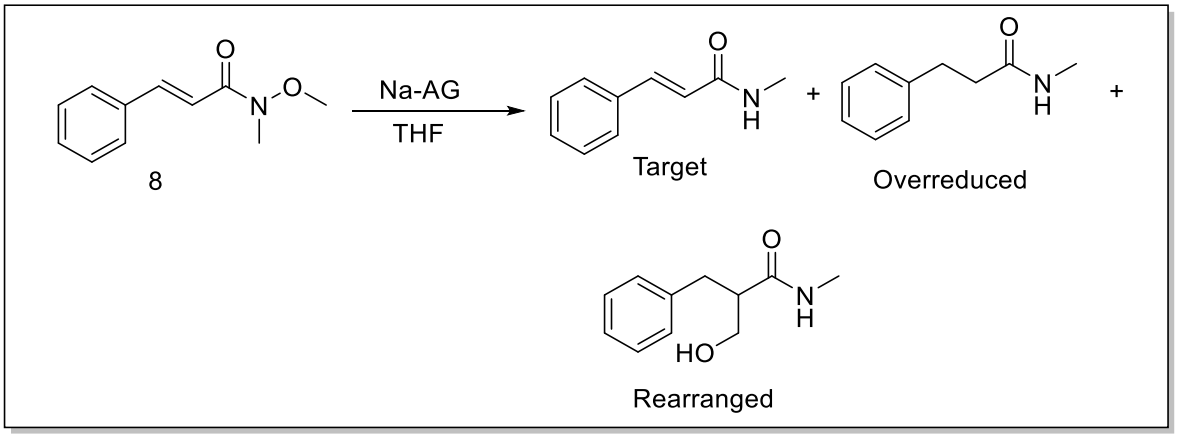
A possible mechanism for homogeneous reduction of WAs by 'super electron donors' as suggested by Murphy *et al.* consists of two single-electron transfers followed by proton addition.[18]

Since Na-AG and Na-SG are such powerful reducing agents, the selectivity between N-methoxy cleavage and the reduction of other groups is of particular interest, as are strategies to modulate such selectivities. Schemes 4 and 5 shows two reactions chosen to probe for reduction selectivity and control. In addition to N–O cleavage, substrate **7** (4-chloro-N-methoxy-N-methylbenzamide) can lose chlorine to form over-reduced N-methylbenzamide (Scheme 3.4), the compound formed upon N–O cleavage of substrate **1** (Table 3.1), and the desired target.



Scheme 3.4: 4-chloro-N-methoxy-N-methylbenzamide reduction

Similarly, substrate **8** (N-methoxy-N-methylcinnamide) gives a mix of the expected N-methoxy cleavage product and over-reduced (hydrogenated) compound (Scheme 5), the same product as that from substrate **3** (Table 1). To our surprise, in addition, substrate **8** yields varying amounts of a third product, as shown in Scheme 3.5; formation of this compound, in which the elements of the WA's methoxy group are retained but rearranged, is further discussed below.



Scheme 3.1: N-methoxy-N-methylcinnamide reduction

Over-reduction is not surprising; alkali metals in silica gel can effect Birch reductions under similar conditions.[23] The relative yields of products and over-reduced compounds vary somewhat from run-to-run, apparently due to batch-to-batch differences in the Na-AG reagent, rather than variations in the methodology used. For example, three reductions run side-by-side with the same reagents and concentrations gave essentially the same product yields. Variations in yield may in part reflect numbers and distribution of the residual Al-OH groups that surprisingly remain in the material after calcination and serve as proton sources.

Though competing reductions of functional groups within a compound do occur, the absence of products in which only the C–Cl bond is cleaved (substrate **7**) or only the pi bond is reduced (substrate **8**) suggest preferential N–OCH_3 cleavage in advance of, or to initiate further reduction

(Scheme 4 and 5 above). Thus, when both reductions occur, it is likely that a single encounter of the WA with the reducing site is involved. Reaction does not appear to depend on special sites; explicit attempts to quench the most reactive sites of Na-AG by pre-treatment with ethanol at 10–30% of the Na content do not alter selectivity. Since each of the reactive sites on a nanoparticle of sodium has many adjacent sodium atoms that can exchange rapidly with a reducing site,[20] multiple reduction steps are possible. If a molecule with two reducible sites stays adsorbed long enough, a second reduction could occur. The resulting reduced but unprotonated products would presumably remain bound to the alumina gel until protonation released them.

Since protonation of intermediates seems required to release products, a number of runs were made with H_2O or D_2O or alcohols added to the THF as possible protonating agents or used to quench reactions which had been run in anhydrous THF. The percentage of desired product increased slightly, but no conditions completely prevented over-reduction. When 5–10% H_2O or D_2O and 2 equivalents of Na-AG were used at 25 °C, five reductions of substrate **8** yielded 37 ± 9% desired product, compared with 19 ± 3% for six runs in anhydrous THF.

Although the formation of over-reduced compounds could not be eliminated, the percent desired reduction at the N–O site alone is influenced by several factors. Complete over-reduction of substrate **8** occurs in 2 h at 25 °C when 4 equivalents of Na-AG are used, but about 25% simple N–O cleavage product is produced with 2 equivalents. Lowering the temperature also yields more of the desired product although higher reagent amounts and/or longer reaction times are required. Consistent with the idea that both N–O reduction and over-reduction processes happen in one encounter, sampling at time intervals through the reaction showed essentially no selectivity variation; except for a slight preference for N–O reduction early in the reaction, the relative ratios of reduced to over-reduced products were essentially independent of reaction progress. If protonation of the amide's N (-) site and release to solution occurred before reduction at the

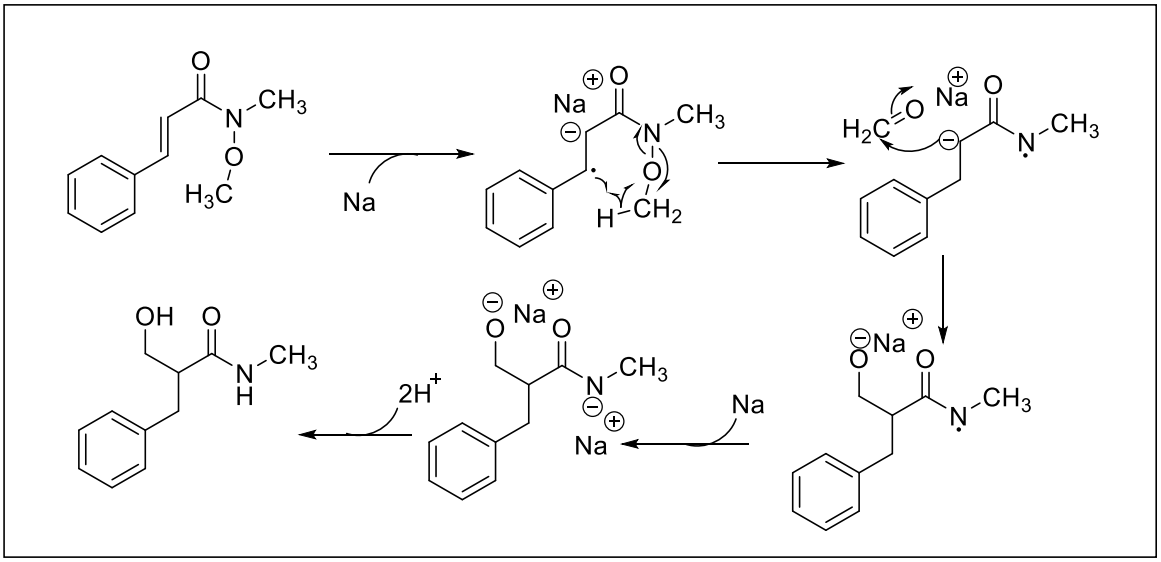
secondary site, the proportion of over-reduced intermediates formed in a second reduction step should vary, and reduced products should undergo further reduction; neither of these outcomes are seen.

The over-reduced product of 4-chloro-N-methoxy-N-methylbenzamide WA (substrate **7**, Scheme 4), has the Cl replaced by H. Similarly, the reduction of the double bond in substrate **8** (Scheme 5) requires the addition of two hydrogen atoms. In an attempt to determine the source of this hydrogen, the normal reduction in anhydrous THF, followed by quenching with saturated NH_4Cl was modified (in separate experimental studies) by (1) reduction in deuterated THF, (2) quenching with D_2O and (3) reaction in THF containing small amounts of H_2O, D_2O, or deuterated alcohols. Product analyses (^1H NMR and GC–MS) in all cases showed at most small amounts (less than 10%)of deuterium in the over-reduced products from either of these experiments. The absence of completely deuterated over-reduced products suggests that the strongly basic amide anion and carbanion intermediates formed are bound to the alumina gel until protonation, which must occur at or near the site of reduction before the products migrate into the solution. Thus, proton donor sites must remain in the AG. Indeed, even after alumina calcination at 600 °C, –OH bands could be seen in FT-IR spectra of the AG, and the formation of hydrogen upon reaction with liquid Na_2K alloy verified the presence of at least 0.9 mmol of reducible Al-OH groups per gram of Al_2O_3, enough to protonate all reduced intermediates. Thus, the residual Al-OH groups on the surface of the alumina nanocrystals, and therefore near the encapsulated sodium, could provide the proton source. The variable density of such sites from sample to sample could also be responsible for the variations of desired versus over-reduced product ratios from run to run. It had been thought that Al-OH groups would be eliminated by hydrogen production during normal preparation (by molten Na treatment at 160 °C) of Na-AG from alumina that had been calcined at 600 °C. However,

careful monitoring of the gas phase during Na-AG preparation revealed that hydrogen is not formed during this incorporation of sodium.

The above findings prompted several attempts in D_2O under hydrothermal conditions to pre-deuterate the alumina used for preparation of the Na-AG. Despite the use of rigorous glassware drying and dry box techniques, no replacement of H by D was seen, either by FT-IR of the dried, calcined AG, nor in either of the over-reduction products from Na-AG treatment of substrates **7** or **8**.

The rearranged byproduct from substrate 8 (Scheme 5) can most simply be understood in terms of base or radical promoted elimination across the HCH_2–ON bond of the Weinreb amide to form formaldehyde. This electrophile, trapped in the pore in proximity to the reduced cinnamate anion evidently undergoes aldol condensation with the amide enolate, forming a hydroxymethyl group vicinal to the amide. Such base-promoted cleavage of Weinreb amides has been observed previously under treatment with strong bases such as LDA.[32] N-Hydroxymethylated amides have been produced in one case,[33] albeit in a Lewis acid context, but formaldehyde adducts directly analogous to the present case have not been reported from such reductions, even under conditions where enolate formation was verified via H/D exchange. Interestingly, in the present case, only the cinnamide **8** yields this product; its saturated analogue (substrate **3**) yields no hydroxymethylation. We speculate in analogy to previous suggestions[32,33] (Scheme 3.6) that the radical anion formed upon addition of an electron to the cinnamide pi system serves as a base to abstract one of the methoxy –OCH_2-H hydrogen atoms, forming the formaldehyde in close proximity to the enolate anion and leaving an unpaired electron on the amide N, which then rapidly accepts an additional electron.



Scheme 3.2: Formation of N-Hydroxymethylated amides

3.5 Summary

In summary, this chapter shows that Na-AG and Na-SG easily and cleanly effect WA reduction in simple, batch reactions under ambient conditions and in modest reaction times. These reactions are not highly selective, but in situations with simple substrates or where global reduction is desired, they are quite effective. Cases where over-reduction occurs show how powerful the reducing agents Na-AG and Na-SG are, and demonstrate unambiguously that even after 600 °C calcination and treatment with molten sodium, the alumina in Na-AG retains a nontrivial load of –OH sites. In the absence of secondary reducible sites, this method can be usefully applied to WAs to form secondary amines under reasonable yield. Though these reagents are not as selective as SmI_2 or Murphy's super electron donors, their simplicity, potent reducing power, and benign byproducts nonetheless make them a useful addition to the synthesis chemist's toolbox.

APPENDIX

APPENDIX – Copyright Permission

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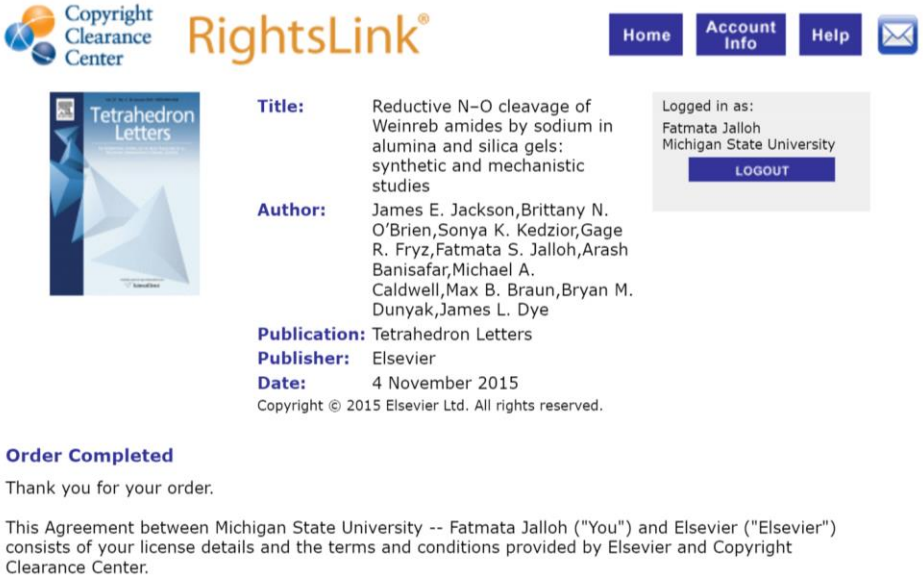

Permission granted to use Figure 3.1: Crystalline and amorphous form of SiO_2.[2] "Reproduced with permission NDT Resource Center and Center for NDE, Iowa State University."

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Chapter 4.0: Reduction of Amides to Amines

4.1 Background

Amines are compounds with a functional group containing a basic nitrogen atom with a lone pair of electrons. They are derivatives of ammonia, in which one or more of the hydrogen atoms is/are replaced with a substituent (example, an alkyl or aryl group). They are categorized into three groups: primary, secondary, tertiary, in addition, secondary or tertiary amines may be cyclic or open-chain.

Amines and their derivatives are important synthetic targets found in various natural products,[1–3] and are key components of many essential biochemicals. For instance, the amine serotonin (5-hydroxytryptamine) is an important neurotransmitter in the brain, gastrointestinal tract, blood platelets, and the central nervous system. In the brain, it regulates anxiety, happiness, and mood, as well as sleeping and waking up. Even more important are the amino acids, the building blocks of proteins.

The unique biological properties of amines make them outstanding products and precursors in the pharmaceutical industries, where they serve as intermediates in the manufacture of drugs and medicines,[4,2] especially for chemotherapy of various diseases.[5,6] For instance, the opiate morphine is an analgesic for the treatment of pain (both acute and chronic) and acts directly on the central nervous system. This drug was first isolated by a German pharmacist, Friedrich Wilhelm Serturner in 1804, who named it after the Greek God of dreams, Morpheus. Morphine was the first alkaloid to be isolated from the poppy, a plant of little known usefulness. However, it was not until 1827, that the pharmaceutical company Merck started marketing it commercially. Since then, it has been widely used for the treatment of both acute and chronic pains.

In this chapter, the chemical and physical properties of amines are briefly discussed along with various methods their synthesis including alkylation, reduction, and other techniques. The successful application of sodium encapsulated into silica and alumina gel to effect the Bouveault-Blanc reduction of esters to alcohols,[7] is herein extended to the reduction of amides to amines as a new research area. Sodium preparations in both silica and alumina gel provide a new reaction route for the reduction of amides to amines.

4.2 Physical Properties of Amines

In general, amines are characterized by their ammonia smell or fish-like odor. Due to the electronegativity of the nitrogen atom in amines, both primary and secondary amines can form hydrogen bonds between the N-atom of one molecule and the H-atom of another. Therefore, they have higher melting and boiling points than their non-polar hydrocarbon counterparts of comparable molar masses.[8] On the other hand, they have lower melting and boiling points than those of the corresponding alcohols or carboxylic acid due to the greater polarity of O-H bonds over the N-H bonds in amines, as shown in Table 4.1 below. Nonetheless, their hydrogen bonding character makes lower molecular weight aliphatic amines highly soluble in water and other solvents. The solubility decreases as the molecular weight of the hydrocarbon part of the molecule becomes larger, making higher molecular weight amines more strongly prefer in less polar solvents relative to water.[8] Aromatic amines on the other hand, exhibit a lower tendency to serve as lone pair donors in hydrogen bonds, but stronger H-donor character, due to the near sp^2 hybridization of the aniline nitrogen.

Table 4.1: Boiling point comparison

Compound	Boiling Point (°C)
Heptane	98.38
Hexylamine	131.50
Hexyl alcohol	157.00
Toluene	111.00
Aniline	184.13
Phenol	181.70

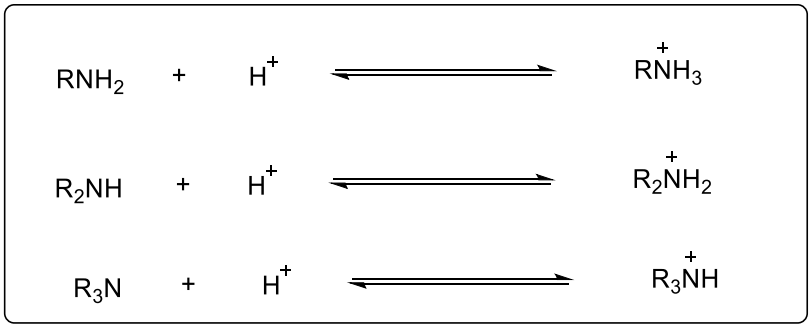
4.3 Chemical Properties of Amines

The chemical reactions governing amines are due mainly to the presence of lone pairs of electrons on the nitrogen atom. This lone pair makes them strong bases and nucleophiles.[8]

Lower molecular weight aliphatic amines are stronger bases than ammonia due to the positive inductive effect.[9] Alkyl substituent which are conventionally viewed as electron-releasing groups, are thought to increase the electron density around the nitrogen and hence, the availability of the lone pair of electrons for donation to Lewis acids. Thus, the basicity is expected to increase with the number of alkyl groups. For aromatic amines, however, delocalization of the lone pair of electrons on nitrogen into the ring results in decreased basicity.

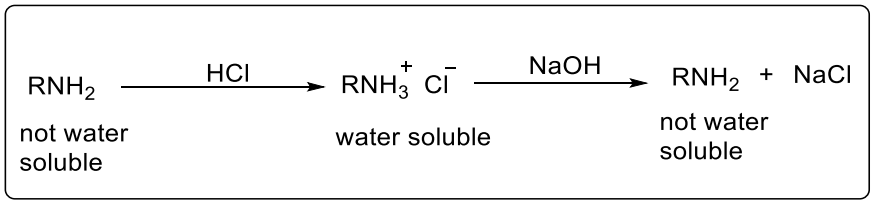
4.3.1 Reactions with Acids

Amines are protonated by acids to form salts, which are typically ionic and non-volatile solids (Equation 4.1). The order of reactivity is tertiary > secondary > primary.



..... Eq. 4.1

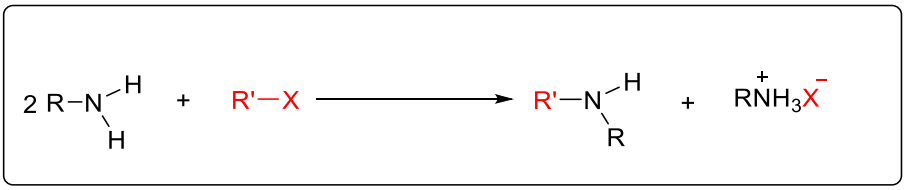
Water insoluble amines can thus be easily separated from non-basic compounds by reacting them with acids to make them water soluble but poorly soluble in non polar solvents (Equation 4.2). From the aqueous acidic solution, the amine can then be regenerated by making the solution alkaline.



..... Eq. 4.2

4.3.2 Reactions with Alkyl Halides (Alkylation)

Amines react with alkyl halides to form amines of higher class via a nucleophilic attack. In this process, the nitrogen lone pairs are donated to the electron deficient carbon, displacing the halide anion (Equation 4.3).

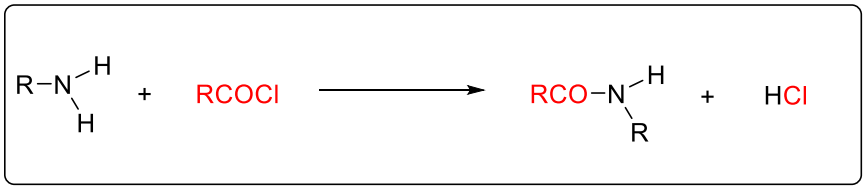


..... Eq. 4.3

This method is widely used to produce higher substituted amines. However, the reaction is difficult to control since the higher substituted amine produced is more nucleophilic than the starting amine, making it prone to further alkylation and ultimately quaternization.

4.3.3 Reactions with Acylating Agents

Only primary and secondary amines can be acylated by reaction with acid halides and anhydrides. (Equation 4.4). The product is an amide. This reaction was first described by two German chemists, Carl Schotten and Eugen Baumann in 1883, and is hence was named the "Schotten-Baumann reaction".

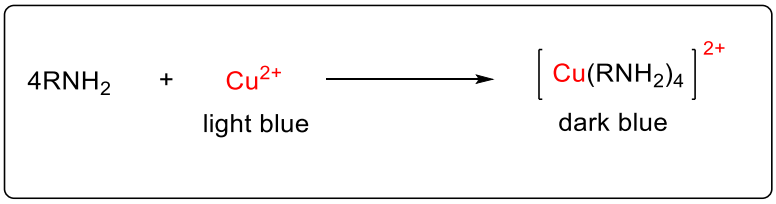


..... Eq. 4.4

As shown in Equation 4 above, the acyl group ($R-\overset{O}{\overset{\|}{C}}-$) is transferred onto the amine nitrogen (acylation), followed by loss of a proton and elimination of Cl^-. This is a common approach employed in the preparation of amides.

4.3.4 Reactions with Transition Metal Ions

Amines have the capacity to form dative bonds with transition metal ions, where they act as ligands, often giving rise to colored complexes as electronic transitions of the metal ions are modified. For example, $Cu^{2+}_{(aq)}$ ions react with amine to give a dark blue complex solution as shown in Equation 4.5 below;

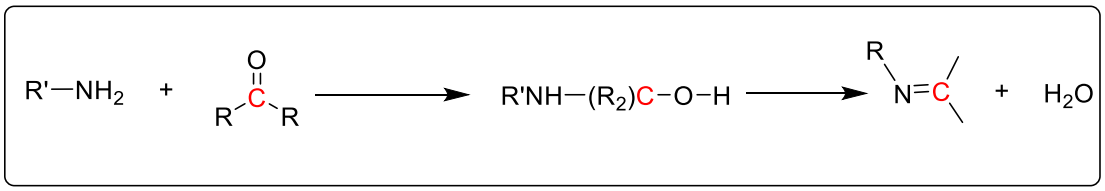


..... Eq. 4.5

Transition metal-amine complexes play important roles among antitumor drugs.[10] For instance, the bis amine complex Cisplatin ($PtCl_2(NH_3)_2$), discovered at MSU, is a drug administered intravenously for the treatment of a number of cancers.[11–13]

4.3.5 Reactions with Aldehydes and Ketones

Primary amines react with aldehydes or ketones in a nucleophilic addition manner to form substituted imines (Schiff's bases). Schiff bases after their discoverer Hugo Schiff, which are key intermediates in various synthetic and biological reactions.[14–17] The reaction with aldehydes and ketones initially results in the formation of carbinolamines, which then undergo dehydration to give an imine (Equation 4.6).[18]

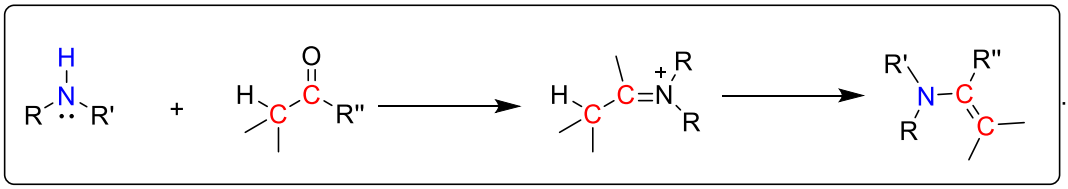


..... Eq. 4.6

However, since it is acid catalyzed to enhance the activation of the C=O of the carbonyl and promote dehydration, the pH of the reaction must be carefully controlled to avoid inhibiting the nucleophile via protonation.

Secondary amines react with aldehydes and ketones to give enamines rather than the imines, in cases where the carbonyl compound has enolizable C-H sites. The reaction proceeds through the formation of iminium intermediate, which can lose a proton to form enamine (Equation 4.7). They

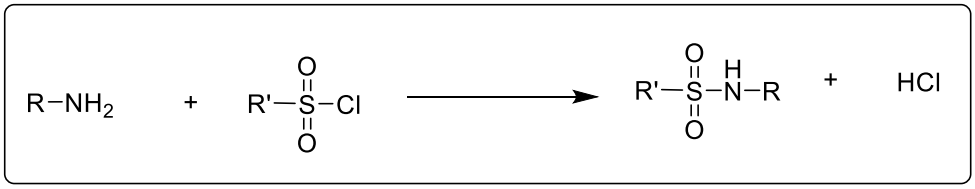
play an important role as an intermediate and blocking group in organic chemistry.[19–22]



..... Eq. 4.7

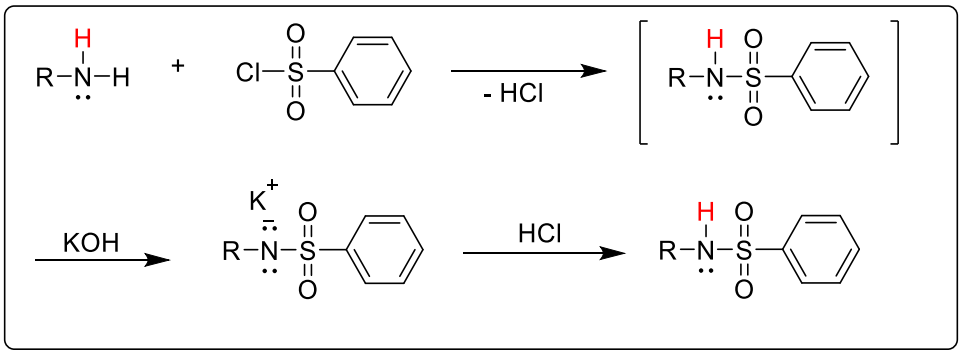
4.3.6 Reactions with Sulfur (Sulfonation)

Amines react with sulfonyl chlorides (Hinsberg reaction) to form sulfonamides (Equation 4.8); a common method for detecting primary and secondary amines.[23]



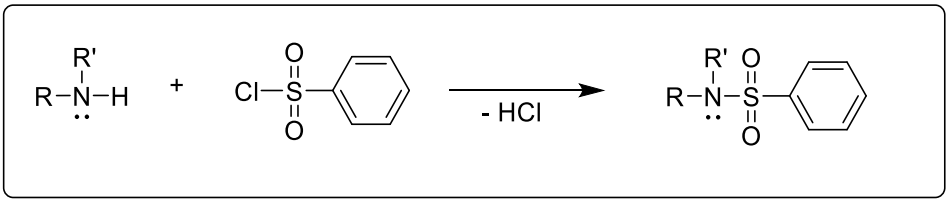
..... Eq. 4.8

The test for primary amines involve their reaction with benzenesulfonyl chloride to form N-substituted benzenesulfonamides, which undergo an acid-base reaction in the presence of potassium or sodium hydroxide to form soluble salts. Acidification of this solution results in the formation of a precipitate (Equation 4.9).



..... Eq. 4.9

Secondary amines on the other hand, react with benzenesulfonyl chloride in aqueous solutions of potassium or sodium hydroxide to form precipitates of N,N-disubstituted sulfonamides (Equation 4.10).



With tertiary amines, no visible change is seen upon reaction with benzenesulfonyl chloride and aqueous solutions of potassium or sodium hydroxide. However, if the tertiary amine is water insoluble, acidifying the mixture deprotonates the amine to form a water-soluble salt.

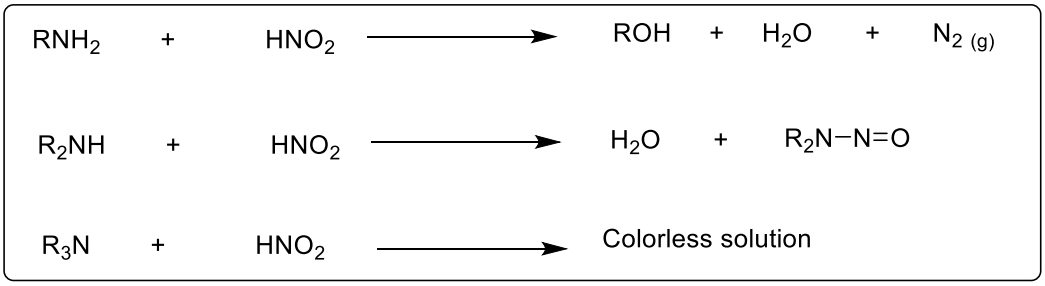
As the first antibiotic drugs to be discovered, sulfonamides have medicinal value and represent a whole class of drugs in the pharmaceutical industry.[24–26] One of their main uses is as bacteriostatic agents, inhibiting growth and multiplication of bacteria by interfering with bacterial synthesis of folic acid.[27,28]

For instance, they are used in the treatment of urinary tract infections in combination with other drugs, and for preventing infection from burns.[29] They are used in allergic treatments, cough, and as antimalaria, and antifungal agents.[24,25,30]

4.3.7 Reactions with Nitrous Acid (Diazotization)

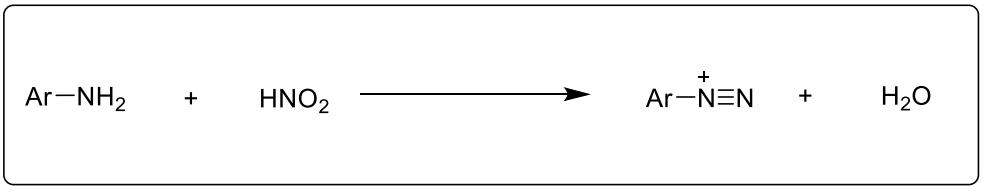
The reaction of amines with nitrous acid can be used as a distinguishing test for aliphatic amines (primary, secondary, and tertiary).[8] While primary amines react with nitrous acid to produce nitrogen gas from a clear solution, secondary amines produce a yellowish oil known as N-

nitrosamine (which is said to be carcinogenic), and tertiary amines give rise to a colorless solution (Equation 4.11).[23]



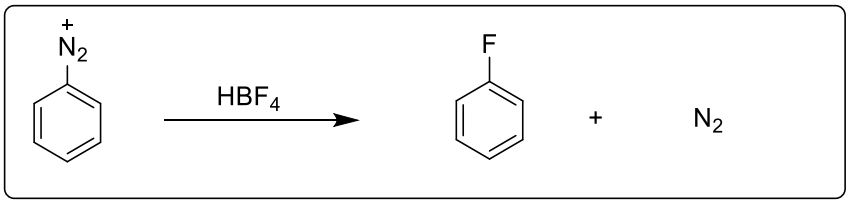
..... Eq. 4.11

Contrary to aliphatic amines, primary aryl amines generally react with nitrous acid to give diazonium salts (Equation 4.12), which are stable enough to be isolate.[8,23]

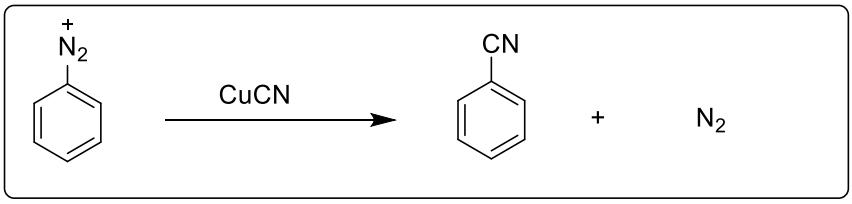


..... Eq. 4.12

These diazonium salts are important intermediates in various chemical transformations involving the replacement of the N_2 group under mild reaction conditions. For instance, aryl diazonium substitution reactions have been used extensively in the synthesis of polysubstituted benzene derivatives (Equation 4.13 and 4.14), without the need to have activating groups (nitro or cyano), at the ortho or para position.[23]

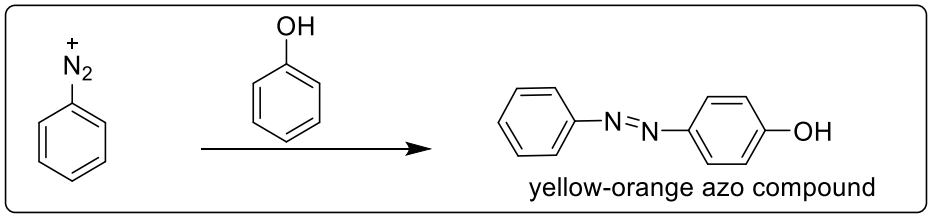


..... Eq. 4.13



..... Eq. 4.14

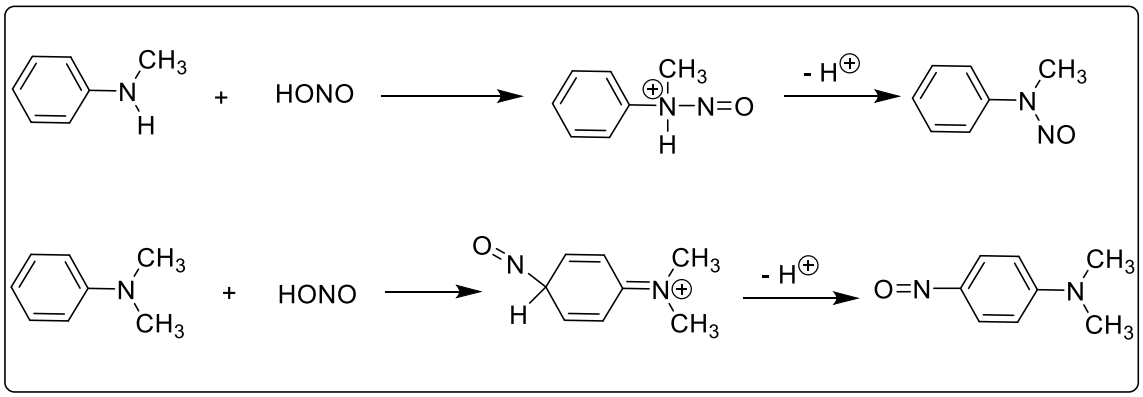
Aryl diazonium compounds are also used extensively in the synthesis of azo compounds in the dye industries.[31,32] Equation 4.15 shows the formation of an azo compound from the coupling of aryl diazonium ion to an electro-rich phenol, to give yellow-orange product, 4-(phenyldiazenyl)phenol.



..... Eq. 4.15

The reaction proceeds via an electrophilic aromatic substitution process, in which the aryl diazonium salt act as an electrophile while the activated arene as the nucleophile.[33] The resulting compounds are bright colored due to the extended conjugation which allows them to absorb light in the longer wavelengths, leading to their applications in the dye industries.[33]

As with secondary aliphatic amines, secondary aryl amines undergo reaction with nitrous acids to form N-nitroso compounds, and tertiary aryl amines undergo electrophilic substitution with the NO^+ of nitrous acid provided there is an unsubstituted para position (Equation 4.16).[23]



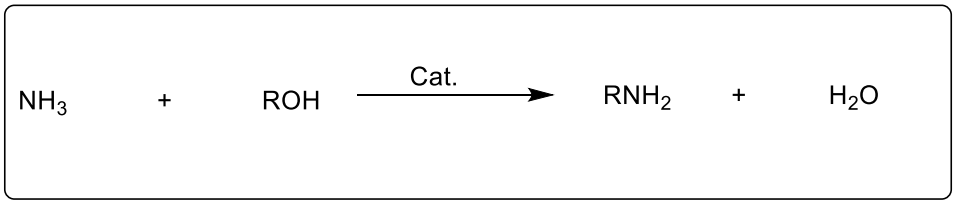
. Eq. 4.16

4.4 Synthesis of Amines

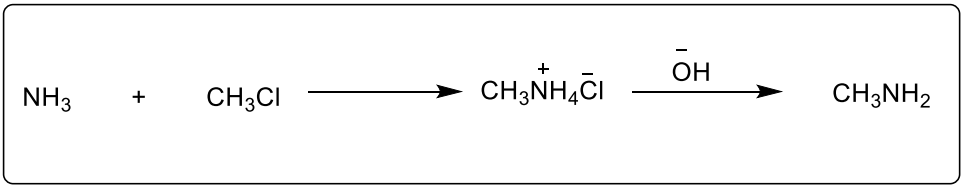
Due to the importance and unique biological properties of amines, many routes have been developed for their synthesis. Broadly considered, the known routes can be grouped into 3 main categories: alkylation, reduction, and other methods.

4.4.1 Alkylation

This method involves the treatment of ammonia with either alcohols or alkyl halides (Equation 4.17 and 4.18 respectively).



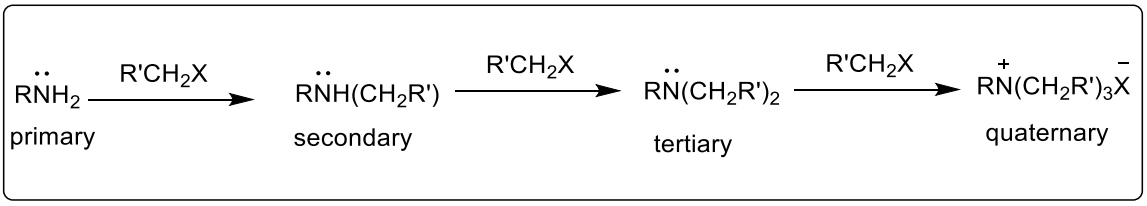
..... Eq. 4.17



..... Eq. 4.18

Alkylations using alcohol are usually employed in industry since they are less expensive, and non-toxic than the corresponding alkyl halides. However, to effectively displace the hydroxyl group, high temperatures and hydrogen activation catalysts (Ru,[34,35] Rh,[36] Fe,[37] Pd,[38] etc.) are required; these reversibly oxidize the alcohol to a carbonyl compound that then condenses with the starting amine, loses H_2O, and is re-reduced, as shown in Equation 4.17 above.

The reaction of ammonia with alkyl halides to form amines is often problematic. This is because ammonia serves as the initial nucleophile but as mentioned above, each alkylation step form higher amine which can still serve as a nucleophile; the result is a mixture of primary, secondary, and tertiary amines, along with quaternary ammonium salts (Equation 4.19).



.. Eq. 4.19

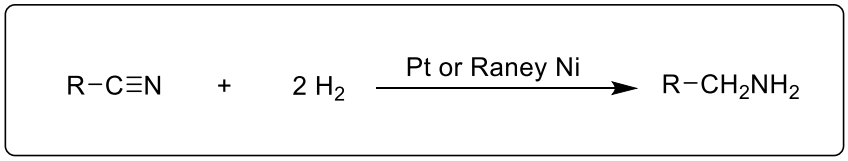
This method can serve as a direct route for the synthesis of quaternary ammonium salts, but in preparation of a primary amine, such mixtures of products are typically avoided by the use of a large excess of ammonia. However, with the growing interest and importance of amine synthesis, various methods involving the use of metal catalyst or base have been developed to overcome this drawback. For instance, Salvatore *et al.*, in 2002, developed a method to prevent overalkylation, where they employed cesium as a base to promote the alkylation of primary amine and suppress the overalkylation to secondary amine with alkyl halides.[39] In 2005, Soloshonok *et al.*, also

reported the synthesis of tertiary amine using Hunig's base (*N*,*N*-diisopropylethylamine) to effect the alkylation of secondary amines with alkyl halides in acetonitrile without over-alkylation to quaternary ammonium salts. In addition, the drawback has been addressed by synthesizing tertiary amines by alkylation of both primary and secondary amines, under microwave irradiation, using aqueous media ($NaOH/H_2O$).[40] Under microwave irradiation at 80-100 °C, tertiary amines were obtained in high yield in 25 minutes.

4.4.2 Reductive Methods

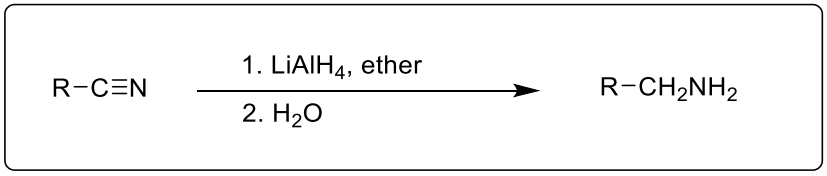
4.4.2.1 Nitrile Reduction

Due to the robustness of the cyano group, nitriles can only be reduced to amines either catalytically or by using potent hydride donors (non-catalytic route).[8] Catalytic hydrogenation (Equation 4.20) involves the use of hydrogen gas in the presence transition metal catalysts such as nickel, or Raney nickel, or platinum dioxide.[41]



..... Eq. 4.20

Although the catalytic routes offer a big advantage in terms of green chemistry, such as waste prevention/minimization, high atom efficiency, and energy consumption reduction,[42,43] non-catalytic routes have been explored as well. For the non-catalytic route, nitriles are reduced by reducing agents such as lithium aluminium hydride, lithium borohydride, or diborane to give amines (Equation 4.21).[8,44,45]

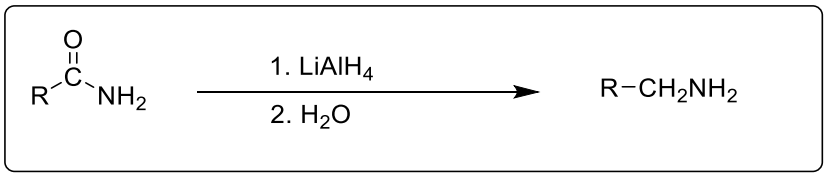


..... Eq. 4.21

Due to the lack of selectivity of strong reducing agents such as lithium aluminium hydride, modifications to improve or control the reactivity of hydride donors to nitriles may involve the addition of a Brönsted,[46] or Lewis acids often transition metal salts,[47–53]especially for mild reducing agents like sodium borohydride. The most common additives are simple cobalt and nickel salts, such as chlorides.[45,52,54–56] In 2000, Caddick *et al*., reported the synthesis of protected primary amines by nitrile reduction using sodium borohydride and nickel chloride in methanol. Addition of di-*tert*-butyl carbonate as a trapping agent allowed the isolation of the protected primary amine in high yield, and avoid the formation of a secondary amine.[54]

4.4.2.2 Amide Reduction

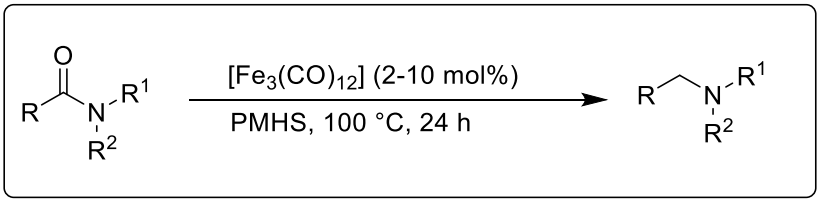
Preparation of amines can be achieved by the reduction of amides with lithium aluminium hydride ($LiAlH_4$), borohydride or diborane[57–60] (Equation 4.22). Depending on the starting amide, primary, secondary, or tertiary amines can be obtained by using this approach.



..... Eq. 4.22

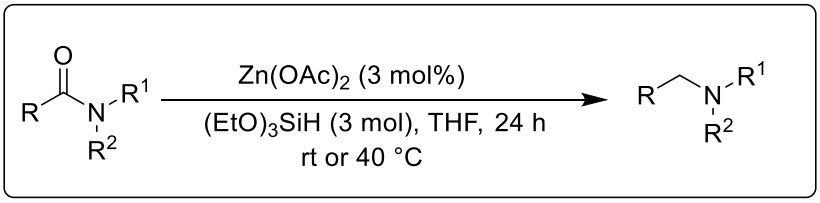
However, due to the air and moisture sensitivity, poor selectivity, and difficult purification process as when of using aluminum-based hydride reagents in this reduction, alternative methods are being developed. In particular, metal-catalyzed hydrosilylations have received considerable interest.[61–64] Although the metal catalysts used for these transformations (rhodium, ruthenium, platinum, etc.)

have proven effective, there is a need to develop cheaper metal catalysts. In 2009, Beller *et al*., reported an iron-catalyzed hydrosilylation of secondary and tertiary amides to amines, in high yield and functional group tolerance (Equation 4.23).[65]



..... Eq. 4.23

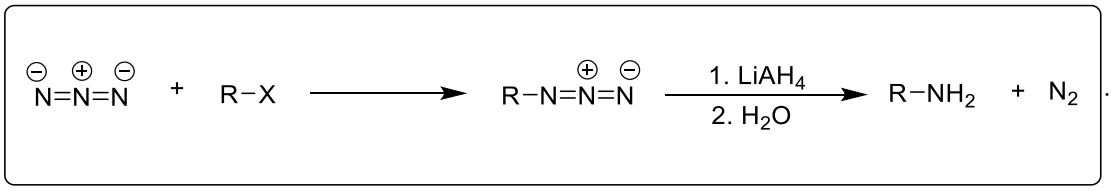
The same group in 2010 reported the chemoselective reduction of amides using silanes under mild reaction conditions, in the presence of an inexpensive zinc catalyst (Equation 4.24).[66]



..... Eq. 4.24

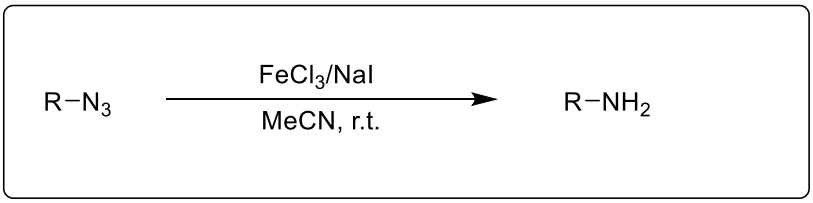
4.4.2.3 Azides Reduction

Both aliphatic and aromatic alkyl azides can be reduced to primary amines by using lithium aluminum hydride ($LiAlH_4$).[67,67] The azide ion is a monovalent nitrogen nucleophile which can react with either primary or secondary halides to form an alkyl azides, which in turn may be reduced by $LiAlH_4$ to a primary amines (Equation 4.25).



..... Eq. 4.25

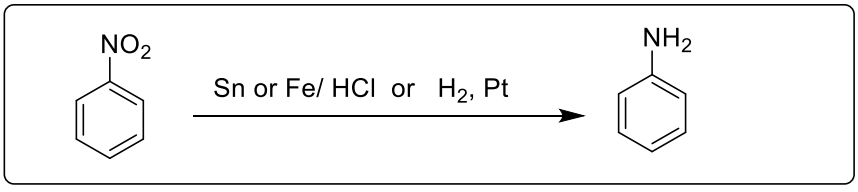
Other reagents, including borohydride,[68,69] SmI_2,[70,71] or hexamethyldisilathiane[72] have been used for such transformations. However, most of these methods have drawbacks such as low selectivity, narrow applicability, or severe reaction conditions, and the search for mild, efficient methods is still ongoing. One recently explored methods involves the use of zinc and ammonium chloride at reflux or room temperature, and was found to be efficient for azides with some functional group tolerance (C=C, benzyl, etc.), giving high yields of the corresponding amines in 10 to 120 minutes.[73] Similarly, the Kamal group has been working on developing other mild and selective methods for the reduction of azides to amines[69,74,75] One of their procedures employed $FeCl_3$/NaI to reduce a wide range of azides in acetonitrile at room temperature (Equation 4.26).[69] This method was found to be selective for the azide functionality in the presence of a nitro group.



..... Eq. 4.26

4.4.2.4 Nitro Compound Reduction

Nitro compounds can be reduced to amines by catalytic hydrogenation with Raney nickel,[76] or platinum oxide,[77], or with reagents such as lithium aluminium hydride ($LiAlH_4$), or samarium diiodide[78], or metals such as iron or tin.[79] This is a commonly known method for the synthesis of aryl amines such as aniline (Equation 4.27).

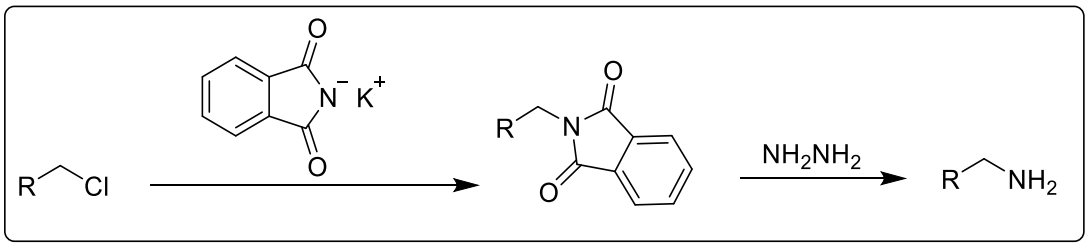


..... Eq. 4.27

4.4.3 Other Methods

4.4.3.1 Gabriel Synthesis

Gabriel synthesis is a method used for the preparation of primary amines from alkyl halides by using sodium or potassium phthalimide (Equation 4.28).[8] The double acylated nitrogen of the phthalimide is acidic enough to deprotonate with common bases, and also presents only one site for alkylation. The resulting compound from this transformation is the corresponding N-alkylphthalimide, which give rise to primary amines upon removal of the phthaloyl functionality, an atom-inefficient process. This reaction was named after a German chemist, Siegmund Gabriel.[80]

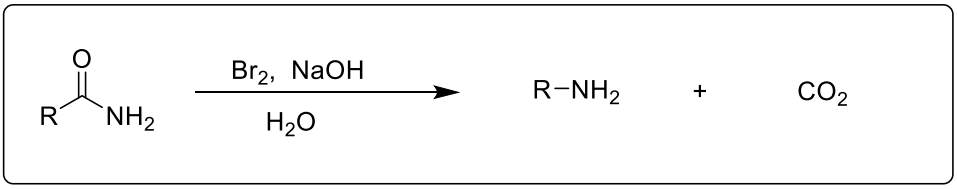


..... Eq. 4.28

However, in most cases Gabriel synthesis fails for secondary alkyl halides. An alternative to this method for the synthesis of secondary amines uses the sodium salt of saccharin as the monovalent nitrogen species; di-*tert*-butyl-iminodicarboxylate is another substituent reported for the phthalimide.[81]

4.4.3.2 Hofmann Degradation or Rearrangement of Amides

This method is only suitable for the synthesis of primary and aryl amines from the reaction of aliphatic or aromatic amides with a halogen (bromine or chlorine) in an aqueous medium of sodium hydroxide (Equation 4.29).[82,76,83] It results in the formation of an amine with one less carbon than the parent starting material.[8] This reaction was developed and named after a German chemist, August Wilhelm von Hofmann.

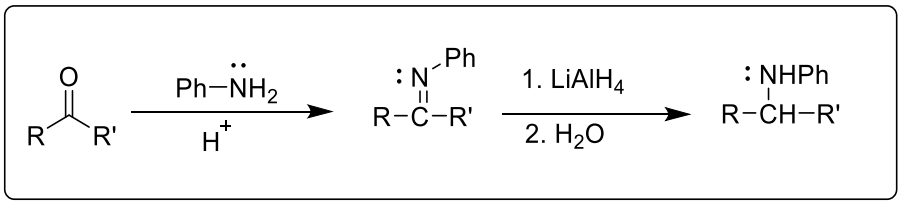


..... Eq. 4.29

However, the yields are usually unsatisfactory[84,85] and as a result numerous modifications have been reported. Some replace the Br_2 used in Hofmann degradation with alternative oxidants such as benzyltrimethylammonium tribromide,[84] the iodine(III) reagents $[PhI(OAc)_2]$,[86] $[PhI(OCOCF_3)_2]$,[87] and [PhI(OTs)OH],[88]or the potent oxidant $Pb(OAc)_4$.[89]

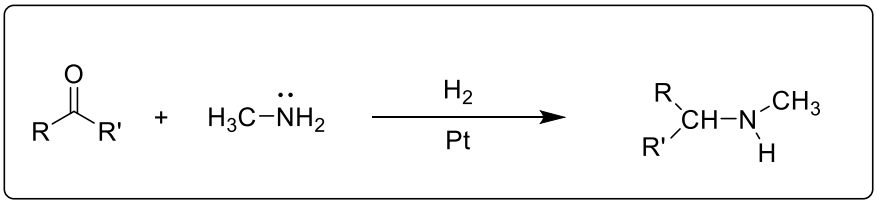
4.4.3.3 Reductive Amination/Alkylation of Aldehydes and Ketones

This is the most common method employed in the pharmaceutical industry for the synthesis of amines.[82] Aldehydes and ketones are converted into amines through the formation of an intermediate imine by using ammonia or primary or secondary amines. In this method, the imine is being reduced, while the amine is alkylated, (hence the term reductive amination or alkylation). The key advantage of this method is that primary, secondary, and tertiary amines can all be produced by having the right combination of amine/ammonia and carbonyl compound.[8] This amination process employs reducing agents, example of such reducing agents are sodium cyanoborohydride ($NaBH_3CN$), sodium triacetoxyborohydride ($NaBH_9OCOCH_3)_3$),[90] and in some cases lithium aluminum hydride ($LiAlH_4$), Equation 4.30.



..... Eq. 4.30

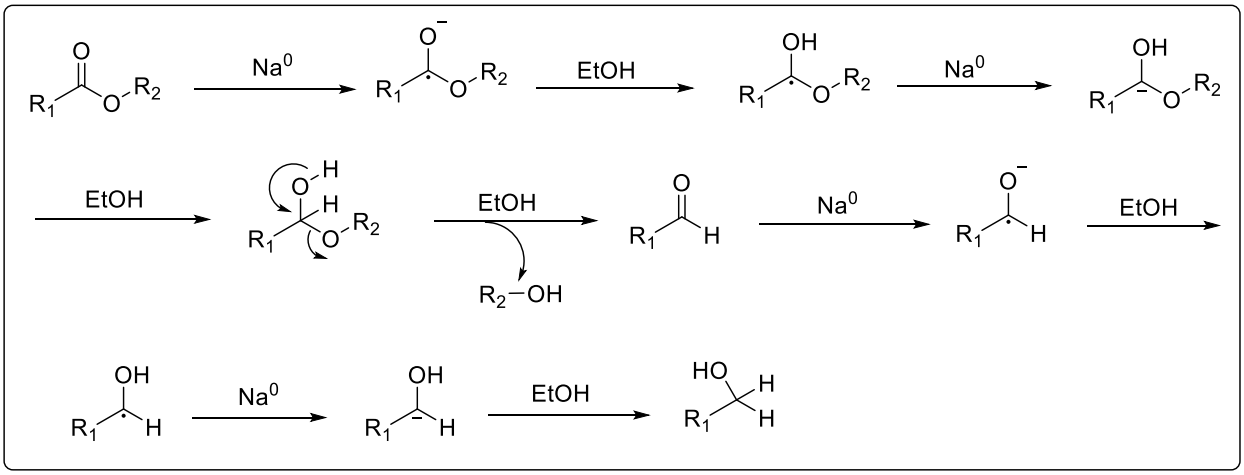
In some cases, this reaction can be achieved by catalytic hydrogenation using Pt in the presence of ammonia or primary amine (Equation 4.31).[8,23]



..... Eq. 4.31

4.5 The Bouveault-Blanc Reduction

In the early 1900s, the Bouveault-Blanc reduction reaction technique for the reduction of esters to alcohols was developed by two French chemists, Louis Bouveault and Gustave Louis Blanc.[91–93] This reaction involves the use of sodium metal and ethanol, where the sodium presumably serves as a single electron donor, and the ethanol as the proton source. The mechanism usually invoked for this reduction process is illustrated in the scheme below (Scheme 4.1).

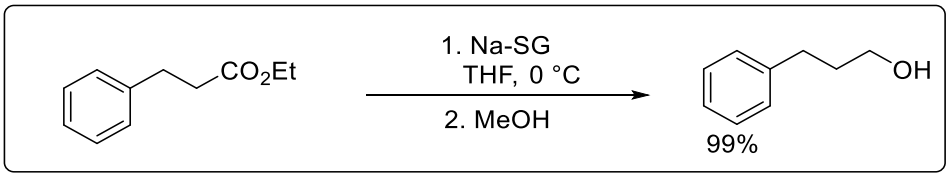


Scheme 4.1: Mechanism of Bouveault-Blanc reduction of ester to alcohol

As is seen in the scheme above, the pyrophoric nature of handling of sodium metal poses some limitations to the utility of the technique. Alternative approaches at an industrial scale employed

so far involve the use of metal hydrides such as lithium aluminium hydride and sodium borohydride while progress in devising techniques that can make alkali metals stable and safe are ongoing.

Today, the classical Bouveault-Blanc reduction has been modified, and several groups, including the Dye group, and Bodnar and colleagues at SiGNa Inc,[7] have reported improved versions for obtaining primary alcohols from the corresponding aliphatic esters. This involves the use of a free-flowing powder of sodium encapsulated in silica gel (Na-SG), and with methanol as the proton source. A complete conversion in 5 minutes was observed (Equation 4.32).[7]

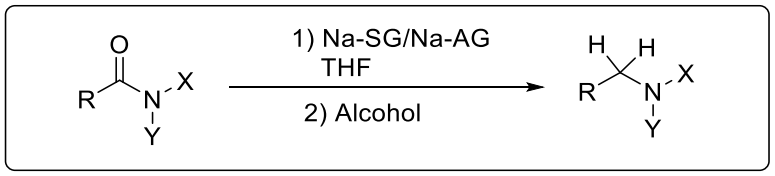


..... Eq. 4.32

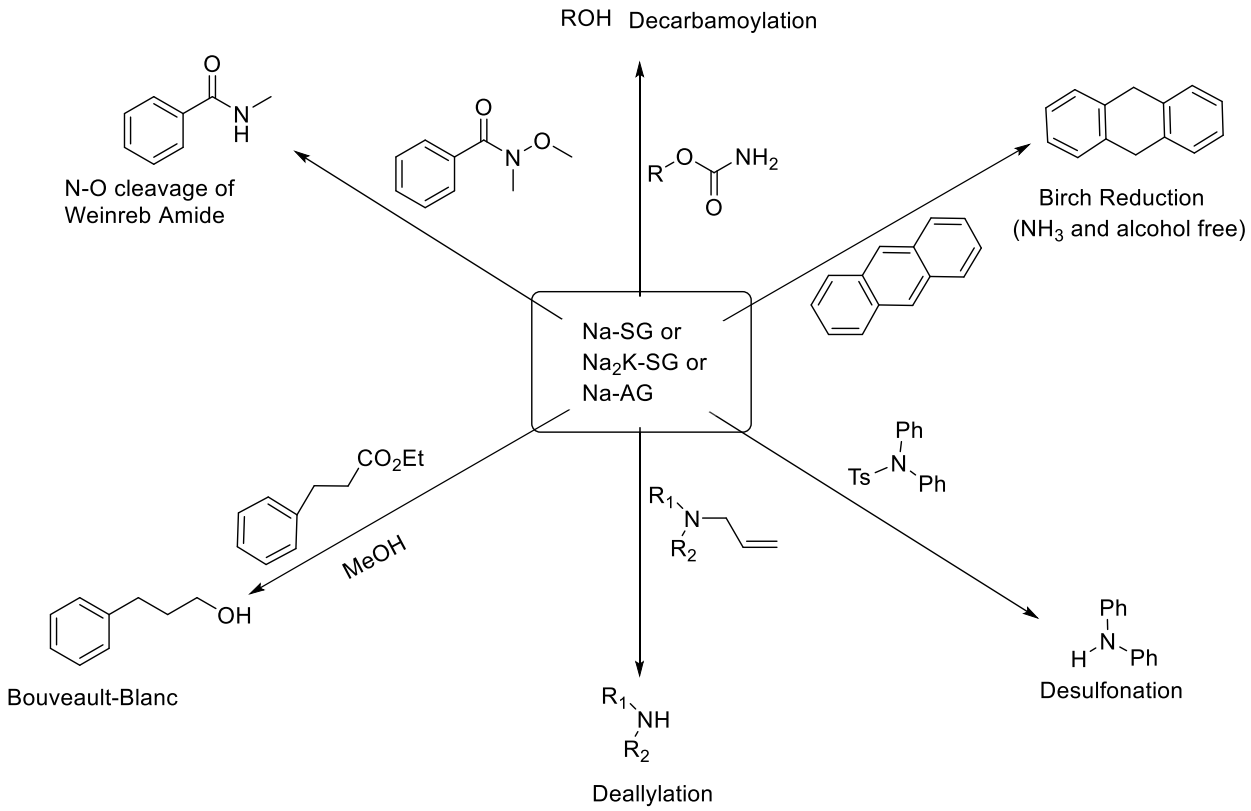
Different reagents involving lithium aluminum hydride ($LiAlH_4$), have been used in the reduction of amides to amines. Although this reagent is effective, their applications have been limited by their high cost, handling difficulty, air and moisture sensitivity, complex work up, ability to reduce other groups in the compound of interest, and their tedious purification processes. By extending the Bouveault-Blanc reduction method to amides under similar reaction conditions, amides may be successfully reduced to amines, using both sodium encapsulated in silica and in alumina gel (Na-SG and Na-AG).

4.5.1 Na-SG and Na-AG as Potent Reducing Agents for the Bouveault-Blanc Type Reduction of Amides to Amines.

In 2005, the Dye group in collaboration with SiGNa Chemistry developed a new technology, which involves the encapsulation of alkali metals and their alloys (Na, Na/K) into silica gel.[94,95] This method reduces the danger associated with handling of these reactive metals. The encapsulated metals (black free-flowing powders) are strong reducing agents which are effective and versatile, and have been applied extensively in various organic transformations. Some of these reactions include Birch reductions of polyaromatic hydrocarbon and conjugated aromatic systems,[96] desulfonation of N,N-disubstituted sulfonamides,[97] amine diallyl- and debenzylation,[98] synthesis of alkyldiaryl- and dialkylarylphosphines,[99,100] an improved Bouveault-Blanc ester reduction,[7] reductive N-O cleavage of Weinreb amides,[101] and decarbamoylation of primary carbamate to release alcohol,[100] as represented in the Scheme 4.2 below. Based on all the above reactions and application of the M-SG and M-AG reagents, we wondered if it could be feasible for the Bouveault-Blanc type reduction to apply to the reduction of amides to amines (Equation 4.33).

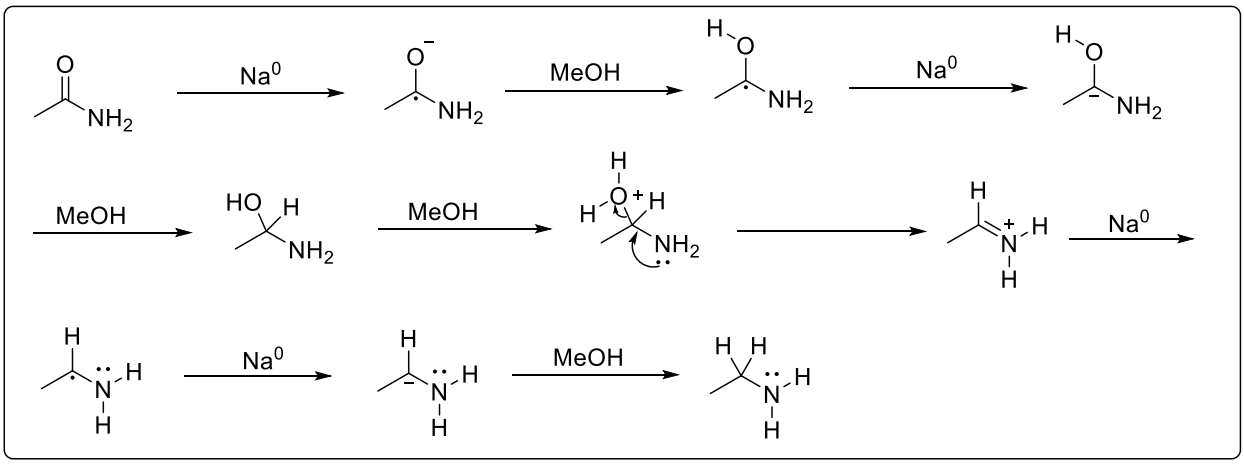


..... Eq. 4.33



Scheme 4.2: Representative examples of Na-SG/Na2K-SG/Na-AG transformations

Therefore, the proposed mechanism analogous to ester reduction is given in Scheme 4.3 below, where sodium in silica or alumina gel serves as a single electron source, and the methanol/alcohol, as the proton donor.



Scheme 4.3: Proposed mechanism of Bouveault-Blanc type reduction of amide to amine

4.6 Experimental Procedure

In a helium-filled glove box, Na-AG/Na-SG (usually containing 42 mmol of Na) was added to a round- bottom flask (100-250 mL flask) containing a magnetic stirrer and a rubber septum. After removal from the glove box, 3 mmol of the organic amide dissolved in 20 mL of anhydrous THF was injected through the septum under a continuous flow of argon. The resulting mixture was stirred at 0 or 20 or 50 °C, followed by the drop-wise addition of alcohol in 5 minutes. The reaction mixture was left with continuous stirring until all the starting material was consumed (30-180 minutes), after which the reaction was stopped by a water quench (~2 mL). The mixture was then extracted with dichloromethane or acid-base extraction and the organic layer was concentrated under reduced pressure with a rotary evaporator. The crude product was purified via silica gel column chromatography, using MeOH/Hexane (80/20) with 1% triethylamine for 1-benzyl-2-pyrrolidinone.

Alternatively, the Na-AG/Na-SG could be added through a solid addition funnel into a 250 mL three-neck round- bottom flask containing the 3 mmol of the amide dissolved in 20 ml of anhydrous THF and 3.1ml of t-BuOH (Figure 4.1).

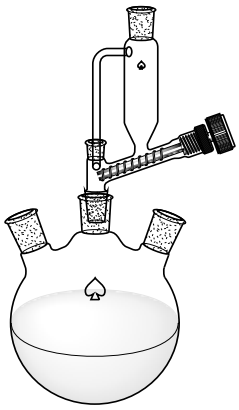
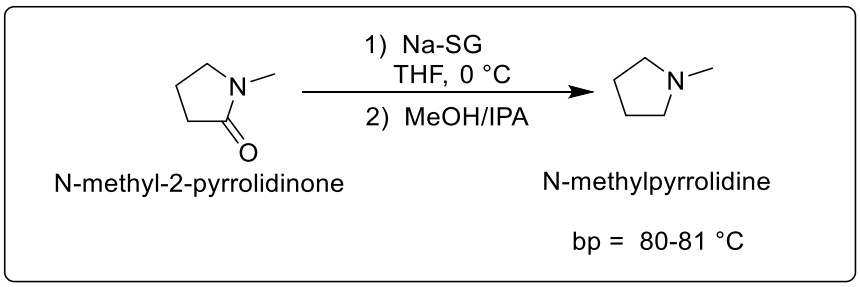


Figure 4.1: Sketch of solid addition funnel set up for amide reduction

4.6 Results and Discussion

4.6.1 Substrate Scope and Preliminary Optimization

Our initial effort towards the application of Bouveault-Blanc type reduction of amides to an amine used N-methyl-2-pyrrolidinone (NMP) as substrate under various reaction conditions, following closely the report by Bodnar *et al*., for the reduction of ester to alcohol.[7] The results are summarized in Table 4.2 and Scheme 4.4



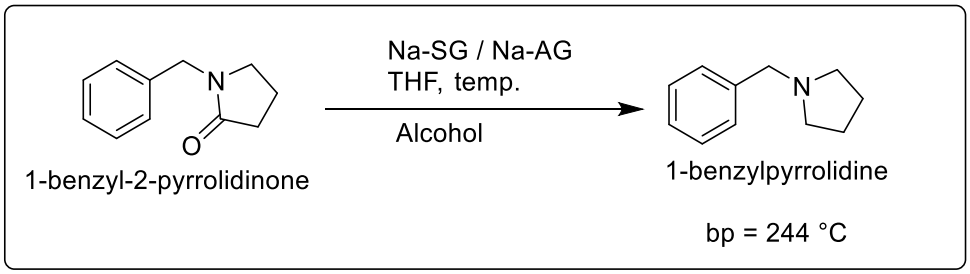
Scheme 4.4: Preliminary optimization of N-methyl-2-pyrrolidinone

Table 4.2: Preliminary optimization of N-methyl-2-pyrrolidinone (NMP) using Na-SG

Conditions for the Reduction of Tertiary Amide to Amine	
Amide (NMP)	3 mmol
Na-SG	42 mmol
MeOH or i-PrOH	74 mmol
Conditions	20 mL THF, 0 ˚C, 3 hrs.
Yield (% conversion)	45[a], 50[b]

Yield is based on the GC-MS conversion of N-methyl-1-pyrrolidinone to N-methylpyrrolidine, [a] conversion from MeOH and [b] conversion from i-PrOH

The results show that complete conversion of NMP to N-methylpyrrolidine was not achieved at 0 °C in 3 hours. Even running the reaction overnight, with warming to room temperature, did not increase the conversion above 50%. Even though this reaction was run with both methanol (MeOH) and isopropanol (i-PrOH), the difference in the percent conversion was not significant, although i-PrOH seems to give about 5% more conversion than MeOH. We proposed two possible reasons for the incomplete conversion of NMP. One could be the amount of alcohol used which could quench the reducing power of Na-SG (even when the amount of Na-SG was doubled, see Table 2) at some point of the reaction and as a result all the starting material was not completely converted. Another reason could be that the product (N-methylpyrrolidine) with a boiling point of 80-81 °C is volatile enough to be lost during rotary evaporation, leading to incorrect results in terms of product formation from starting material. Hence, we decided to change the substrate in order to form a reduced product with a much higher molecular weight and higher boiling point. Using 1-benzyl-2-pyrrolidinone (Scheme 4.5), reaction conditions were further optimized in terms of reducing agent (Na-SG and Na-AG), alcohol (MeOH, i-PrOH, and t-BuOH), and temperature (0 °C, room temperature, and 50 °C).



Scheme 4.5: Preliminary optimization of 1-benzyl-2-pyrrolidinone

The reaction conditions used to optimize 1-benzyl-2-pyrrolidinone reduction are given in Table 4.3. Initial results showed that conditions in column 3, Table 4.3 resulted in the highest yield of the product. Therefore, we kept these parameters and optimized further in terms of reducing agents and alcohols (Table 4.4).

Table 4.3: Reaction conditions for optimization

Optimization parameter grid	1	2	3
Na-SG/Na-AG	84 mmol	42 mmol	42 mmol
i-PrOH /MeOH/ t-BuOH	74 mmol	37 mmol	24.7 mmol
1-benzyl-2-pyrrolidinone	3 mmol	3 mmol	3 mmol

We decided to explore the use of sodium in alumina gel (Na-AG) also since in previous studies, it was more difficult to quantitatively recover all the products from silica gel than from alumina gel.[101] Indeed, the percent conversion for Na-AG was greater in all cases than for Na-SG (Table 4.4), with t-BuOH giving the highest yield (22.1%) at 0 °C in 3 hours. Since the conversion was still low in general, we decided to run the reaction at different temperatures to optimize its rate and selectivity (Table 4.5).

Table 4.4: Optimization of reducing agents (Na-AG vs. Na-SG) and alcohol at 0 °C

Optimization parameter grid	Na-AG (% conversion)	Na-SG (% conversion)
t-BuOH	22.1	9.8
i-PrOH	10.3	6.5
MeOH	7.7	1.9

Percent conversion is based on GC-MS

Results from temperature optimization shows higher conversion at room temperature (20 °C) than at 0 °C, especially with t-BuOH (57.8%, Table 4.5), and no significant further change was observed when the temperature was increased to 50 °C. Since Na-AG, 20 °C, and t-BuOH gave higher conversion of starting material to product, optimization of the right quantity of t-BuOH was further pursued to obtain complete conversion (Table 4.5).

Table 4.5: Optimization of temperature using Na-AG

Temperature	0 °C	20 °C	50 °C
t-BuOH	23.2	57.8	58.1
i-PrOH	10.6	15.3	15.8
MeOH	8.1	12.7	14.5

Percent conversion is based on GC-MS

Although the alcohol (t-BuOH) serves as the proton source (Scheme 4.2), having too much of it would quench the reducing power of Na-AG, resulting in an incomplete reaction. Hence

optimization to figure out the right amount of t-BuOH was carried out and results are given in Table 4.6 below. Result showed that 3.1 mmol of t-BuOH gave almost complete conversion of 1-benzyl-2-pyrrolidinone to 1-benzylpyrrolidine (98.2%) by GC-MS. The final optimized conditions for the reduction of amide to amine are summarized in Table 4.7. With the optimal condition, three different experiments were run with 1-benzyl-2-pyrrolidinone to determine the mass recovery using different extraction methods, Figure 4.2.

Table 4.6: Optimization of t-BuOH using Na-AG at room temperature (20 °C)

Amount (mmol)	% Conversion
24.7	59.1
6.3	75.5
3.1	98.2

Percent conversion is based on GC-MS

Table 4.7: Optimal condition for amide to amine reduction

Reduction of Amide to Amine	
Na-AG	42 mmol
t-BuOH	3.1 mmol
Amide	3 mmol
THF	20 ml
Temperature	20 °C

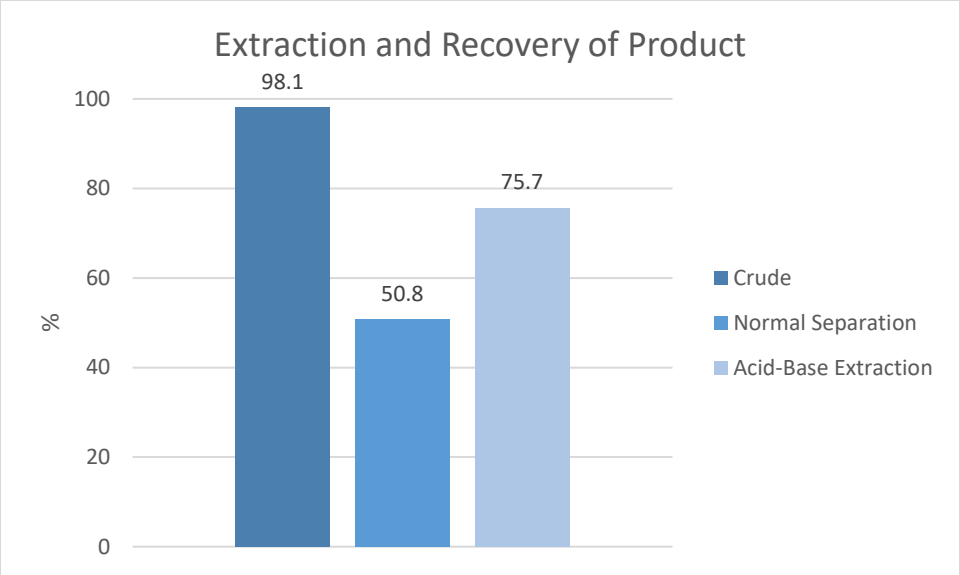


Figure 4.2: Graph of mass recovery of 1-benzyl-2-pyrrolidinone reduction

4.7 Summary

This chapter demonstrates the first Bouveault-Blanc type reduction of amides to amines using Na-AG as the reducing agent, and t-BuOH as the proton source. Many substrates remain to be explored, but the results obtained show that this method for reduction of amides to amines has the potential of becoming a useful application of Na-AG and Na-SG. From the GC-MS results, no cleavage of the C-N bond to give alcohol was seen, and high conversion to product was observed, even though complete mass recovery remains elusive.

4.8 Future Directions

From the results obtained, two future directions are proposed.

First, the investigation of mass recovery is necessary. However, the interesting question that one may ask is why we are not getting a 100% mass recovery. Could it be a result of some product

being trapped in the silica or alumina gel or what? One way to address this question is by purchasing an amine product (eq. 1-benzylpyrrolidine), dissolve a known quantity in THF, and stir it with Na-AG and Na-SG for specific time and extract it to see if all the amine is recovered or if some of it is tied up or trapped in the pores of the silica or alumina gel.

Secondly, with the optimal conditions, more substrates need to be explored. This could include open-chain amides (not lactams), unsaturated systems, etc. Some examples include 1-(2-methylpropanoyl)-piperazine, 6-phenyl-2-piperidinone, etc.

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