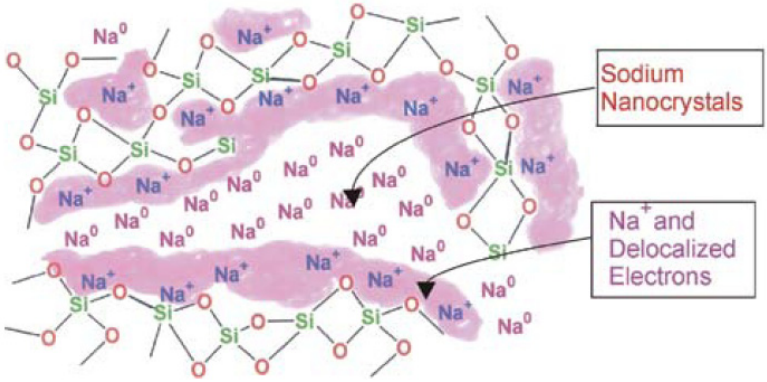
Encapsulated, Stabilized Alkali Metals for Birch Reductions and Other Dissolving Metal Reductions

Sold in collaboration with SiGNa

metals · inorganics · organometallics · catalysts · ligands · custom synthesis · cGMP facilities · nanomaterials

11-1005	**Sodium-silica gel, 35-40% alkali metal in silica gel (Stage I)**	5g
HAZ	black pwdr.; 35-60 mesh	25g
	moisture sensitive	100g
11-1020	**Sodium potassium (K_2Na)-silica gel, 35-40% alkali metal in silica gel (Stage I)**	5g
HAZ	black pwdr., 35-60 mesh	25g
	moisture sensitive	100g

SiGNa Chemistry has developed a technology for encapsulating alkali metals into nano-structured porous oxides, such as silica gel and alumina. Encapsulation reduces the dangers associated with the handling of alkali metals while retaining the reducing power of the metal. Sodium and sodium-potassium alloys in silica gel (Na-SG, Na_2K-SG, and K_2Na-SG) are free-flowing, non-pyrophoric solids that are easy to handle in the lab, pilot plant, and commercial manufacturing facility. They are typically produced with loadings of up to 40 wt. % alkali metal. The powders can be utilized in batch and continuous processes at ambient temperatures and pressures and do not require the use of liquid ammonia. The by-products and waste-streams associated with these materials are non-toxic and environmentally safe (sodium silicate). A number of synthetic applications have been found for alkali metals in silica gel, validating their use in safer, sustainable syntheses.[1]

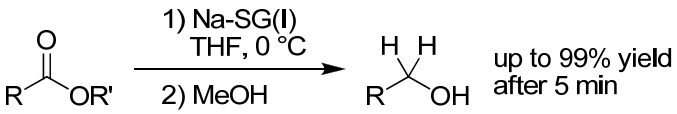


- non-pyrophoric solids
- free flowing
- easy to use

Example #1: Ester Reduction Using Stabilized Alkali Metals

SiGNa has developed an improved procedure for ester reduction using Na-SG(I) in place of lump sodium or sodium sand (as in the Bouvault-Blanc reaction) to reduce a variety of aliphatic ester substrates (Scheme 1).[2,8]

Scheme 1



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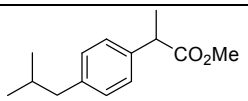
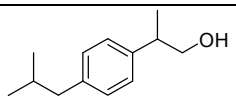
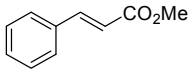
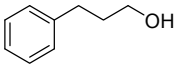
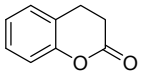
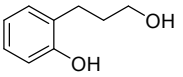
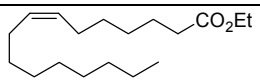
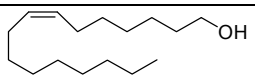
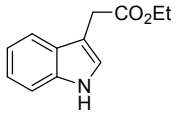
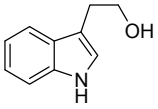
Before the advent of widely available hydride reagents, reduction of esters to primary alcohols was generally performed with alkali metals in ethanol -- Bouveault-Blanc reduction. Because of the hazards associated with alkali metal handling and the vigorous reaction conditions, this procedure has become much less useful. Classic procedures for ester reduction using sodium metal involve rapid mixing of the ester, sodium metal, and alcoholic solvent at elevated temperatures, which can cause excessive foaming and even fires.

In a typical procedure, the ester is added to a slurry of Na-SG(I) in THF at 0 °C, followed by the slow addition of methanol. Within minutes after the addition of methanol, the reaction is complete and high yields of primary alcohols are obtained after an aqueous workup (Table 1).

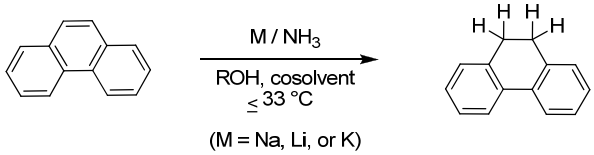
Table 1

Starting Material	Product	Yield
		96%
		95%
		92%
		99%
		95%

#2: Birch Reductions Using Stabilized Alkali Metals

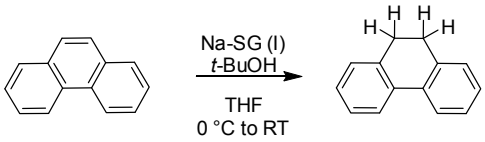
The Birch reduction[3] is an alternative to hydrogenation that yields cyclohexadienes. It has the potential for widespread use in the synthesis of drugs and complex natural products.

Scheme 2



SiGNa has developed a safer and more convenient modification of the classic Birch reduction that avoids the use of liquid ammonia and cryogenic temperatures. This modification utilizes Stage I sodium in silica gel, Na-SG(I), a safer form of metallic sodium than either lump sodium or sodium sand. SiGNa materials can be weighed out in open air without loss of reactivity and allows for a safer quench and post-reaction work up procedure (Scheme 3).

Scheme 3



In a typical procedure, phenanthrene and Na-SG(I) are charged into a reactor and stirred under an inert atmosphere. THF is added, and the slurry is cooled to 0 °C. The proton source, *tert*-butanol, is added in one portion and the reaction is allowed to warm to room temperature. The desired product is isolated in 60% yield after an aqueous work-up.

This method has been used to produce a variety of structurally diverse Birch products as shown in Table 2.[4,5]

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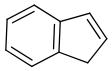
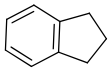
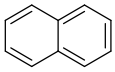
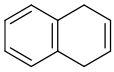
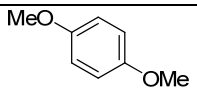
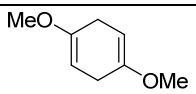
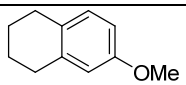
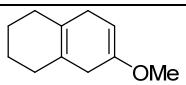
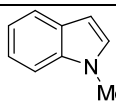
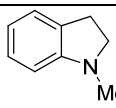
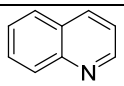
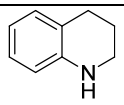
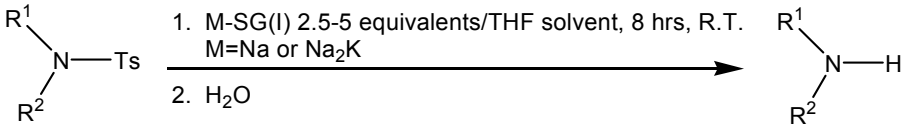
Table 2

Starting Material	Product	Yield
		89%
		87%
		68%
		85%
		94%
		91%

Example #3: Cleavage of Toluenesulfonamides Using Stabilized Alkali Metals

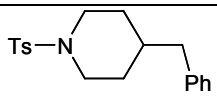
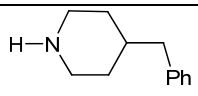
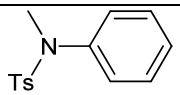
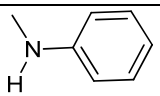
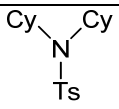
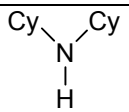
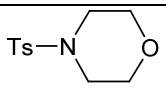
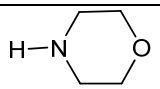
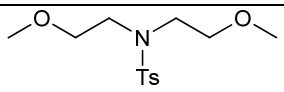
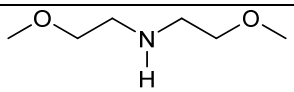
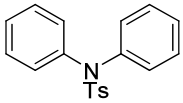
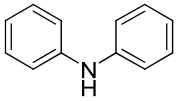
SiGNa also has reported a novel method to cleave toluenesulfonamides to amines using stabilized alkali metals (Scheme 4).[7]

Scheme 4



Treatment with M-SG is a mild and general solution process to desulfonate protected amines. Various sulfonamide substrates were investigated. Detosylation with Na_2K-SG(I) tolerates phenyl and ether moieties and is successful for both cyclic and acyclic amines (Table 3).

Table 3

Starting Material	Product	Yield
		96%
		81%
		83%
		79%
		85%
		99%

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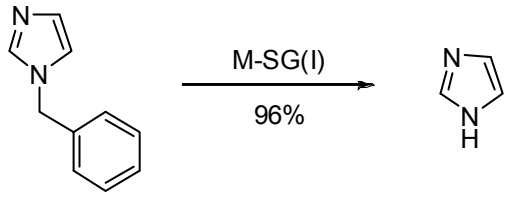
Example #4: Other deprotections such as debenzylations and de-allyations

The removal of residual heavy metals from the product of a chemical process is a major issue, especially in active pharmaceutical ingredients (APIs). Many industry professionals prefer not to use heavy metals at any step of the process to prepare an API. Procedures have been developed to remove benzyl groups, benzhydril groups, sulfonamide groups, allyl groups, trityl groups and other protecting groups from amines and alcohols without the use of heavy metal. A process that uses Na-SG(I) for deprotection, avoids the introduction of palladium and other heavy metals.[6]

Scheme 5



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8. Bodnar, B.S.; Vogt, P.F. *J. Org. Chem.*, **2009**, *74*, 2598-2600.

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