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DEVELOPMENT OF ALKALI METAL IN SILICA GEL (M-SG) AS A REAGENT IN ORGANIC REACTIONS

presented by

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DEVELOPMENT OF ALKALI METAL IN SILICA GEL (M-SG) AS A REAGENT IN ORGANIC REACTIONS

By

Partha Nandi

A DISSERTATION

Submitted to Michigan State University in partial fulfillment of the requirements for the degree

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ABSTRACT

DEVELOPMENT OF ALKALI METAL IN SILICA GEL (M-SG) AS A REAGENT IN ORGANIC REACTIONS

By

Partha Nandi

This thesis dissertation describes development of alkali metal absorbed in silica gel as reagents (M-SG reagents) for organic reactions. Importance and background of alkali metal mediated reactions are described in Chapter 1. Alkali metals in silica gel (M-SG) reagents are a class of material that is made by absorbing the alkali metals or their alloys in the nanoporous silica (pore diameter ~ 190 Å) by treatment of heat. The development, physical and chemical nature of the reagent is described in Chapter 2. Chapter 3 describes the preparation and analysis of the M-SG reagents.

Chapter 4 describes desulfonation (primarily focused on detosylation reactions but demesylation was also shown feasible) reactions of amines using Stage-I M-SG reagents. This methodology work with both primary and secondary amines and with both alkyl and aryl substituents. More challenging detosylations of protected aziridine and peraza[2.2.2] ligand that failed in many other traditional deprotection methods were feasible under the current protocol.

Chapter 5 describes another class of cleavage reactions namely deallylation and debenzylation reactions of amines using stage I M-SG reagents. The deallylation reactions are feasible with both aliphatic and aromatic tertiary allyl amines yielding secondary amines in moderate yields. This methodology is

extended to cleavages of tertiary benzyl and substituted benzyl groups such as benzhydryl and trityl groups and cleavage reactions of O-benzyl groups.

Chapter 6 is focused on de-arylation reactions of triaryl and diaryl phosphines. The diaryl phosphide solutions can be cleanly generated under the reaction conditions and can be used for further reactions. Alternatively, in same reaction pot it can be alkylated and subjected to further dearylation reaction condition. This would yield dialkylated aryl phosphines. Monoaryl dialkylphosphines were however resistant to dearylation reactions. The usefulness of this procedure was demonstrated in the preparation of DIOP ligand.

Chapter 7 describes Birch reduction with stage I M-SG reagents. In addition to substrate scope of the reaction, this work describes a reduction method that is devoid of liquid ammonia and corresponding cooling or any other additives. dedicated to my parents and family

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LIST OF ABBREVIATIONS

- 18C6 18-Crown-6
- Boc *tert*-butyloxycarbonyl
- BuOH butanol
- Cbz carbobenzyloxy
- CD circular dichroism
- DBB Di-*tert*butylbiphenyl
- DIOP [2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)dioxolane]
- DME 1,2-dimethoxyethane
- DMF N,N-dimethylformamide
- DSC differential scanning calorimetry
- EDA Ethylenediamine
- EtOH Ethanol
- Et₂O Diethylether
- EXAFS Extended X-ray absorption fine spectra
- Fmoc 9-fluorenylmethyloxycarbonyl
- GC/MS Gas Chromotography/Mass Spectrometry
- HMDS Hexamethyldisilazane
- *i*-PrOH isopropanol
- LDA lithium diisopropylamide

PDF	Pair distribution function
THF	tetrahydrofuran
MAS-NMR	Magic angle spinning nuclear magnetic resonance spectroscopy
M-SG	alkali metal in silica gel
МеОН	Methanol
Ms	methanesulfonyl or mesyl
PCBs	polychlorinated biphenyls
SET	single electron transfer reaction
SG	silica gel
RT	room temperature
EtOAc	ethyl acetate
XPS	X-ray photoelectron spectroscopy
Ts	paratoluenesulfonyl
XRD	X-ray diffraction

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CHAPTER 1

NATURE OF ALKALI METAL ABSORBED IN POROUS SILICA GEL (M-SG) REAGENTS

1.1 BACKGROUND

Theoretical studies of adsorption of metal atoms (Cu, Pd and Cs) on regular and defect sites of SiO₂ surfaces indicate that the bridging oxygens, Si–O–Si of silica are unreactive.¹ The weak dispersion interaction between metal and these sites is the dominant factor. The weakness of this interaction indicates that given a chance, the metals could aggregate and form local clusters. The adsorbed metals in the Si–O–Si framework were found to be neutral in all cases (Pd, Cu) except for Cs. The reactivity of lithium metal with silica is very different than that with sodium due to the unusually high ionic potential of the cation.²

Contrary to the theoretical predictions the weakening of glass in the presence of alkali metal and alkali metal derived bases has been known for a long time.³ The glass-alkali metal interaction, however, is still not fully understood. Powdered glass turns black upon absorbing sodium vapor,⁴ but then recovers its clarity between 200-500 °C under high vacuum.^{5,6} The discoloring and the photoemission spectra of sodium on oxidized Si(113) surface indicates ionization of the sodium at room-temperature to form Na⁺

closely related species such as amorphous SiO_2 and $Na_2Si_4O_9$ have been performed. One important finding of this study is that the bond polarizability of O–Si is a strong function of near neighboring silicon bridging via oxygen, degree of polymerization of silica, and presence of sodium.⁸

Stereochemical ordering around sodium in amorphous silica has been investigated via XPS and EXAFS methods in ultra high vacuum conditions.⁹ Mazzara and coworkers⁹ inferred that alkali metal ions occupy the available sites in the silica network, which reduces the stress without bringing in additional constraints. The EXAFS studies indicated that once inserted in the silica, the sodium atoms are surrounded with a first shell of oxygen atoms, mostly from Si–O–Si bridges.

1.2 M-SG REAGENTS:

In 2005 alkali metals absorbed in porous silica gel were reported.¹⁰ The porous silica gel (average pore diameter of 150 Å, Davisil 646 from Grace) used for these preparations has a large void volume ($\approx 1 \text{ cm}^3/\text{g}$). The grain size is of the order of 0.2-0.5 mm, making these materials easily handled granular substances. It is to be noted that a grain is an aggregate of much smaller particles (see Figure 1.1 below). These powders have a high internal surface area compared to the external surface area. The internal pores are large enough to hold metal nanocrystals that individually contain some 60,000 metal atoms. This silica gel consists of 10-20 nm size particles, interconnected by filament oxide strands to form channels and pores in the same size range.



Scheme 1.1: Reaction of residual Si-OH groups with alkali metal

Addition of alkali metal can remove any residual Si–OH groups (also referred to as *defect* sites) via the above reaction to evolve H_2 (Scheme 1.1). Prior to adding alkali metal, the above commercial silica gel is initially heated at 200-300 °C to remove absorbed water and then heated at 600 °C to remove some of the surface Si–OH groups (Scheme 1.2).



Scheme 1.2: Dehydration from adjacent Si-OH groups

When this reaction occurs, the amount of H_2 formed by a subsequent reaction with water is less than that expected from the amount of alkali metal used in the preparation. For example, if we prepare 40 wt % Na₂K-SG we might, because of this reaction, obtain hydrogen equivalent to only 38 wt% metal. This would tell us that about 2% of the metal had been used to reduce surface groups and produce M^+ . On a molar basis for this example, about 5% of the Si atoms would carry OH groups after calcination.

It has not been possible to determine which particular defect sites are responsible for *sticking* or the first hand attachment of metal.



Figure 1.1: Morphology of silica gel (reproduced with permission from Grace Davisil web site)

The loading of the metals such as Na or alloys of Na-K could be as high as 35-40 % w/w. Table 1.1 summarizes different versions or "stages" of M-SG reagents. M-SG (0) refers to shiny black solid where the metal alloy is slowly added to silica gel at ambient temperature. M-SG (I) refers to annealed version of M-SG (0) (e.g., for alloys of Na-K in SG), where the shiny appearance of M-SG (0) is lost and transformed into a less air reactive solid. Samples of M-SG (I) were found to be almost non reactive on slow exposure to dry air or dry O₂.

Designation	Temperature of Preparation	Comments
Stage 0	Room Temperature to 40 °C.	Applicable only to liquid metals and alloys such as Na–K alloys.
Stage I	120–150 °C for 6–10 h Na-K alloys, 165 °C for 10 h for Na-SG.	Produces hydrogen with EtOH. (Note: Some Stage IIA is always formed as well).
Stage IIA	Some is formed when Stage I is prepared at 100- 165 °C.	No H ₂ formed with EtOH, but reacts with H ₂ O completely. May have formed M^+-O^Si species.
Stage IIB	Temperature kept below 300 °C for 24 h.	Probably contains Si-Si bonds but still has Na ⁰ .
Stage IIC	Heated to 400 °C for 24 h.	Reaction has removed Na ⁰ and produced elemental Si but not NaSi. Does not produce H ₂ with EtOH.
Stage IID	Na–SG heated to 400-450 °C for 24 h and has at least 40% Na	Na has reacted with Si to produce NaSi. Produces H ₂ with EtOH.

 Table 1.1.
 Various Stages of Alkali Metal in Silica Gel

The DSC of the material after annealing at 120-160 °C (stage I M-SG) did not show the same endotherm as the precursor metal or its alloy. Instead, it showed a broad melting endotherm. The DSC also showed an exotherm after 90-120° C corresponding to 400-700 J/g (depending on

metal and percent loading). MAS ²³Na NMR revealed that the Na is partially ionized in the Na-SG (I). The extent of the ionization was found to be a function of the percent of Na loaded, the average pore size and the temperature.¹¹ Noticeable peak broadening in the MAS ²³Na NMR was observed. In contrast a sharp peak of Na⁰ is seen with Na absorbed in γ alumina. This broadening of the peak could be ascribed to a variety of environments of Na in the pores of silica gel; e.g., the metallic nature of Na on the surface of silica might be different from that inside the metallic cluster deep inside the pore. The peak broadening was also seen in a mesoporous Na-SG sample, suggesting that the broadening is not due to the distribution of pore sizes alone. Heating of the Na-SG sample in the sealed guartz MAS NMR tube showed an increase in Na⁺ over Na⁰, signifying an increase in the ionization of the metal (this experiment was performed by Prof. James L. Dye). This increment in ionization with temperature was not observed with Na in alumina. In what way the porous silica gel support assisted in the ionization of the metal or caused the broadening of Na peaks remained a mystery. Figure 1.2 and Figure 1.3 shows MAS ²³Na NMR spectra, where the Na⁺ signals appear at 0 ppm, whereas the Na⁰ appears at ~1100 ppm. The shift of Na⁰ signals at a more downfield region compared to Na⁺ can be explained by the Knight shift.¹² Knight shift is due to the conduction electrons of sodium. The shift comes mainly from two sources - (1) Pauli paramagnetic spin



Figure 1.2. Effect of silica gel pore size on the relative amplitudes of the signals from Na^0 and Na^+ at 10% (wt/wt) loading of Na in silica gel. The curves are diplaced vertically for clarity.



Figure 1.3. Effect of metal loading (% wt/wt) on the relative amplitudes of the signals from Na⁰ and Na⁺ in Na-SG(I) made from silica of ~150 Å pore size. The curves are diplaced vertically for clarity.

The fate of the electron post-ionization is unclear. Possibilities to be considered are – (i) delocalization of the electron into a band of SiO₂, (ii) Partial breakage of Si–O–Si bonds in silica to form Si–O–Na⁺ and Na⁺Si⁻, (iii) expanding the coordination number of Si and subsequent formation of a valence electron silvl anion (iv) ionization of metal to form M⁺ and M⁻ can be considered. Powder XRD analysis of 25 wt % and 40 wt % Na–SG (I) yielded metallic peaks of Na⁰ that are identical in line width was independent of loading. The Scherrer equation¹³ gives a relation between the line width and particle size. In this equation, t = $0.9I/BCos\theta_B$, t is thickness, B is full width at half maxima, I is a lattice dimension and θ_B is the angle of diffraction. This equation yields the same crystallite sizes of about 100 Å for both loadings. This surprising result indicates that the metal is not uniformly distributed among the pores, but rather tends to form full and empty pores. In other words, surface energy effects tend to cause small metal particles to agglomerate into larger ones.

Pair distribution function (PDF) studies indicated the presence of *crystalline* sodium nanoparticles with coherence lengths up to 40 Å. The PDF of Na₂K-SG-I showed similar order, but had the simple bcc structure of Na rather than the known hexagonal structure of Na₂K. Although in both cases, large thermal factors indicated significant disorder, the metal particles were not liquid, in spite of the fact that Na₂K was above its melting temperature. Together with the previously described changes in the melting endotherm for Stage I Na₂K-SG, this provides additional evidence for the formation of Na-rich particles in the pores, perhaps by preferential ionization of potassium. The PDF of Stage IID Na-SG is dominated by the crystal structure of Na₂SiO₃. The addition of the known structure of Na₄Si₄ improved the data fit

considerably. So we concluded that the stoichiometric overall reaction that occurs when Na-SG is heated at 450 °C is the production of Stage IID.

$$5Na + 3SiO_2 \rightarrow 2Na_2SiO_3 + NaSi$$

Stage I M-SG was surprisingly non-reactive in air. This is in sharp contrast to other dispersed forms of alkali metals such as sodium sand or sodium in alumina gel. What protects the stage I M-SG from ready oxidation in air is not yet clear. Na-K alloy in contrast undergoes oxidation in air to make superoxides and peroxides that can subsequently lead to violent reactions.¹⁴ Potentially, the relatively small entry channels that lead into the pores can get partially oxidized and block subsequent passage of O2 deeper into the pore. The fate of absorbed O_2 in M-SG (I) is unknown. The MAS ²³Na NMR spectra of Na-SG that was exposed to dry air and freshly made Na-SG (not exposed to O_2) were identical with no significant differences in the Na⁺ peak. Interestingly, the DSC of stage I M-SG exposed to dry O₂ showed an additional exotherm just above the melting temperature of Na that was absent in freshly prepared stage I M-SG. Due to the high ratio of the area of internal surfaces relative to the outside surface of the particles, the majority of M^0 can remain un-oxidized. Thus, this material can liberate H₂ in near quantitative amounts on reaction with water.

The usefulness of M-SG(I) was shown in flow syntheses, desulfurization reactions, Wurtz coupling and Birch reductions. This type of

M-SG reagent offers a new alternative to conventional methods of alkali metal delivery for reduction, such as solutions in liquid ammonia, dispersions in oil, liquid alloys of Na-K, K intercalated in graphite (C₈K), Na-Hg, sonication in organic solvents, refluxing in xylene, or using lumps of metal with electron transfer agents such as naphthalene or di-tert-butyl-biphenyl (DBB). Synthetic methodologies were developed by using M-SG materials, including (i) desulfonation of amines,¹⁵ (ii) reductive cleavage of aryl C–P bonds in phosphines¹⁶ (iii) reductive deallylation, debenzylation, debenzhydrylation and detritylation¹⁷ (iv) Bouveault-Blanc reaction for ester reduction¹⁸ (v) C–X cleavage reactions such as Wurtz coupling, reduction of chlorofluorocarbons and polychlorinated biphenyls (vi) Birch reduction.¹⁹

M-SG (I) reagents were found to react with water rapidly to give off H₂. However, a lower reactivity was found with all alcohols (e.g., *t*-BuOH, *i*-PrOH, *n*-BuOH, EtOH, MeOH). Only up to 70-90% of the expected amount of H₂ was liberated on reaction with M-SG (I) and EtOH in 2 h and the yield did not improve to any significant extent with longer time. Studies were performed to examine the effect of temperature and time on the extent of H₂ evolution from EtOH and M-SG (I). With Na₂K-SG (0) and K₂Na-SG (0), the reaction with EtOH yields more than 90% of the expected amount of H₂ and the remainder was liberated on reaction of the alcohol-reacted product with water. With increasing temperature of annealing the yield of H₂ from EtOH decreased and that from water increased. The portion of the M-SG (I) that did not react with

alcohol but reacted with water to evolve hydrogen was termed stage IIA M-SG. The presence of stage IIA in stage I M-SG can partially explain why excess M-SG (I) is often required for organic reactions with this material.

Stage IIA M-SG has not been fully characterized. The isolation of pure stage IIA from mixtures has not been possible. The ²³Na NMR of Na-SG (I) that had been reacted and washed with EtOH showed only a Na⁺ peak. Stage IIA M-SG could be viewed as originating from breakage of Si–O–Si bonds in strained rings leading to the formation of Si–O⁻Na⁺ and Na⁺Si⁻. The silyl anion at this point is still connected to three oxygens and may be inert in the reaction with alcohols. Alternatively, Si–Si bonds may already have formed. Attempts to monitor the nature of Si during the course of reaction via solid state ²⁹Si NMR were unsuccessful due to the long relaxation time and quadrupolar nature of the Si nucleus.

To summarize, the reaction between alkali metal and silica gel is believed to be complex and consists of a multitude of different processes. Physical characterizations such as solid state NMR, DSC, powder XRD, Raman spectroscopy and PDF studies revealed some important aspects of this reaction, such as the ionization of the metal in the pores, net enthalpy of the reaction, differential melting behavior of metals in the pores, and the nature of M⁰ and M⁺ during the course of the reaction. However, the fate of the electron after ionization of the metal remained elusive. The nature of stages IIA, IIB, IIC and IID is still largely speculative. How discrete these

stages are in terms of uniformity and identity of their chemical constituents needs to be answered. To understand M-SG materials better, studies on the metal-silica interactions by varying pore sizes, surface areas and modes of thermal treatment are necessary.

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CHAPTER 2

CHEMISTRY OF SODIUM, POTASSIUM AND THEIR ALLOYS

2.1 BACKGROUND

Alkali metals are known for their high reduction potentials and the resulting high chemical reactivities. The history of alkali-metal mediated reactions dates back to 1807 when Sir Humphrey Davy first isolated sodium in its elemental form by the electrolysis of NaOH.¹ Since then a variety of reactions have been developed that use alkali metal in some form or other. This review discusses two members of this family; namely sodium and potassium, together with their alloys.² Numerous powerful reducing systems³ have been developed from these metals, so the main focus here will be on reductions, reductive cleavages and the formation of superbases, highlighting advances made in recent years in controlling and exploring their chemical reactivity, handling and modes of delivery.

Historically, alkali metal dispersions such as sodium sand in oil and alkali metals dissolved in liquid ammonia have been widely used in organic reductions.⁴ Both of these most common routes have limitations.⁵ Metalammonia mediated reactions require the use of low temperature conditions and are therefore energy intensive. The use of a large excesses of ammonia or the introduction of finely dispersed reactive solid alkali metals are

particularly challenging for industrial scale processes.⁶ Sodium dispersions in hydrocarbon oil require extra process steps to remove the hydrocarbons either before or after reaction. The relatively milder alkali metal mercury amalgams have been widely useful but the toxicity of mercury limits their use in large scale reactions especially those of pharmaceutical interest. Use of alloys is not intrinsically safer; indeed, the liquid alloy of sodium and potassium is pyrophoric and dangerous to handle, as it can readily form explosive KO₂.⁷ More recently developed delivery systems include alkali metal "tamed" by intercalation in graphite or by dispersion in NaCI, polyethylene, alumina, and silica. These systems will be discussed below.

An interesting feature of alkali metals, extensively studied in our laboratories, is that except for lithium, they can exist not only in +1 and elemental (0) oxidation states but also as anions^{8,9} (M⁻) under suitable conditions. Typically crown ether or cryptand complexation of the cations enables formation of these metal anion species, known as *alkalides*.^{10,11} These powerful reducing agents readily effect two-electron reductions.¹² Although the solvated electron had been long recognized in ammonia and amine solutions,¹³ work at MSU has also led to isolation of the solid *electrides*,¹⁴ crystalline salts in which the electrons behave as anions and are separated from the metal counter-cations by crown ethers and cryptands. Applications of *alkalides* and *electrides*¹⁵ as reagents in synthesis remain nearly unexplored because their preparation requires scrupulously dry solvents and sublimed complex ligands. In addition, except for two recent

examples (themselves challenging synthesis targets), solid alkalides and electrides are unstable at room temperature,¹⁶ decomposing by electron attachment and C-O cleavage of the complexant's vicinal ether linkages. Replacement of the ether oxygens in cryptand[2.2.2] by tertiary amines enabled the recently reported formation of the first room-temperature stable alkalides¹⁷ and electride.¹⁸

A parallel, contemporary approach to address shelf-life and other problems of alkalide-electride research led to the development of inorganic electrides.¹⁹ Alkali metal dispersed in alumino-silicate zeolite cages were considered similar to electrides and some even contained alkali metal anions.²⁰ All-silica zeolites were found to be suitable for the preparation of inorganic electrides.²¹ In 2005 the adsorption of alkali metals (Na, K and their alloys) into silica gel was reported.²² A number of interesting physical and chemical aspects of these new reagents/materials have been studied.²³ The physical and chemical reactivity studies indicate that most of the alkali metals in the pores of silica gel remain in the elemental form. The reducing power of the encapsulated metals can be harnessed in a variety of reactions. What makes these new reagents useful compared with most other forms of alkali metal dispersions are their non-reactivity with dry air. Sodium and its alloys with potassium in silica gel (Na-SG and Na₂K-SG in particular) can be "tamed" by slow treatment with dry O₂ in such a way that it does not undergo further oxidation in dry air. Even after such "taming", the material can still fully react with water or alcohol to evolve hydrogen.²⁴

This tutorial review highlights the recent advances in reactions that use sodium, potassium and their alloys and also showcases the differences in intrinsic reactivities and selectivities based on various delivery modes of the metals to the substrates. While the development of new reactions based on transition metal catalysts (e.g., for hydrogenation reactions, debenzylations) and on electrochemical reductions provide alternatives to alkali metal reactions, the benign nature of the products of alkali metal based reagents, their relatively low cost and high reactivity are advantageous.

2.2 REDUCTION OF CARBON-CARBON MULTIPLE BONDS, CARBONYLS, IMINES, AMIDES, AND ESTERS:

Reductions are the most important reactions of elemental alkali metals. Conventionally, Na or K in ammonia^{25–27} (the so-called "dissolving metal conditions", Scheme 1a) serve as powerful reducing agents for aromatics^{28,29} (Birch reduction), carbonyls,^{30,31} internal alkynes,³² allenes^{33,34} and imines, enamino ketones,³⁵ conjugated ketones and amides. Unlike metal-ammonia solutions, Na-K alloy in THF in the presence of 18-Crown-6 (which forms K⁺ and Na⁻) reduces an internal alkyne directly to the alkane (Scheme 1b), and reduces toluene to a mixture of 1- and 3-methyl cyclohexenes, thus demonstrating the different reducing behavior of alkalides compared with elemental metals.^{36,37} Inclusion of t-BuOH as an in situ proton source facilitates reduction but requires an excess of reducing agent.³⁸ With ketones, alkalide solutions in aprotic solvents afford primarily a mixture of enolate and alcoholate.³⁹ Sodium and isopropanol under refluxing conditions reduce α , α -

disubstituted terminal amides to α -amino alcohol⁴⁰ and 1,3-diimines⁴¹ to γ diamines. Peptide bonds in proteins have been subjected to sodium-ammonia reduction, reduction of aromatic substituents of α -substituents (e.g., Phenyl ring of phenylalanine) and cleavage of the amide bonds (e.g., with proline amides) were the predominant outcomes of this studies.⁴² Reduction of aliphatic nitrile to imine is reported with sodium in pentane.⁴³ Under aprotic conditions, the bimolecular reduction of ketones with Na in the presence of a catalytic amount of bromobenzene is known to give pinacol or glycols.^{44–46}

In recent years, alkali metals dispersed into a variety of supports have become important. For instance, C₈K has been successfully used to reduce the double bond of conjugated acids, carbonyls,³⁸ and imines (Scheme 1d, 1e, 1f). Sodium on alumina is used to reduce ketones, esters and oximes.⁴⁷ We have recently reported an ammonia free, room temperature Birch reduction of polyaromatic compounds that are readily capable of forming radical anions. In most of these reactions, the carbanion salt of the alkali metal is formed which is subsequently quenched by water (Scheme 1g).⁴⁸

The Bouveault-Blanc reduction⁴⁹ refers to the reduction of an ester with sodium and alcohol (typically ethanol). Sodium serves as a single electron donor reagent and alcohol serves as a proton source. With bulk sodium this reaction gives a mixture of desired alcohol product along with the acyloin condensation product (usually in high yield if the amount of proton source is not adequate).⁵⁰ Sodium and potassium dispersions on polyethylene, sodium chloride, glass and TiO₂ were reported to be effective reagents for acyloin
condensation.⁵¹ Recently sodium in silica gel was reported as an effective alternative to conventional LiAlH₄-mediated ester reduction (Scheme 1h).⁵² It is interesting to note here that Barret, Barton and coworkers observed that the reduction pathway of esters with alkalide solutions in the presence of t-BuNH₂ leads to the formation of an alkane and a carboxylate anion instead of alcohol or acyloin products.^{53,54}

£



Scheme 2.1: Representative examples of reductions with alkali metals. Numbers in parentheses are corresponding references.

2.3 CLEAVAGE OF CARBON-CARBON, CARBON-HETERO ATOM (N, P, O, S, HALOGENS) BONDS, S-N, N-N BONDS:

Reductive cleavage reactions with alkali metals are well known. Typically molecules with low lying LUMOs can readily accept electrons from Na, K or Na-K alloys. The liquid-liquid reaction with Na-K alloys or Na-Hg are preferred for this purposes rather than Na or K metal alone. Metal dispersions in hydrocarbon oil, dissolved metal reaction conditions and Na with an electron transporter such as naphthalene, ethylenediamine (EDA) are used for conducting the cleavage reactions.

2.3.1 Cleavage of C-C bonds:

Reductive removal of cyanides can be achieved (Scheme 1.2 a) with C₈K.⁵⁵ K/Al₂O₃ has been used to reductively cleave alkyl cyanides in good yield.⁵⁶ 1-benzyl naphthalene is reductively cleaved with Na-K alloy in presence of glyme to afford naphthalene and toluene (Scheme 1.2 b) regioselectively.⁵⁷ Similarly, Na-K alloy in the presence of HMPA in THF is known to cleave (Scheme 1.2 d) 1,2-dinaphthylethane.⁵⁸ Potassium in 1,2-dimethoxyethane (DME) is known to cleave diarylfluorenes.⁵⁹ Bibenzyl is cleaved at the benzylic position with Cs-K-Na alloy (Scheme 1.2 e).⁶⁰ Similar cleavage reactions are observed for bibenzyl, diphenyl methane and related substrates with Na-K-glyme-triglyme combinations.⁶¹ Na-K alloy has been used to carry out Grob-type fragmentation reactions of 2-halo-adamantanone systems.⁶² C-C cleavage reactions are known for strained ring and fused ring

compounds.^{63–66} Rabinovitz recently observed a unique sequential reductive dimerization followed by reductive cleavage in indenocorannulene.⁶⁷ In all of the examples below, a low lying π^{*} LUMO seemed necessary in order for the cleavage reaction to occur.



Scheme 2.2: Examples of reductive C-C cleavage with alkali metals

2.3.2 Cleavage of C-N bonds:

Reductive amine debenzylations, debenzhydrylations and detritylations are known under dissolving metal reaction conditions.^{68,69} Recently, we reported amine debenzylation and deallylation reactions (Scheme 2.3) with M-SG reagents (Na-SG and Na₂K-SG).⁷⁰ These reactions were found to be versatile, effectively deprotecting both aromatic and aliphatic amines. For secondary allyl amines the under the M-SG reaction conditions, isomerization of the allyl group was observed that led to a mixture of enamines and imines and the desired allyl cleavage was not observed.



Scheme 2.3: Examples of C–N cleavage

2.3.3 Cleavage of C-P bonds:

Aryl C–P cleavage with alkali metal ammonia solutions,⁷¹ sodium dispersion in oil,^{72,73} ultrasonically dispersed potassium⁷⁴ and sodium naphthalide solutions⁷⁵ have been reported in the literature. Metal-ammonia solutions can lead to over-reduction (of aromatic rings) in addition to aryl C-P cleavage. In other cases, the diarylphosphide solution is subsequently reacted with suitable electrophiles to form diphenyl phosphines.^{76,77} Compared to Li,

Na/K-mediated cleavage of triaryl phosphines is advantageous because the other product of the reaction, the arylmetal salt is consumed by protonation with the solvent for Na and K, while for Li the PhLi has to be quenched in a separate step using t-BuCl at -10° C.⁷⁸ Recently we have reported (Scheme 2.4) a room temperature cleavage reaction of triarylphosphine with alkali metal in silica gel reagents (Na₂K-SG and Na-SG). We found that adding ethylenediamine in these reactions causes significant rate acceleration. We have extended this methodology to provide a second aryl-phosphorous cleavage (after a 1st electrophilic quenching step) in the same pot using additional equivalents of M-SG reagent.⁷⁹

$$\begin{array}{c} Ar P^{Ar} \underbrace{1. M-SG}_{Ar} P^{Ar} \underbrace{1. M-SG}_{E} Ar^{P} \underbrace{1. M-SG}_{2. E-X} e^{E'} \\ I E \underbrace{1. M-SG}_{2. E-X} e^{E'} \underbrace{1. M-SG}_{E} e^{E'} \end{array}$$
(79)

Scheme 2.4: Cleavage of arylphosphines

2.3.4 Cleavage of C-O bonds:

Cleavage of ethereal C–O bonds under dissolving metal reaction conditions is well precedented in the literature.⁸⁰ Allyl and benzyl ethers^{81,82} are cleaved with alkali metal dispersions in THF. Cleavage of C–OBn with Na-Hg is used for making long chain conjugated polyolefins (Scheme 2.5 a).⁸³ A similar reaction was observed with Na-K alloy.⁸⁴ Methoxy aryl ethers can be cleaved at alkyl-oxygen or aryl-oxygen bonds to obtain phenols or arenes respectively.^{85,86} Remarkable differences were observed in the rates of cleavage of dimethoxy substituted benzenes.⁸⁷ Recently aryl-methoxy cleavage was coupled with activation of the benzylic position and the products were subsequently alkylated.⁸⁸ The outcomes of these reactions were heavily influenced by choice of alkali metal and were reasoned due to differential ion-pairing between the alkali metal cations and the aromatic radical anions. Note that the decomposition of alkalide and electrides themselves do represent cleavage but they are mostly reactive because of being vicinal.¹⁷ Phthalans (Scheme 2.5 b) have been reductively cleaved with Li, Na, K and Na-K alloy in aprotic solvents.⁸⁹



Scheme 2.5: Examples of C–O cleavage

2.3.5 Cleavage of C-S bonds:

Alkali metal mediated C–S bond cleavage⁹⁰ is of importance in destroying diarylsulfides contaminants in fuels. Desulfonation of alkyl

sulfonate esters is reported with C_8K^{67} (Scheme 2.6a, 2.6b), sodiumamalgam⁹¹⁻⁹⁵ (Scheme 2.6c, 2.6d, 2.6e) potassium⁹⁶ (Scheme 2.6f) and sodium naphthalide.⁹⁷ Cleavage of the sulfinyl group at the final step of Julia olefination is reported with sodium-amalgam.⁹⁸ Dithianes are reductively cleaved with sodium-ammonia in good yield.⁹⁹ Na-K alloys have proven to be more effective than Na or K metals in removing sulfur impurities from benzene.¹⁰⁰ M-SG reagents can also desulfurize diaryl sulfides²⁶ (Scheme 2.6g).



Scheme 2.6: Examples of C–S Cleavage

2.3.6 Cleavage of C-X (halogen) bond:

The cleavage of C-X (X = F, Cl, Br, I) bonds is widely used for generation of carbanions to form metal alkyl salts, reductive coupling reactions¹⁰¹ (e.g., the Wurtz reaction), generation of carbenes and subsequent reactions.¹⁰² polycarbynes¹⁰³ preparation of (Scheme 2.7a). polyphenylcarbyne,¹⁰⁴ polysilynes,¹⁰⁵ and polymethylcyclosilanes.¹⁰⁶ The mechanism of Wurtz coupling reactions has been debated with radical and S_N2 pathways being considered.^{107,108} Reductive coupling reactions are also applied in preparation of strained rings^{109,110} and in total syntheses.¹¹¹⁻¹¹³ Dehalodeuteration has been accomplished with Na-Hg and D₂O¹¹⁴ (Scheme 2.7b). Similar deuterium incorporation on haloaromatic substrates is achieved with Na-Hg in MeOD¹¹⁵ (Scheme 2.7c). Alkali metals have become important in a number of environmental remediation processes such as dehalogenation of PCBs and chlorofluorocarbons.¹¹⁶ Although C-F bonds are kinetically more resistent to reductive cleavage than C-Cl, C-Br and C-I bonds, with alkalide solutions they react rapidly.^{117,118}

a
$$R \xrightarrow{CI}_{CI} \frac{Na-K}{THF} [R-C]_{n}$$
 (104)
 $R = Me, Ph$
b $H \xrightarrow{Br}_{CO_{2}H} H \underbrace{Na/Hg, D_{2}O}_{H \xrightarrow{CO_{2}H}} \xrightarrow{D}_{H \xrightarrow{CO_{2}H}} H$ (115)
 $C = Br \xrightarrow{CI}_{CI} \underbrace{Na/Hg, D_{2}O}_{H \xrightarrow{CO_{2}H}} \xrightarrow{D}_{G8\%} D \xrightarrow{CO_{2}H} \xrightarrow{D}_{D}$ (116)

Scheme 2.7: Examples of C-X cleavage

2.3.7 Cleavage of S–N bonds:

Metal ammonia solutions^{119–121} and sodium naphthalide^{122–125} have been used to cleave^{126,127} the tosyl group of *para*-toluenesulfonamides. Sodium amalgams have been used to carry out similar reactions (Scheme 2.8 a).¹²⁸ Alkalide solutions cleave sulfonamide and sulfonate esters.¹²⁹ Recently we have developed a method to do these deprotections (Scheme 2.8 b, c) with M-SG reagents (using Na-SG and Na₂K-SG).¹³⁰ At room temperature stirring the reactions with M-SG reagent, (except for the tosyl aziridine) followed by a water quench afford deprotected amines in good yields. This method was applicable to deprotection of primary amines and cleavage of other related sulfonamides (i.e., mesyl and benzene sulfonamides).



Scheme 2.8: Examples of S–N cleavage

2.3.8 Cleavage of N–N bonds:

Reductive N–N bond cleavage under dissolving metal conditions is observed in cases where a low lying π acceptor orbital is in close proximity.¹³¹ This cleavage reaction provides access to useful chiral amine ligands.¹³² In some cases trans annular N–N bond cleavage can lead to formation of a large ring.¹³³ Cleavage of N–N bonds with Na-Hg in azide leads to formation of amines.¹³⁴ We have found tandem N–N bond cleavage and reduction of benzophenone hydrazone to afford benzhydryl amine.⁷¹ In the case of allyl benzotriazole we observed N–N cleavage with M-SG reagent leading to aniline.⁷¹



Scheme 2.9: Examples of N–N cleavage

2.3.9 Other Cleavages:

Studies of Na-naphthalide mediated reductive cleavage reactions of aryl phosphates found a preference for C–O cleavage in the inverse addition mode (i.e., [arenide] > [substrate]). During normal addition of Na-naphthalide, ([arylphosphate substrate] > [arenide])¹³⁵ preferential P–O cleavage was observed in THF. Reaction of Ph₂P–PPh₂ with sodium generates diphenylphosphide salts.¹³⁶ Likewise, C–Sb bonds were found to be cleaved with sodium in ammonia.¹³⁷ Trialkylgallium (R₃Ga) compounds can be reduced with alkali metals in benzene to afford R₃GaPh⁻ and R₃GaH⁻.¹³⁸ Subvalent silicon species generated from the cleavage reaction of dichlorobis(diethylamino)silane and related compounds undergo spontaneous unusual aromatic C-H insertion reaction with benzene and biphenyl to afford aryl-substituted aminosilanes.¹³⁹

2.4 Catalytic Reactions:

There are many industrial processes that are based on the presence of catalytic amounts of Na and Na-K alloy. Na supported on alumina is used for isomerization of 5-vinyl norbornene (VNB) to 5-ethylidene norbornene (ENB).^{140,141} This reaction can be carried out in a fluidized bed in quantitative yield.¹⁴² Sodium and potassium based superbases are also known to be effective for this (Scheme 2.10a) transformation.^{143,144} A similar superbase derived from potassium is used for isomerization of 1-hexene.¹⁴⁵ Side chain alkylation of alkyl benzene (e.g., Scheme 2.10b) is accomplished by NaK alloy in THF or by superbases derived from Na or K.¹⁴⁶⁻¹⁵⁰ Heterogeneous bases derived from Na, K and Cs in zeolite are known to be effective for alkylation of toluene to ethylbenzene with methanol.¹⁵¹

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Scheme 2.10 : Examples of catalytic reactions using alkali metals

2.5 Applications in Organometallics and Inorganic Syntheses:

Organosilicon and organo-mercury compounds have been made (Scheme 2.11a, 2.11b) using alkali metals.¹⁵² Recently this strategy was employed in the stereoselective synthesis of disubstituted piperidine.¹⁵³ Unusual organo-cobalt compounds have been made by using Na-Hg.¹⁵⁴ Na-Hg has found applications in the preparation of metal imido complexes (Scheme 2.11d) of Fe¹⁵⁵ and Mo.^{156,157} A metallacyclopentadiene (Scheme 2.11e) based on Ti was made by reductively coupling dialkylacetylene and Ti(OAr)₂Cl₂.¹⁵⁸ N-based tetrameric aluminum(I) compound was made using Na-K alloy as reducing agent.¹⁵⁹

An organoplatinum metallacycle was prepared by reductive coupling of dibromoolefin in presence of Pt(PPh₃)₄ and Na-Hg.¹⁶⁰ Tetra-tertbutylboratetetrahedrane was made from the reduction of Me₃CBF₂ by Na-K alloy.¹⁶¹ Sodium-potassium alloys as well as alkalide solutions in THF or Me₂O have been found to be kinetically and theromodynamically effective in reducing a variety of metal salts into metal nanoparticles (with particle sizes as low as 3-15 nm).¹⁶² Low valent titanium reagents are made from the reduction of TiCl₃ with Na-arenide, Na-Hg and Na-K alloy.¹⁶³ Aromatic radical anions generated with alkali metals have been extensively used by Reike in preparing metal nanoparticles.¹⁶⁴ Reduction of As with Na-K alloy followed by a quench with Me₃SiCl yields trimethylsilylarsine.¹⁶⁵ A water soluble polyhydroxylated derivative of C₆₀ were made by vigorous stirring of C₆₀ and Na-K alloy in presence of oxygen.¹⁶⁶ Anionic boron compounds such as dimesitylphenylborane dianion¹⁶⁷ have been made with Na-K alloy as reducing agent.

<u>,</u>



Scheme 2.11: Examples of alkali metal mediated reactions in organometallic and inorganic synthesis

2.6 Initiation of Polymerization:

Use of alkali metals for the anionic polymerization of 1,3 butadiene has been known for a long time.¹⁶⁸ Solutions of alkalides and electrides in THF were first used for anionic polymerization by Boileau, Kaempf, Lehn and Schue.¹⁶⁹ Jedlinkski et al. have reported ring opening of β -lactone rings (Scheme 2.12a, 2.12b) with K anion generated from K and 18-Crown-6.¹⁷⁰ The generated radical anion accepts another electron from K to form a carbanion which is subsequently quenched with suitable electrophiles or used in a block copolymerization reaction. Similar strategies with the potasside ions yielded dianion of propylene oxide and dianion of styrene which were subsequently used for coploymerization reactions to afford styrene-ester block copolymers.^{171,172} In addition, an unusual methyl methacrylate carbanion was generated using sodide via a 2 e transfer process.¹⁷³



Scheme 2.12: Examples of alkali metal mediated polymerization reaction

2.7 Future Scope and Conclusions:

With the rapid depletion of non-renewable petroleum based chemical inventory, discovery of new pathways that transform biomass into chemical feed-stocks are gaining increased significance. Reduction reactions may hold the key to these transformations as most of the biomass can be viewed as oxidized forms of hydrocarbons. Even 150 years after their discovery, they still remain some of the most powerful reductants in syntheses. New discoveries made in the last 50 years are mostly centered on new delivery modes of reactive alkali metals, the discovery of new reactions and the discovery of alkali metal anions. The chemistry of these latter highly reactive species is still largely unexplored. So far attempts to observe solvent-induced CD for alkalide solutions in enantiopure crown ethers have been unsuccessful suggesting weak interactions between anions and the crown complexants.¹⁷⁴ Chiral induction in reactions of alkalides and electrides therefore remains a challenge.

For a long time the relatively high cost of crown ethers and cryptands and short shelf-life of alkalides and electrides in solutions were prohibitive to industrial developments in the field. However, with the discovery of new room temperature stable inorganic electrides, mapping out their chemical reactivity may become an attractive direction.¹⁷⁵

Alkali metals absorbed in silica gel have also been shown to be effective reagents for carrying out a variety of reactions. There are chemical details such as the fate of the electrons derived from the ionization of the metal on the surface that also need to be addressed. The possibility of "finetuning" the reduction potentials of encapsulated alkali metals in porous support depending upon the solvent used (solvent-M-SG surface) and surface interactions (e.g., ionizations and unusual bonding of metal to the heterogeneous support) are intriguing.

In addition to being powerful reducing agents, alkali metals such as Na, K are also useful in making powerful superbases for both homogeneous and heterogeneous reactions. The ability to control basicity, size and shapes of the heterogeneous superbases offer unique opportunities for development of new and efficient chemical processes.

In summary, in this section, we have showcased the major

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developments in the chemistry of alkali metals in our group and elsewhere in last more than 50 years of research. The focus of this discussion was alkali metals in their zero-valent and anionic forms and modes of delivery of the reducing power in reactions.

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CHAPTER 3

ALKALI-METALS IN SILICA GEL (M-SG): A NEW REAGENT FOR DESULFONATION OF AMINES

3.1 BACKGROUND

In organic synthesis, many protecting groups have been developed for the amine functionality.¹ In pharmaceutical chemistry, amine protections are often accomplished with groups such as Cbz (carbobenzyloxy), Boc (tbutoxycarbonyl) and Fmoc (9-fluorenylmethyloxycarbonyl).² But for some uses these protecting groups are too labile. Sulfonamides, formed by reaction of amines with sulfonyl chlorides, are more robust, and have the advantage of being easy to isolate and purify by recrystallization. But practical desulfonation of sulfonamides, *p*-toluenesulfonamides specifically, can be difficult. This problem has arisen in our own ongoing work on functionalized polyamine cages for assembly of organic alkalides and electrides.³

Existing methods for sulfonamide deprotection can be broadly grouped as: (a) strong acid treatment,⁴⁻¹⁰ (b) cleavage by strong bases/nucleophiles,¹¹⁻¹⁴ (c) microwave irradiation,¹⁵⁻¹⁶ (d) photoreduction¹⁷⁻¹⁸ with various reagents, (e) electrochemical reduction,¹⁹⁻²⁰ and (f) metal-based reductive cleavage.²¹⁻³⁹ Acidic deprotections of tosylated amines use severe conditions such as H₂SO₄.^{4,5} 48% HBr,⁶ AcOH-HClO₄,⁷ HBr with

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PhOH,⁸ and HF-pyridine with anisole.⁹ Of recent interest is a "green" phase transfer catalyzed cleavage by NaOH and KOH that deprotects tosylated aromatic and heteroaromatic amines.¹⁴ But for secondary amine detosylation, many of these procedures are too harsh and/or reagent-intensive, or lack generality due to limited substrate scope, functional group intolerance, or demanding separations on workup. Super-electron-donor (SED) reagent bisimidazolylidene reagent in presence of refluxing DMF is shown to be capable of desulfonating activated secondary amines.⁴⁰ However, with unactivated aliphatic toluene sulfonamides this reaction fails.

The last and most general group, metal-based reductions, use powerful reagents such as sodium naphthalenide,³⁴⁻³⁶ Ni(acac)₂ with Grignard reagent,²³ Li-NH₃³⁰ or Na-NH₃,^{31,32} Al-Hg²⁵ and Na-Hg,²⁶ Red-Al,²⁹ Na-isopropanol,²¹ Mg-MeOH,³⁶ low valent titanium reagents,²⁶ mischmetal with TiCl₄,²⁷ Sml₂ with Bu₃SnH²⁴ and Sml₂ with pyrrolidine in water.⁴¹ Although they generally produce the desired amines in good yield, these approaches can be difficult to scale⁴² up and suffer from issues such as: a) reagent instability, b) moisture sensitivity, c) reagent pyrophoricity, d) difficult removal of reagent by-products, e) the need for cryogenic reaction temperatures, f) reagent toxicity, g) waste handling and h) high cost. There remains a need for a simple general desulfonation which harnesses the reductive power of alkali metals without the associated safety and economic issues.

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Recently, solid alkali metal-based reductions in organic solvents became easier with the finding that these metals can be made significantly less pyrophoric by thermal absorption into nano-structured silica to form the metal-silica gel (M-SG) reagents.⁴³⁻⁴⁵ Herein, we report a novel method to cleave toluenesulfonamides to amines by using M-SG.⁴⁶ Specifically, we have used M-SG (Stage I) where M is Na or Na₂K. The overall general transformation is analogous to sulfonamide cleavage by alkali metal arenides and is thought to proceed via two single-electron transfers with subsequent cleavage to form the alkali metal amide and sulfinate salt (Scheme 3.1).⁴⁷⁻⁴⁹ As described below, treatment with M-SG is a mild and general procedure to desulfonate protected amines.



Scheme 3.1: M-SG-mediated desulfonation of protected secondary amines (Ar = p-tolyl)

3.2 RESULTS AND DISCUSSION

Various sulfonamide substrates were investigated to explore the scope of M-SG desulfonations (Table 3.1). The reactions were conducted in ethereal solvents, typically in THF with 2.5-5 equivalents of Na₂K-SG(I) at room temperature over 8 hours and subsequently quenched with water, except where noted.⁵⁰ Detosylation with Na₂K-SG (I) tolerates phenyl (entries 1, 2, 4, 9, 11) and ether moieties and is successful for both primary (entry 9) and secondary amines (entries 1- 8, 11). The reaction's success with the bulky aza-cryptand (entry 8) where both HBr/AcOH and Na-NH₃ methods failed promises to be useful in our ongoing synthetic studies of azacryptands directed to preparation of alkalides and electrides.³ Perhaps most interesting, however, is the (modified) reaction's success in detosylating aziridine, a special class of secondary amine (vide infra).

Modifications and Extensions:

For reactions in 1,2-dimethoxyethane (entries **7** and **9**), the addition of a catalytic amount (20 mol% relative to the sulfonamide starting material) of ethylenediamine (EDA) accelerates N-S bond cleavage, bringing reactions to completion in 3-4 hours instead of the 8-10 hours seen without EDA.

The mesyl moiety is cleanly cleaved from 4-benzylpiperidine, a simple secondary amine (entry 10), suggesting that the tosyl group's aryl

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ring is not critical to the electron capture and reductive cleavage process. Similarly, in a preliminary study, the benzenesulfonyl group was removed from bis-(2-methoxyethyl)amine with essentially the same efficiency as tosyl group cleavage.

Entry	Substrate	Product	Yield
1	₽h _{`Ņ} ∽₽h	Ph _{`Ņ} ´Ph	93 ^a
2	ˈᠯs Ph∖Ŋ́	H Ph、N	81 ^b
3	Ts Cy _{∖N} ∠Cy Ts	H Cy∖ _N ∕Cy H	81 ^{C,g}
4	Ts-NPh		96 ^a
5	Ts-N_O	H-NO	75 ^C
6	N	H N O N	85 ^a
7	Ts-N_N-Ts	H-N_N-H	76 ^{a,d}
8	$N \rightarrow N \rightarrow$		68 ^a
9	Ph	PhNH ₂	76 ^{a,d,f}
10	Ms-NPh	H-NPh	89 ^a
11	Ts N ◯───────────────────────────────────	H N Ph	61 ^{a,e}

Table 3.1: Evaluation of substrate scope.

^aIsolated yield, ^bYields from NMR, ^cIsolated as HCI salt ^dDME used as solvent at 60 °C (in all other cases THF was used as reaction solvent at room temp). ^e 3 eq Na-SG(I) was used at -60 °C in THF (in all other cases Na₂K-SG was used) ^f5eq Na₂K-SG was used, in all other cases 3-4 eq Na₂K-SG were used. ^g Similar yields were observed in runs with 4-6 eq. Na₂K-SG(I) and solid acids such as (NH₄)₂HPO₄, NH₄CI, HCO₂NH₄ included in situ.
As entries to the strained aziridine (azacyclopropane) framework, the N-tosyl protected aziridines are relatively easily synthesized.⁵¹ Their desulfonations, however, are synthetically challenging.⁵² For example, 2benzyl-*N*-tosylaziridine gives substantial ring opening products on treatment with Na/NH₃, Sml₂, or phenyldimethylsilyl lithium.^{49,53} At ambient temperatures, Mg/MeOH,²⁴ activated by sonication, does give modest aziridine yields.⁴⁹ And Li/arenide (arene = naphthalene or 4,4'-di-t-Bubiphenyl [DBB]), or Na/naphthalene deprotections are also effective at low, but not at ambient, temperatures.⁵⁴

Attempts at our usual M-SG deprotection (Na₂K-SG in THF, room or low temperature; H₂O quench) of 2-benzyl-*N*-tosylaziridine showed both desulfonation and ring opening. However, the milder Na-SG reagent in THF cleanly detosylates 2-benzyl-1-tosylaziridine at -60 to -78 °C without any electron transporting species (Table 3.1, Entry **11**). Not surprisingly Na-naphthalide generated from Na-SG at -50 °C also gave 67% yield of the desired product.

In the general M-SG desulfonation procedure, as an alternative to a post-reduction aqueous quench, the quenching proton source can be included with the M-SG reductant. Organic-soluble proton sources such as acetic acid or alcohols reacted directly with the M-SG, evolving hydrogen and diminishing reducing capacity. However, relatively insoluble solid proton sources in intimate contact with M-SG can neutralize the soluble amide shortly after its formation without direct rapid reaction of the proton

source with the M-SG. In the detosylation of Cy_2NTs solid inorganic acid salts, such as $(NH_4)_2HPO_4$, NaH_2PO_4 , NH_4CI and potassium hydrogen phthalate were found to react with the metal amides, affording clean dicyclohexyl amine product in THF at room temperature.

To demonstrate one-pot detosylation and trapping with a nonproton electrophile, the M-SG(I) deprotection was applied to *N*-tosyl pyrrole (5), with benzoyl chloride serving as the electrophile in the final quench (Scheme 3.2). This reaction was complete in 6 hours with an 85% yield of *N*-benzoyl pyrrole (6).



Scheme 3.2: Generation of alkali metal amide and electrophilic quenching in situ. Conditions: THF, 25 °C, 6 hr.

As a first probe of selectivity, Ph₂NTs and Cy₂NTs, simple time course studies by ¹H NMR were run in single substrate reactions and a 1:1 mixed substrate reaction. For these rate studies, solvents freshly distilled from NaK alloy were used and 1.5 eq of M-SG(I) was found to be sufficient to drive the reactions to completion. As expected, deprotection of Ph₂NTs by Na₂K-SG(I) is ca. two-fold faster than that of Cy₂NTs. No evidence of competitive inhibition was seen, i.e., the rate of detosylation of Cy₂NTs did not slow down to any significant extent in the presence of an equal amount of Ph₂NTs, and the 2:1 rate ratio was observed in the mixture as

well, suggesting (a) independent reactions and (b) that there is little difference in electron accepting ability or access to the metal sites between these two substrates, despite the very large difference between the pKa values of the Ph_2NH and Cy_2NH product amines.

3.3 CONCLUSIONS

In summary, M-SG materials (Na or Na-K alloys absorbed in silica gel) can act as efficient reagents for removing sulfonyl protecting groups from primary and secondary amines. These M-SG reagents offer simple alternatives to the other alkali-metal based reagents such as Na-NH₃ or Na-arenides often used for sulfonamide deprotections in total syntheses.

3.4 EXPERIMENTAL SECTION

3.4.1. Procedure for Preparation of Sulfonamides:

A secondary amine (10.5 mmole) in a 100 mL round bottom flask equipped with a magnetic stir bar is dissolved in 40 mL THF. A THF solution (20 mL) of sulfonyl chloride (10 mmole) is then added, followed by a slight excess of Et₃N (1.3-1.6 mL, 1-1.2 g, 10-12 mmol) and the reaction is stirred overnight. The solvent is evaporated off and the reaction mixture is extracted with brine and ethyl acetate. The organic layer is concentrated under aspirator vacuum and purified by column chromatography (neutral alumina column with 20% EtOAc in hexane) to afford the corresponding sulfonamide derivative in 60-95% yield.

3.4.2: Representative Procedures for Desulfonation of Amines:

Prior to carrying out any deprotection reaction, the reducing ability of M-SG (I) is tested by measurement of hydrogen evolution upon reaction with ethanol in a closed system equipped with a digitized pressure gauge. The volume of hydrogen produced is used to calculate the number of equivalents of alkali-metal(s) in a given reagent.

3.4.2.1: Detosylation of secondary amines:

In a round bottom flask equipped with a glass-coated magnetic stir bar and a rubber septum, dicyclohexyl-*para*-toluenesulfonamide (Cy₂NTs, 335 mg, 1

mmol) and Na₂K-SG(I) (400 mg, 40% w/w loading of metal alloy in silica gel, 5 mmol, 2.5 equiv*) are placed under an inert atmosphere. To this flask 3-5 mL of rigorously anhydrous THF is added and stirred at room temperature for 6-8 h. After this time the reaction mixture is quenched with 3-5 mL of water, and the solids/aqueous layer are extracted via washing with an additional 20 mL (2X10 mL) of ether.** After separation, the combined organics are passed through a basic alumina plug to afford a clear solution that is concentrated on a rotary evaporator. The product Cy₂NH is obtained as a clear oily liquid (150 mg, yield = 83%).

*Because a two-electron S-N bond cleavage is this chapter's focus, the molar equivalency of the M-SG reactants is reckoned as, the total number of moles of alkali metal therein. Thus, if reaction efficiency were perfect, one equivalent, so termed, would cleave a mole of tosyl amides. Similarly, upon reaction with ethanol, one equivalent of M-SG forms one mole of H₂ gas.

**For these desulfonation procedures, it is observed that addition of stoichiometric or near stoichiometric amounts of water (~100 μ L) in the quenching step is not sufficient to phase separate the silica from the organic solvent. Later gel formation (presumably via Ostwald ripening) is seen upon concentrating the organic layer. This difficulty can be avoided by using excess water (1.6 mL or more) and conventional drying of the organic phase by passing through basic alumina or treatment with Na₂SO₄ prior to concentration.

3.4.2.2: Detosylation of a primary amine:

In a 100 mL roundbottom flask equipped with a glass-coated magnetic stir bar and a rubber septum, N-(2-phenylethyl)toluenesulfonamide (275 mg, 1 mmol) and Na₂K-SG(I) (802 mg, 40% w/w loading of metal alloy in silica gel, 10 mmol, 5 equiv.) are assembled under an inert atmosphere. After DME (10 mL) is added, the reaction is stirred at room temperature for 7 h, followed by quenching with 5 mL cold water. The organic layer is decanted and the residual solids washed with an additional 2X10 mL portions of Et₂O. The combined organic solution is passed through a plug of basic alumina and the concentrated on a rotary evaporator to afford phenethylamine as an oily liquid (92.3 mg, yield = 76.3%).

3.4.2.3: Detosylation of an aziridine:

In a He drybox, Na-SG(I) (1.51g, 19.5 mmol) is placed in a 100 mL round bottom flask equipped with a glass jacketed stir bar and rubber septum. To this flask, after removal from the box, anhydrous THF (25 mL) is added by syringe with gas venting via needle. The closed flask is chilled in a cryobath set at -60 °C for 20 minutes; then a THF solution (10 mL) of 2-benzyl-1-tosylaziridine (900 mg, 3.14 mmol) is added via syringe. The reaction is stirred for 6 h at this temperature with monitoring by TLC. At reaction completion, the organic layer is decanted from the solids and quenched in a separate flask containing 0.4 mL water. The silica gel residue is washed with 10X2 mL portions of ether and the combined organics are dried over Na₂SO₄ and placed on a rotary evaporator for solvent removal. Pure 2-benzylaziridine (256.4 mg, 61.4% yield) is isolated from the resulting pale yellow oil by flash chromatography over deactivated silica gel using ether/ethanol as eluting solvent.

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CHAPTER 4

PREPARATION OF DIPHENYL PHOSPHIDE AND SUBSTITUTED PHOSPHINES USING ALKALI METAL IN SILICA GEL (M-SG)

4.1 BACKGROUND:

Diarylphosphides of alkali metals are important organic reagents for many organic transformations such as dehydroxylation of α-hydroxy ketones,¹ stereoselective reduction of gem-dihalides,² regio- and stereospecific cleavage of silylated and stannylated epoxides³⁻⁵ demethylation of methylammonium salts⁶ and methyl aryl ethers,⁷ stereoselective displacements of secondary mesylates and tosylates in steroids,⁸ the Staudinger type reaction⁹ and bromouracil functionalization.¹⁰ Diarylphosphides are also key building blocks for the many substituted phosphine¹¹⁻¹⁶ ligands that enable homogeneous catalytic processes including hydroformylations,¹⁷ asymmetric hydrogenations and other asymmetric syntheses.^{18,19}

Literature routes to alkali metal phosphides generally use the reaction of the alkali metal with diaryl-,^{20,21} diarylhalo-,²² or triarylphosphines.²³ This last reaction²⁴⁻²⁷ has the advantage that many triaryl phosphines are commercially available and air stable.²⁸⁻³⁰ Others are readily made via metathesis reactions of arylsodium, aryllithium, or aryl Grignard reagents with PX₃ where X can be a halide, phenoxide, or alkoxide.³¹ Reductive cleavage of triarylphosphine is the most used, but can be hard to run and especially to scale up since it requires

sodium dispersions in oil.^{32,33} Classic metal ammonia reduction introduces problems of handling, over reduction and operational safety. Solutions of Nanaphthalide have been effective in preparing unsymmetrical diphosphines.³⁴ However, the presence of co-reagents and/or impurities that arise from these routes can introduce challenges in isolation, purification and subsequent reactions.³⁵

Alkali metals absorbed in porous silica gel^{36,37} provide an alternative reagent that is non-pyrophoric in dry air, a free flowing dry powder and free of contamination by oily hydrocarbons or ammonia. Herein, we report³⁸ a new method for preparation of diaryl phosphide salts of alkali metals that uses triarylphosphine and alkali metal absorbed in silica gel. The clean diarylphosphide solution thus generated can be decanted and used for subsequent reactions. We report here on comparisons of sodium vs. sodiumpotassium alloys, and the effects of solvents and additives such as ethylenediamine. The method's versatility is tested with various electrophiletriarylphosphine pairings to form substituted diarylphosphines. These monoalkylated phosphines can be further functionalized in a subsequent step to afford aryldialkyl phosphines. This approach conveniently accesses substituted phosphines while avoiding transition metals such as Pd or Ni used to mediate couplings.39

4.2 RESULTS AND DISCUSSIONS:

The conditions for cleavage of triarylphosphines to diarylphosphides were investigated by using triphenyl phosphine as a model substrate. Cleavage of the aryl C-P bond was found to occur under ambient conditions in ether solvents such as THF and DME at room temperature with 2.5 equivalents or more of Na-SG(I) and Na₂K-SG(I). The aryl-metal (e.g., phenyl sodium or phenyl potassium) carbanion is formed initially, but does not survive under the reaction conditions. Traces of electrophile functionalized aryl compounds were seen in a few mid-reaction samples (Scheme 4.1), but never at reaction completion. If need be, however, decomposition of the Ar-M (M = Na or K) species can be ensured by brief warming of the reaction mixture to 40-50 °C. In contrast, the cleavage of triarylphosphine with lithium metal gives phenyl lithium and lithium diphenyl phosphide. Phenyl lithium in THF is long lived and has to be guenched with tert-butyl chloride at a lower temperature in an additional step.⁴⁰ The alkali metal (Na or K) diarylphosphide salt solutions can be quenched in situ or first decanted or filtered under inert atmosphere to remove the M-SG solids and then guenched. Quenching with alkyl halides gave alkyldiarylphosphines in good to high yields (for example 1-bromobutane vielded n-butyldiphenyl phosphine in 77% vield).

$$Ar \xrightarrow{Ar} Ar \xrightarrow{M-SG} M^{\oplus} P_{\ominus}^{(G)} + [PhM] \xrightarrow{RX} R^{-} P_{Ar}^{(Ar)}$$

Scheme 4.1. Reductive cleavage of triaryl phosphine to generate diarylphosphide.

Cleavage occurred faster in 1,2-DME than in THF, and faster with Na₂K-SG(I) than with Na-SG(I). Reaction with Na-SG(I) was, however, accelerated by addition of catalytic ethylenediamine (EDA), finishing in 3 h vs. the 6 h required in its absence. The blue color seen in these reactions before phosphine addition suggests formation of Na⁻ ions in solution, presumably balanced by the EDA-Na⁺ complex. The faster rates seen when EDA is added to Na-SG(I) and when Na₂K-SG(I) was used in place of Na-SG(I) hint at a two-electron transfer from Na⁻ as opposed to sequential SET steps from elemental Na. Indeed, addition of 18-Crown-6, a complexant known to form sodide with Na metal, led to similar accelerations.⁴¹

The scope of this reaction was studied with different aryl substituents and electrophiles as summarized in Table 4.1. The diphenyl phosphide product reacts cleanly with both aliphatic and aromatic halide electrophiles (Entries 1-6). The reductive cleavage takes place with more electron rich phosphines such as tris(p-tolyl)phosphine and tris-(3,5)-xylylphosphines, but at a slower rate (Entries 7, 8). With tris(p-fluorophenyl) phosphine (Entry 9) even a modest excess of Na₂K-SG(I) and longer reaction time yielded only defluorination products, and an 18-fold excess led to diphenylphosphide, as expected from plain

triphenylphosphine cleavage. No reaction was seen with tributylphosphine (Entry 10).

Table 4.1. Preparation of monosubstituted diarylphosphines from triarylphosphine.

Ar Ar ^P	`Ar ⁻	M-SG	⊕ Ar M P(☉ + Ar	[PhM]	Ar - R-P(Ar
	Entry	PAr3	Electrophile	Product Yiel	d (%) or onv.
	1	PPh3	n _{BuBr}	n _{BuPPh2}	77 ^b
	2	PPh3	TMSCI	TMSPPh ₂	80 ^a
	3	PPh3	Mel	MePPh ₂	75 ^a
	4	PPh3	CyBr	CyPPh ₂	70 ^b
	5	PPh3	C ₆ F ₆	C ₆ F ₅ PPh ₂	70 ^C
	6	PPh3	4-lodo-tol	(4-tol)PPh ₂	67 ^C
	7	P(4-tol)3	ⁿ BuBr	ⁿ BuP(4-tol) ₂	74 ^b
	8	P(3,5-xylyl)	3 ⁿ BuBr	ⁿ BuP(3,5-xylyl) ₂	77 ^b
	9	P(4-F-Ph)3	n _{BuBr}	ⁿ BuP(4-F-Ph) ₂	0 ^a
	10	P ⁿ Bu ₃	Mel	No reaction	0 ^a
	11	PPh3	≫∽∽ Br	Ph ₂ P	76 ^b

In all cases 2.5-3 equiv. Na₂K-SG(I) was used at room temperature in THF unless mentioned otherwise.⁴² ^aConversion measured by ³¹P NMR; ^bIsolated yield obtained from the quench of the electrophile in same pot;

(table 4.1 continued) ^cIsolated yield from the decanting of PPh_2^- and quench with electrophile in a separate flask.

Quenching of the diphenylphosphide with butyl or homoallyl bromides achieved mono-functionalization in good yield (Entry 11), but activated electrophiles such as benzyl- and allyl bromides formed quaternary salts.

Next we looked at cleavage reactions of monoalkyl diarylphosphines to see if we could further functionalize them. The targets would be phosphines bearing three different substituents, and hence chiral (albeit racemic). Interestingly, alkyldiarylphosphines also underwent cleavage losing an aryl ring to afford the corresponding alkyl aryl phosphide solutions. However, dialkyl arylphosphines resist cleavage completely.

Understanding the factors controlling selectivity in the cleavage of alkyldiarylphosphines may allow design and control of stereochemistry and redox potentials of organometallic complexes.⁴³ Such reactions have been studied⁴⁴ but mostly in the context of P-arylated bisphosphines with varying spacers. ⁴⁵⁻⁵⁰ For cleavage of the simpler butyldiphenylphosphine, we find nearly exclusive dearylation to form butylphenylphosphide. This result seems sensible in terms of the relative stabilities of phenyl vs butyl carbanion salts ($pK_a(R-H) = 43$ and 50 respectively⁵¹), assuming they are formed directly in the cleavage. However, since alkyl-H bond dissociation energies are typically 5-15 kcal/mol lower than aryl-H, if the severed group departed as a radical, diarylphosphide formation might be expected. This latter process may explain the previously reported

selective cleavage of trimethylsilyldiphenylphosphine to form diarylphosphide,²⁶ a result we have confirmed as well.



Scheme 4.2: Reductive cleavage of diarylalkylphosphine to alkylarylphosphide

Scheme 4.2 above summarizes results of cleavage of non-symmetric phosphines. These reactions could be carried out via two sequential dearylation/alkylation cycles in one pot without the need for isolation of the intermediate monoalkylated phosphines. As long as sufficient M-SG was added in the second cycle, no difficulties arose due to the presence of slight excesses of alkyl halide quenchers such as 1-bromobutane and bromocyclohexane. Overall product yields were between 68-89%. This approach did not, however, extend to a third cycle; like their trialkyl congeners, the dialkylaryl phosphines (e.g., Et₂PPh) did not undergo any detectable cleavage reactions with M-SG reagents.



65%

Scheme 4.3: Preparation of DIOP from diarylphosphide solution.

Finally as an illustration of its synthetic utility, this new method was used the chiral to make ligand (Scheme 4.3) DIOP [2.2-dimethyl-4.5bis(diphenylphosphinomethyl)dioxolane]. DIOP is used widely as a ligand for asymmetric versions of hydroformylation.⁵² hydrogenation,⁵³⁻⁶⁰ allylic alkylation,⁶¹ radical addition and polymerization⁶² reactions. This is an attractive ligand as it can be directly accessed from tartaric acid via acetal formation, esterification, reduction with LiAIH₄ and activation by tosylate formation. The final step involves a nucleophilic displacement of OTs by PPh₂. K₂Na alloy has been used for this purpose in synthesis.⁶³⁻⁶⁵ Here we have shown the effectiveness of the more convenient and less hazardous Na₂K-SG(I) reagent for accomplishing the same reaction in comparable yields instead of using K₂Na alloy.

4.3 CONCLUSIONS

To summarize, alkali metals absorbed in silica gel have been shown to be efficient reagents for carrying out the cleavage and derivatization of di-and triarylphosphines. The diaryl and alkyl aryl phosphides that this method cleanly generates are useful as reagents and as building block for modified arylphosphine ligands.

4.4 EXPERIMENTAL SECTION

4.4.1. General Information of estimation and purification of reagents:

Prior to carrying out any C-P cleavage reactions the reducing ability of M-SG (I) was tested by measurement of the hydrogen evolved upon reaction with ethanol in a closed system equipped with a digital pressure gauge. The volume of hydrogen produced was used to calculate the number of equivalents^{*} of alkalimetal(s) in a given reagent. Available reducing equivalents were found to be typically 10-25% less than indicated by the simple mass proportion of metal. Thus, a 1 g sample of 40% w/w Na₂K-SG (I) would typically provide 11-13 mmol of electrons, not the full 14.1 mmol computed from the original reagent's recipe. In the procedures below, the reported numbers of equivalents represent titration-derived values.

Triphenylphosphine was recrystallized from hot ethanol. (D. D. Perrin, W. L. F. Armarego, D. R. Perrin, Purification of Laboratory Chemicals, 2nd ed.; Pergamon: New York, 1980; p 455)

4.4.2.1 Procedure for preparation of mono-functionalized phosphine :

In a 100 mL round-bottom flask equipped with a glass-coated magnetic stir bar and a rubber septum, triphenylphosphine (PPh₃, 526 mg, 2 mmol, 1 equiv.) and Na₂K-SG(I) (871 mg, 40% w/w loading of metal alloy in silica gel, 9.8 mmol, 2.45 equiv* by titration, 3.07 equiv* by mass %) were placed under an inert atmosphere. To this flask 10 mL of anhydrous THF was added and the mixture was stirred at room temperature for 6-8 h, changing from colorless to dark orange. To monitor the reaction's progress, 100 µL aliquots of reaction mixture were diluted with 1 mL THF, quenched with 20 µL of 1-bromobutane, and analyzed by ³¹P NMR. Upon completion, the reaction was guenched with 1-bromobutane (750 µL, 955 mg, 7 mmol, added all at once), which changed the color of the reaction mixture from intense orange to colorless. After stirring for 10 minutes, residual unreacted M-SG was guenched by dropwise addition of water (3-5 mL). After separation, the solids/aqueous layer were extracted via washing with an additional 40 mL (2x20 mL) of toluene. The combined organics were then passed through a celite pad in a sintered glass funnel to afford a clear solution that was concentrated on a rotary evaporator. The product ⁿBuPPh₂ was obtained as a clear oily liquid (374 mg, yield = 77%). The product purity was verified by ¹H, ¹³C, ³¹P NMR and by GC-MS.

*Because a two-electron C-P bond cleavage is this paper's focus, the molar equivalency of the M-SG reactants is reckoned as one-half the total number of

moles of alkali metal therein. Thus, if reaction efficiency were perfect, one equivalent, so termed, would cleave a mole of triaryl phosphine to Ar_2PM and ArM. Similarly, upon reaction with excess ethanol, one equivalent of M-SG corresponds to two moles of metal, and forms one mole of H₂ gas.

4.4.2.2. Procedure for the preparation of di-functionalized phosphine:

In a 100 mL round bottom flask equipped with glass coated magnetic stirrer and rubber septum triphenyl phosphine (524 mg, 2 mmol, 1 equiv.) and Na₂K-SG (I) (1 g, 10.2 mmol, 2.5 equiv) were assembled. To this flask 10 mL of anhydrous THF was added and stirred at room temperature for 8 h. Cyclohexyl bromide (300 µL, 400 mg, 2.45 mmol) in 2 mL THF was added dropwise to the reaction cooled in an ice-bath. The reaction was stirred at room temperature for another 1 h followed by addition of Na₂K-SG (I) (1.1g, 11.3 mmol, 2.6 eq) under inert atmosphere (in a N₂ glove bag). 5 mL additional THF was added and the reaction was stirred for another 6 h, followed by guench with 1-bromobutane (330 µL, 420 mg, 3 mmol). The reaction was stirred for another 30 mins followed by a water quench (~ 3-5 mL). The clear organic layer was extracted in toluene (~ 100 mL) and filtered through a celite pad on a sintered funnel. A clear filtrate was obtained that was dried under N₂ stream. A clear liquid of *n*-butyl cyclohexyl phenyl phosphine (n-BuCyPhP) weighing 440 mg was obtained (89% yield). The product purity was verified by ¹H, ¹³C, ³¹P NMR and by GC-MS (m/z = 248.1).

¹H (δ in ppm): 7.53 (t, 7 Hz, 2H), 7.2-7.0 (m, 3H), 1.8 (d, 10 Hz, 1H), 1.7-1.6 (m, 3H), 1.58-1.48 (m, 5H), 1.32-1.26 (m, 5H), 1.08-1.02 (m, 4H), 0.77 (t, 5 Hz, 3H).

¹³C (δ in ppm): 138.32 (d, 18.5 Hz), 133.83 (d, 19.6 Hz), 128.94, 128.43 (d, 7.1 Hz), 38.34 (d, 10.75 Hz), 30.07 (d, 15.1 Hz), 29.86 (d, 12.6 Hz), 28.92 (d, 15 Hz), 27.28 (d, 10 Hz), 27.16 (d, 10 Hz), 26.7, 25.00 (d, 14.3 Hz), 24.75 (d, 11.9 Hz), 13.95. ³¹P (δ in ppm): -14.7

4.4.2.2. Procedure for the preparation of DIOP :

In a dry box, triphenylphosphine (526 mg, 2.01 mmol) and Na₂K-SG(I) (847 mg, 9.27 mmol, 2.3 equiv.) were combined in a 100 mL round-bottom flask equipped with glass coated magnetic stirrer and rubber septum. To this flask 10 mL freshly distilled anhydrous THF was added via a glass syringe. The reaction was gently stirred overnight (8 h). The stirring was then stopped and a 3 mL portion of the orange diphenylphosphide solution was withdrawn via syringe and put into a separate flask containing a solution of 4,5-bis(tosyloxymethyl)-2,2-dimethyl-1,3-dioxolan (238 mg, 0.5 mmol) in 3 mL THF in a N₂ glove bag. The color of diphenylphosphide was immediately discharged and the solution was filtered through a celite pad in a glass sintered funnel in a glove-bag. The solid was washed with 2x10 mL aliquots of toluene. The combined organics upon solvent removal gave pale yellow oil that was triturated with a 1 mL portion of ice-cold methanol to yield a white solid that was filtered and dried. The dried

residue weighed 161.5 mg (65%). (Procedure adapted from Murrer, B. A.; Brown, J. M.; Chaloner, P. A.; Nicholson, P. N.; Parker, D. *Synthesis*, 1979, 350).

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CHAPTER 5

REDUCTIVE AMINE DEALLYL- AND DEBENZYLATION WITH ALKALI METAL IN SILICA GEL (M-SG)

5.1 BACKGROUND:

Cleavage of the C-N bond is important in functional group interconversions and in deprotection reactions such as deallylation and debenzylation.^{1,2} Reductive methods using metal ammonia solutions,^{3,4} Pdreagents,⁵⁻⁹ low valent Ti,¹⁰ or Ni-based reagents^{11,12} have conventionally been used for these transformations.¹³ Mild oxidative methods, such as the aziridine debenzhydrylation with O₃ followed by excess NaBH₄¹⁴ and the recently reported debenzhydrylation of azetidinone with NBS and catalytic Br₂ in the presence of light¹⁵ offer useful strained ring deprotections. A particularly selective example is the amine N-debenzylation with diisopropyl azodicarboxylate (DIAD)^{16,17} in a sugar also protected with O-benzyl and N-tosyl groups. Though much more common for alcohols, amine detritylation under acidic condition is known.¹⁸ Grubbs's catalyst¹⁹ and other Ru and Rh(III) based reagents²⁰⁻²² have proven useful for efficient deallylation of amines. However, these agents initiate reaction by isomerization of the double bond^{23,24} which can be problematic for certain substrates.²⁵ Thiol-mediated radical cleavage of allylic amines have been used to deprotect secondary amines.^{26,27}

The above deprotections represent elegant and selective tools for organic synthesis. However, a single reagent able to generally cleave N-allylic and -benzylic amines would enhance the toolbox. For example, sodium in ammonia was used in the final step for global deprotection in the total synthesis of an oligosaccharide natural product.²⁸ Similarly, Li in isoprene was shown to be capable of cleaving a variety of protecting groups bound to imidazole.²⁹

5.2 RESULTS AND DISCUSSIONS:

Alkali metals absorbed in porous silica gel (or the M-SG reagents) are free flowing dry powders that are free of contamination by oily hydrocarbons and are non-pyrophoric upon brief exposure to dry air.³⁰⁻³² Our interest in exploring the usefulness of these materials in amine deprotections such as amine desulfonations³³ prompted us to investigate reductive C-N cleavages in the context of deallylation, debenzylation, debenzyhydrylation, and detritylation. Although the focus of this section is on deallylation (Scheme 5.1), a few examples of the other deprotections are also described herein.³⁴



Scheme 5.1. Deallylation of allyl protected amines

Several allyl amine substrates were cleaved by treatment with Na₂K-SG (I) at ambient temperature in ethereal (e.g., THF and 1,2-DME) solution under an inert atmosphere. These experiments are summarized in Table 6.1. A substoichiometric amount (20 mol%) of ethylenediamine (EDA) was found to be necessary to activate reaction of the aliphatic substrates, which were then cleanly deprotected over 16-24 h. Examples include N-allylpiperazine (Entry 1), N-allylhexamethyldisilazane (Entry 2), N-allylpiperidine (Entry 3), and a hindered substrate, N-allyl-dicyclohexylamine (Entry 4). Aromatic substrates (Entry 5, 6, 7) reacted relatively faster, affording the corresponding amines in 8-10 h without the need of EDA. Over-reduction of the aromatic rings was not observed in these cases.


 Table 5.1: Deallylation of tertiary amines:

^aIsolated yield, ^bIsolated as HCI salt, ^cConversion by NMR, ^dPerformed in 1,2-Dimethoxyethane (DME), ^eYield with Na-SG, ^f5 equiv. of metal was used in this case.

The expected propene byproduct of deallylation was observed by analysis of the gas phase via GC-MS. No 1,5-hexadiene, the allyl radical homodimerization product, was seen in the reaction mixture. This finding suggests that an allyl metal intermediate likely formed during the cleavage reaction. However, attempts to trap the allyl metal reagent with electrophiles such as benzophenone at -78 °C did not give any substantial nucleophilic adduct. Apparently, the allylmetal species, if formed, does not survive for long in ethereal solvent. Alkyllithiums in the presence of lithium alkoxide can readily abstract protons from ethereal solvent above -60 °C.³⁵ In a similar way, in the presence of dialkylamide salts, allyl metal species could be highly aggressive in proton abstraction reactions with ethereal solvents (typical procedures for preparation of allylsodium is carried out in hydrocarbon solvents). In the case of N-allylbenzotriazole, besides the intended allyl group removal, loss of N₂ was observed, yielding aniline. Secondary N-allyl-amines, such as N-allyl-cyclohexyl amine, also encountered difficulties in these deprotections. Although some cyclohexylamine product was observable, a complex mixture of other products was obtained.



Table 5.2: Other amine deprotections

^aIsolated yield, ^bIsolated as HCI salts, ^cConversion by GC, ^d1,2-DME was used as solvent

Exploratory work on reductive cleavages of other related protecting groups of amines are summarized in Table 5.2 above. Effective removal of benzyl (Entry 1, 2), benzhydryl (Entry 3) and trityl (Entry 4, 5) groups were demonstrated. For debenzylations (Entry 1, 2), the expected toluene byproduct was detected, while debenzhydrylation and detritylation gave the corresponding diphenylmethane and triphenylmethane products. It is noteworthy that the debenzylation of the aliphatic amine piperidine (Entry 2) proceeded to completion without the need for activation by ethylene diamine. From a brief exploration in oxygen deprotection we also found that benzyl nopyl ether (Entry 6) cleanly yielded the bicyclic alcohol nopol in less than 3 h. A more detailed study on debenzylation reactions is underway and will be reported elsewhere.



Scheme 5.2. One pot reduction and debenzhydrylation of benzophenone hydrazone

An additional extension of this deprotection method was the successful one-pot reduction/deprotection of benzophenone hydrazone (Scheme 5.2), enabling reduction to amine via N-N bond cleavage, or full reduction to the diphenylmethane. In the reaction above, the use of 2.5 equivalents of metal yielded benzhydryl amine as the predominant product

(NMR detection). However, with 5 equivalents of metal, diphenylmethane was the major product.

5.3 CONCLUSIONS:

To summarize, alkali metals in silica gel (M-SG) are capable of reductive cleavage of the C-N bonds in tertiary allyl, benzyl, benzhydryl and trityl amines. The simplicity of the reaction, ease of work-up and isolation, low cost of the reagent precursors, and low toxicity make this method a useful addition to chemists' toolbox.

5.4 EXPERIMENTAL SECTION

5.4.1. General Information of estimation and purification of reagents:

Prior to carrying out any C-N cleavage reaction the reducing ability of M-SG (I) was tested by measurement of the hydrogen evolved upon reaction with ethanol in a closed system equipped with a digital pressure gauge. The volume of hydrogen produced was used to calculate the number of equivalents^{*} of alkalimetal(s) in a given reagent. Available reducing equivalents were found to be typically 10-25% less than indicated by the simple mass proportion of metal. Thus, a 1 g sample of 40% w/w Na₂K-SG (I) would typically provide 11-13 mmol of electrons, not the full 14.1 mmol computed from the original reagent's recipe. In the procedures below, the reported numbers of equivalents represent titration-derived values.

5.4.2. Procedure for deallylation of tertiary allyl amine :

In a 100 mL round-bottom flask equipped with a glass-coated magnetic stir bar and a rubber septum, N-allyl-3,5-dimethylpyrazole (92 μ L, 136 mg, 1 mmol, 1 equiv.) and Na₂K-SG(I) (400 mg, 40% w/w loading of metal alloy in silica gel, 4.96 mmol, 2.48 equiv* by titration) were placed under an inert atmosphere. To this flask 10 mL of anhydrous THF was added and the mixture was stirred at room temperature for 8-10 h. The reaction was monitored by tlc to ensure complete conversion. The reaction mixture was then quenched by addition of ~2

mL water. The organic layer was washed with additional 2×10 mL of ether and the combined organics was dried over Na₂SO₄, filtered and concentrated on a rotary evaporator. The product 3,5-dimethylpyrazole was isolated as solid. (86 mg, yield = 91%). The product purity was verified by ¹H and ¹³C NMR.

For aliphatic allylamine such as N-allyl-N,N-dicyclohexylamine 20 mol% (15 μ L of EDA per mmol of allylamine substrate) was added to the reaction after adding solvent and the reaction was carried out in the identical way.

*Because a two-electron C-N bond cleavage is this chapter's focus, the molar equivalency of the M-SG reactants is reckoned as one-half the total number of moles of alkali metal therein. Thus, if reaction efficiency were perfect, one equivalent, so termed, would cleave a mole of tertiary allylamine to R_2NM and AllylM. Similarly, upon reaction with excess ethanol, one equivalent of M-SG corresponds to two moles of metal, and forms one mole of H₂ gas.

5.4.2. Procedure for other deprotections:

Identical procedure to the above (5.4.1) was adapted in these cases without the need of EDA.

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CHAPTER 6

BIRCH REDUCTIONS AT ROOM TEMPERATURE WITH ALKALI METALS IN SILICA GEL (Na₂K-SG(I))

6.1 BACKGROUND

Conventional Birch reductions¹⁻³ of aromatic compounds are performed with alkali metals in liquid ammonia (the so-called dissolving metal conditions) in the presence of alcohols at or below the –33 °C reflux temperature of liquid ammonia. The reaction outcome can be tuned by varying temperatures, metals,⁴⁻⁶ additives, proton sources or quenching agents. The Birch reductions are often combined with other reactions in tandem sequences.⁷⁻¹⁴ A cathodic Birch reduction has been reported for a limited class of substrates.¹⁵ The hydroxide ion has been used as an electron source for the photochemical Birch reduction of a naphthalene derivative.¹⁶ Birch reduction variants also include reactions in THF with gaseous ammonia as a solvent component and the reaction atmosphere.¹⁷

The class of substrates described herein can also be reduced by transition metal-^{18,19} or lanthanide²⁰ salt- mediated hydrogenation reaction conditions by which complementary selectivities may be achieved.²¹ Toxicities of transition metals²² and low temperature requirements of conventional Birch reductions remain areas of concern for future process development research and scale up.²³ Additionally, alkali metal-arenide salts can form stable

complexes with ammonia, which can later cause violent reactions during quenching.²⁴

Alkali metals in silica gel^{25,26} have been developed as dry, free-flowing, powdered reagents.^{27,28} The usefulness of these reagents in replacing dissolved metal conditions has been illustrated in the context of several reductive cleavage reactions.²⁹⁻³¹ These reagents are also found to be effective in reduction of functionalized aromatic compounds and esters.³²

6.2 RESULTS AND DISCUSSIONS

Herein we report³³ the applications of the Na₂K-SG(I) reagent in reductions of polyaromatic hydrocarbons and conjugated aromatic systems. In addition to conventional stirred-batch mode reaction conditions, we report here on the feasibility of Na₂K-SG (I) reagent's use in flow reactor settings.

Table 6.1. Birch Reductions using Na₂K-SG (I)



Table 6.1 continued:



^aR=n-butyl, ^bReaction carried out in presence of HMDS (Hexamethyldisilazane), ^cConversion by 1H NMR, ^dConversion by GC-MS (done with 2.5 equiv Na-SG), others are isolated yields

Table 6.1 shows representative examples of Birch reductions performed with Na₂K-SG(I) reagent. Some of the products (e.g. dialkylated phenazines³⁴) are attractive for photochromic and electrochromic applications.³⁵ Reduced acridine derivatives are important cores of therapeutic agents that target the central nervous system.³⁶

Entries 1-3 show reduction of anthracene and its alkyl and aryl substituted derivatives. In these cases no other byproducts were observed. This finding, verified by deuterium oxide (D₂O) quenching, suggests formation

of dianion salt intermediates, consistent with similar reports³⁷ with Li. For entry 3 the ratio of cis:trans isomers was 1:2.

Entries 4-6 show reduction of N-heterocycles, i.e., reduction of acridine, phenazine and guinoline respectively. Unlike guinoline, the reduction of naphthalene was relatively sluggish and gave only 1,4-dihydronaphthalene as product (determined by GC-MS) with 3 equivalents of Na₂K-SG(I). Phenazine (Entry 5) was isolated as the dialkylated product to provide increased stability and ease of handling. Entry 7 shows reduction of phenanthrene. Alkenes and alkynes conjugated to aromatic rings were shown to undergo reduction (Entries 8, 9) without any detectable reduction of aromatic rings. Presumably, these reactions occur via dianion salts as has been previously reported for stilbene and related olefins with sodium.³⁸ Interestingly, in the absence of a proton source, diphenyl acetylene underwent dimerization and cyclotrimerization to give a mixture of 1,2,3,4-tetraphenyl butadiene (major) and hexaphenylbenzene (minor). Entry 10 shows dehalogenation-Birch reduction done in tandem. Entry 11 shows the reduction of indene. Additional information about the functional group compatibility of these reagents under essentially identical reaction conditions has been reported in previous publications.²⁹⁻³²

When applied to biphenyl and related polyaromatic hydrocarbons such as pyrene and acenaphthene, the Na₂K-SG(I) reduction gave mixtures despite the clear generation of the arenides' colors. The mixtures can be understood in terms of the distribution of negative charges among various positions in the dianions.³⁹ Not surprisingly, more electron rich rings such as xylene and

mesitylene did not undergo any detectable reduction. With 3,3'-dimethoxy biphenyl, in addition to the desired Birch reduction, cleavage of Me–OAr and MeO–Ar bonds was seen.

Some of the reactions above (Entries 1 and 7) were carried out in small Pasteur pipette columns. In this method, a solution of the desired substrate in THF was passed through the column (containing a total of 7.5 metal equivalents) under an inert atmosphere. The collection flask contained enough water to quench the ether solutions of dianions (e.g., dianion of anthracene) generated in the column.

Entries 1, 7, 8, 9 were shown to be feasible with solid acids such as NH_4CI and HCO_2NH_4 as in situ proton sources. However, when t-BuOH was used as a homogeneous proton source the reaction, assembled with 2.5 equivalents of metal, did not go to completion. When the number of reducing equivalents was increased to 5, over-reduction of the product appeared along with the desired target compound.

We have found that if the Na₂K-SG(I) reagent is handled quickly in lab air (~40 sec), reactions give essentially the same results for anthracene reduction as those obtained with Na₂K-SG(I) handled in a drybox. However, exposing the Na₂K-SG(I) in lab air for 30 minutes caused a loss of reducing power to the extent of 45% (from 40% to 22%). These results are variable as a function of humidity levels. Therefore we recommend that the end user exercise standard precautions by handling this reagent like other air sensitive materials such as LiAlH₄, NaH, and Cu(I)CI (e.g. storing in drybox or N₂ glovebag or in

vacuum dessicator) or correct for the loss of reactivity by adding an excess of the reagent during use. These reductions can be also carried out with Na- $SG(I)^{40}$ and K₂Na-SG(I).

The procedure described here shows promise for development of flow reactors that could rapidly generate a solution of alkali metal carbanion species for reduction or other uses. Tandem reduction-alkylation (cf. entry 5, Table 1) and reduction-dehalogenation (entry 10) have also been shown to be feasible with the Na₂K-SG(I) reagent.

6.3 CONCLUSIONS

In summary, as an alternative to classical liquid ammonia conditions, we have provided a simple and convenient method for carrying out room temperature Birch reductions of a series of polynuclear aromatic substrates in THF in the absence of co-reagents.

6.4 EXPERIMENTAL SECTION

6.4.1. General Procedure for M-SG Birch reductions:

In a 100 mL round-bottom flask equipped with a glass-coated magnetic stir bar and a rubber septum, anthracene (178 mg, 1 mmol, 1equiv.) and Na₂K-SG(I) (420 mg, 40% w/w loading of metal alloy in silica gel, 4.9 mmol, 2.45 equiv) were placed under an inert atmosphere (in a He dry-box). To this flask 10 mL of anhydrous THF was added and stirred at room temperature for 6-8 h. The reaction color changed from colorless to dark blue. After this time the reaction mixture is guenched with water (2 mL). It was added all at once and the color of the reaction mixture changed from intense blue to colorless and the reaction was allowed to stir for 10 minutes. The organic layer was decanted and the solid residues were washed with additional 3×10 mL Et₂O. After separation, the combined organics were passed through a celite pad on a sintered glass funnel to afford a clear solution that was concentrated on a rotary evaporator. The product 9,10-dihydroanthracene was obtained as a white solid (160-173 mg, yield = 88-97%). The product purity was verified by 1 H, 13 C NMR and by GC-MS (m/z = 180).

¹H NMR (δ ppm): 7.29 (m, 2H), 7.19 (m, 2H), 3.93 (s, 2H)

¹³C NMR (δ ppm): 136.5, 127.3, 126, 36.

6.4.2. Procedure for the in-situ reduction :

In a 100 mL round bottom flask equipped with glass coated magnetic stirrer and rubber septum diphenyl acetylene (178 mg, 1 mmol, 1 equiv.) and Na₂K-SG(I) (2 g, 20.4 mmol,0.5 equiv) was assembled. To this flask 2 mL HMDS and 10 mL of anhydrous THF was added and stirred at room temperature for 8 h. Reaction progress was monitored by tlc. The reaction was stopped by a water quench (~ 1-2 mL). The clear organic layer was decanted and the solid residues were washed with additional 2×10 mL ether and filtered through a celite pad on a sintered funnel. A clear filtrate was obtained that was dried under N₂ stream. Bibenzyl was obtained as solid product (~165 mg, 90%). The product purity was verified by ¹H, ¹³C NMR.

6.4.3. Procedure for the reduction in column:

In a Pasteur pipette glasswool was plugged and then packed with 1g of Na_2K -SG(I) (11.3 mmol, 7.5 equiv.). The column was capped with a septum on both ends. In a vial containing a 5 mL solution of anthracene (132 mg, 0.75 mmol, 1 equiv) in THF was prepared and was injected through this column via a syringe. The solution of anthracene was allowed to flow under gravity and a deep blue color from the generation of anthracenide anion was observed. The eluted

solution was collected in a round bottom flask containing 1 mL of water as a quenching agent.

After the passage of anthracenide anion the column was eluted with THF

(2 mL) to wash off any residual product. The eluted organics were dried on Na_2SO_4 . Upon removal of the solvent by rotary evaporator, 9,10-dihydroanthracene was obtained as white solid (108 mg, 80%).

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APPENDIX

PREPARATION, ASSAYS AND HANDLING OF M-SG REAGENTS

A.1 PREPARATION

A.1.1 Calcination of Silica-Gel

(1) 100 g silica gel (SG) (Davisil 646 from Grace) is placed in a porcelain tray and heated at 200-250 °C for 4-6 h.

(2) The temperature of the furnace (Thermolyne 114300) after the above period was raised to 600 °C and left at this temperature overnight (12-16 h)

(3) After the heating is turned off the SG is covered with aluminum foil while it is cooling down to minimize re-absorption of moisture. The SG is next transferred into the He dry-box (VAC model M040-1).

3.1.2 General Preparation of M-SG (0)

(1) Freshly cut 46 g (2 moles) of Na and 39 g (1 mole) of K is assembled in a flask inside the dry-box. The solid mixture started to gradually turn into liquid alloy at the points of contact of Na and K pieces. With gentle swirling the formation of liquid alloy is driven to completion.

(2) Any small amount of oxide that was present on the solid Na or K pieces starts to appear on the liquid surface and is removed by carefully soaking it into a Kimwipe held with a pair of forceps.

(3) 60 g of calcined SG is weighed out and spread in a stainless-steel tray inside the dry-box. To this tray the Na₂K alloy (~3-5g) is added with a Pasteur pipette as small droplets. The droplets initially sit on the SG and then gradually start to soak into the SG, turning it silvery. Upon thorough mixing it becomes shiny black. These steps are repeated a few times with the rate of absorption increasing as the process goes on. Though black in appearance, this material still carries metal alloy on the surface and is pyrophoric when poured in air.

The above method is also used for preparation of K₂Na-SG (0).

Caution: If the liquid Na₂K or K_2 Na alloy is added all at once instead of drop wise followed by pauses to allow uniform mixing with a spatula, a localized and highly exothermic runaway reaction occurs which depletes the net reactivity of the material.

A.1.3 Preparation of M-SG (I)

A.1.3.1 Na-SG(I)

(1) Sodium rods are peeled inside a He dry-box with a potato peeler to get rid of any sodium oxide surface coating. This leaves shiny metallic pieces.

(2) Inside the dry-box, a 40 g chunk of the fresh sodium is cut into small pieces (10-15), placed together with 60 g of calcined silica gel in a rotary steel Parr reactor (Parr Instruments Company, model 452 HC, Item T-316033004 29118) and sealed with a TEFLON or graphite gasket.

(3) The steel reactor is taken out of the dry-box and tumbled in a furnace (Cenco Instruments Co., model 95052-16) set at 100 °C for 3-4 h.

(4) The furnace is heated to 165 °C and tumbled overnight (12-16 h). The heat is then turned off and the reactor is allowed to cool in room temperature air for 1 h. After it is transferred into the dry-box and opened, the reactor yields 100 g of black free-flowing granular Na-SG (I).

A.1.3.2 Na₂K-SG (I)

(1) Inside the He dry-box, 100 g of Na₂K-SG (0) is placed in a steel Parr reactor and sealed.

(2) The steel reactor is brought out from the dry box, placed in a furnace (Cenco Instruments Co., model 95052-16) and tumbled initially at 100 °C for 3-4 h followed by heating at 120 °C overnight (12-16 h). Return to the dry box and

opening results in recovery of a black free-flowing powder (the shiny appearance of M-SG (0) is now gone), that is non pyrophoric when poured in dry air.

The preparation procedure for $K_2Na-SG(I)$ is identical to that of $Na_2K-SG(0)$, except for the amounts of Na and K used.

Stage IIA (100-165 °C for 12 h), IIB (~ 300 °C for 24 h) or IIC (~ 400 °C for 24 h) can be made by heating M-SG (I) samples to higher temperatures.

A.2 ASSAYS

A.2.1 H₂ evolution

(1) In a He dry-box, ~300 mg of Na-SG (I) is placed in a dry 50 mL round bottom flask equipped with a greased vacuum stopper and pumped down in a rough pump.

(2) This flask is taken out of the box, hooked up to a vacuum line, and pumped down to $\sim 10^{-4}$ torr. The vacuum line is connected to another flask containing freeze-pump-thawed EtOH (~30-35 mL).

(3) The flask containing M-SG (I) is chilled in a liquid N_2 Dewar flask.

(4) EtOH (~ 2-4 mL) is distilled onto the M-SG (I) via cold distillation for 3-5 minutes. The flask containing the M-SG + EtOH and the flask having outgassed EtOH are closed.

(5) The M-SG + EtOH flask is allowed to warm up to room temperature and equilibrate for ~2 h, enabling the reaction of EtOH with Na-SG. The pressure of the resulting H₂ gas in the known volume of the vacuum system is measured via a digital pressure gauge (Cecomp electronics, model no. ARM760B-5) and the temperature is simultaneously noted. The flask is then chilled again in liquid N₂ followed by pumping off of the H₂ produced.

(6) The M-SG + EtOH flask is again allowed to warm up to room temperature and the vapor pressure of the mixture is noted. This is usually close to the vapor pressure of pure ethanol (38 torr at 298 K).

(7) This flask is chilled in liquid N₂ bath and ~ 1 mL H₂O (freeze-pump-thawed through at least 2 cycles in a separate flask) is distilled onto the EtOH + M-SG (I) mixture for 3 minutes. The flasks are closed and again allowed to warm up to room temperature. The reaction flask is allowed to stand for 30 minutes.

(8) As in steps (5)-(6), the pressure reading of the mixture and H_2 was recorded. The flask is chilled in liquid N_2 bath, followed by pumping off any H_2 that is produced.

(9) The reaction flask is warmed up to room temperature again and the vapor pressure of the mixture is recorded.

From the pre-determined total volume of the system, the pressure of H₂ (vapor pressure corrected) and the temperature, the molar quantity of H₂ made in each step is determined. From this the total amount of reducing power is computed. The amount of H₂ made in the 1st (EtOH) and 2nd (H₂O) quenching steps corresponds to the respective amount of M-SG (I) and M-SG (II) present in a sample. For organic reductions, it is desirable to maximize the relative proportion of stage I material.

A.2.2 Differential Scanning Calorimetry (DSC):

DSC (instrument model Q200 made by TA instruments) of M-SG samples ran in hermetic (sample sealed inside the drybox) aluminum pan shows the approximate amounts of metal or alloy inside the pore vs bulk metal outside. In

Figure A.1 below the melting endotherm of sodium in the pore appears ~ 80 °C instead of 97.7 °C for the bulk sodium. Figure A.1 shows that the melting endotherm of sodium slowly decreases with time from 8.25 J/g (22.46 min) to 6.77 J/g (345.24 min), indicative of consumption of metal and possibly leading to the formation of stage IIA.



Figure A.1. DSC showing melting endotherm of Na-SG(I) (made by heating at 120 °C for 14 h) 20% (w/w) with time at 150 °C

A.2.3 Reaction with Biphenyl:

The formation of biphenylide salt from biphenyl and M-SG (0) (\sim 50 mg) happens in dry (dried under benzophenone, sodium still) THF (at \sim 0.1 M concentration) and at room temperature almost instantaneously, while with M-SG

(I) (~50 mg), it takes more time (~ 5 min). The stage II M-SG does not react with biphenyl.

A.2.4 Titration with standardized HCI solution:

Titration using phenolphthalein indicator with standardized HCI solution allows quantitation of the total amount of metal present in the water-quenched M-SG sample. The difference between the above H₂ evolution measurements and the overall metal titration provides a measure of the amount of reducing capacity lost during preparation and handling.

A.3 PASSIVATION WITH DRY AIR OR DRY OXYGEN:

Stage I M-SG reagents (Na-SG and Na₂K-SG) can be *slowly* exposed (by inter-diffusion with helium or nitrogen or by passage of dry air through a column) to dry air or to dry oxygen with little loss of reactivity or reducing power. We believe that this passivation occurs by formation of metal oxide or peroxide at the entry channels of the big pores that are filled with metal in the zero-valent state. These reactive bound oxygen species (could be a peroxide) upon reheating in a DSC pan shows a exothermic shoulder between 100-160 °C (Figure A.3) that was not present in the freshly made sample (Figure A.3). Presumably, due to a large ratio of the amount of metal in the pores to that of exposed metal on the surface, this results in an insignificant loss of reducing capacity and blocks entry of oxygen to access the metal in the pores. In water, alcohol or organic solvents these metal oxide barriers could be dissolved and the reducing power of the metals in the pores can be harnessed. This passivation is not achieved when an evacuated flask containing M-SG (I) is rapidly exposed to dry O₂ or air. In this case a sudden thermal run-away reaction occurs that converts most of the Stage I M-SG to stage II along with the formation of metal oxide. The resulting material is almost completely inert in its reaction with alcohols. But this material still reacts with water and gives off H₂ and the total reducing capacity is almost fully retained from the original sample that was not passivated under air.



Figure A.2. DSC of a freshly prepared Na₂K-SG (I) sample (dashed line) vs DSC of same sample after exposure to dry oxygen (solid line)

A.3.1 Procedure for taming M-SG (Na₂K-SG-0, Na₂K-SG-I or Na-SG-I):

- Inside a He glove box, 2-5 g of Na-SG is placed In a 50 mL round bottom flask. This flask, closed with a vacuum stopper, is brought out and hooked up in a vacuum line equipped with a digital pressure gauge.
- Air (mostly oxygen, moisture and argon) is allowed to condense in an open condenser trap in a Dewar flask filled with liquid N₂.
- 3) The trap is opened briefly to the vacuum line such that the pressure inside the vacuum system goes up from 0 torr to 500 torr.
- 4) The M-SG flask under He (the atmosphere it had from the glovebox) is now opened and allowed to equilibrate with the dry oxygen gas in the line for five minutes with gradual swirling of the M-SG flask.
- The M-SG flask and entire vacuum line is now partially pumped down from 530 torr to ~ 50 torr.
- 6) Fresh O₂ mixture is again admitted slowly so that the pressure inside rises again to 500–600 torr of an atmosphere more enriched in O₂. Step 3, 4 and 5 are repeated and the whole cycle is repeated another 2-3 times before completely evacuating the flask and returning the sample into the He dry-box again for further analysis.

In multiple passivation or taming runs it was observed that the net reducing power of the M-SG (measured by hydrogen evolution with ethanol) remained essentially identical before and after passivation. This
strategy of taming gave best results with Na-SG and Na₂K-SG; K₂Na-SG (I) was found to be more reactive (exothermic) to oxygen and a loss of \sim 20% of the reducing capacity was observed.

Exposures of tamed and untamed samples to ordinary lab air resulted in similar losses of reducing capacities for all samples. While exposure for ~5 minutes resulted in ca. 20% loss of reducing capacity, nearly ~50% was lost after a 30 minute exposure. As expected, these rates are sensitive to the air's relative humidity and the degree of annealing in a given sample (as judged by the DSC).

In light of their degradation by ambient moisture, end users of these reagents are recommended to use a N_2 bag or an Ar blanket and mass samples in closed vials by difference for best results. Users not having access to nitrogen or argon can briefly handle the reagent in lab air and use an excess amount of the reagent to compensate for moisture-induced loss of reducing capacity.

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