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Editor-in-Chief
Leo A. Paquette

Volume 7

Sod - Trim

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The Ohio State University, Columbus, OH, USA

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Preface

The extent to which organic synthetic methodology has developed and flourished during the past several decades has placed unusually heavy demands on the broad range of scientists who utilize chemical reagents. There exists the vital need to know which reagent will perform a specific transformation. Since a number of reagents are often amenable to similar objectives, a researcher's ability to access readily a comparative summary of those features that distinguish one reagent from another can result in a considerable economy of time. The purpose of the *Encyclopedia of Reagents for Organic Synthesis* is to incorporate into a single work a genuinely authoritative and systematic description of the utility of all reagents used in organic chemistry. Its comprehensiveness is further served by an unrivaled ease to locate any specific entry or topic.

These objectives have been met by inviting practicing chemists from throughout the world to provide specific contributions in their area of expertise. Furthermore, the masthead for each of the 3000 reagents provides valuable information concerning physical data, solubility, form supplied in, purification, and, where relevant, preparative methods. The CAS registry number, handling/storing information, and precautions will further serve potential users. The first literature reference in each entry provides reviews, if available, dealing with the subject reagent. The critical coverage of all relevant literature is extensive.

The goal of the *Encyclopedia of Reagents for Organic Synthesis* is to serve as a reference work where the retrievability of useful information concerning any specific reagent is made facile. For this reason there is a detailed subject index and, in addition, a formula index of all the reagents, and also two further indexes that list the reagents by structural class and by function.

In any undertaking of this type, it is important that the term 'reagent' be clearly defined. The guideline that has dominated the thinking of the members of the Editorial Board is that a reagent be an agent or a combination of agents which with some generality effects the transformation of a substrate into a product. In addition, many useful building blocks have been included. As a consequence, we anticipate that a work has been produced that will serve biochemists, material scientists, pharmacologists, and chemical engineers, in addition to chemists from all disciplines, in that manner most conducive to accelerating progress in their respective fields of research.

The entries highlight the various uses characteristic of each reagent, with specific examples illustrative of these chemical reactions. The contributions are organized alphabetically and the cross-referencing to other reagents is liberal. Thus, a concerted effort has been made to bring together in one place a detailed compilation of the uses of those reagents that will serve both the beginning and experienced investigator. The wealth of facts contained within the *Encyclopedia of Reagents for Organic Synthesis* has been assimilated in a manner which will cause all scientists to want this source of information kept in close proximity to their laboratory.

A work of this magnitude could not have been brought to realization without the input of a great deal of time, effort, and dedication on the part of a large number of highly responsible individuals. I am especially indebted to the editors – Steven Burke, Robert Coates, Rick Danheiser, Scott Denmark, David Hart, Lanny Liebeskind, Dennis Liotta, Anthony Pearson, Hans Reich, James Rigby, and William Roush – for their tremendously valuable enthusiasm, intensive work, and unstinting persistence. A most critical role has been played by Colin Drayton, not only in conceiving the project but also as a consequence of his range of knowledge of the publishing business in steering us continually in the proper direction and in overseeing the massive editing operation. James Edwards and Mark Volmer are also to be thanked for their central role as assistant section editors. The body of this encyclopedia was composed by over 1000 authors from 40 countries around the world. The knowledge and expertise contributed by these experienced investigators in the form of authoritative treatises dealing with reagents with which they are thoroughly familiar constitutes the scientific underpinning of the entire undertaking. The enlightening end product of their contributions will have a major impact on the conduct of research in organic chemistry and I thank each of these individuals for their insightful entries.

The large contingent of organic chemists alluded to above, directly and indirectly, expects the *Encyclopedia of Reagents for Organic Synthesis* to play a vital role in stimulating creative research in organic chemistry in the years immediately ahead. All of us hope that you will share in this excitement by perusing its many pages and creatively adapting the valuable information contained therein.

Leo A. Paquette
The Ohio State University
Columbus, OH, USA

Foreword

This Encyclopedia covers comprehensively over 3000 reagents, alphabetically arranged using IUPAC nomenclature. The articles are self-contained but **Bold Italics** are used within each article to indicate other reagents that have their own entries in the Encyclopedia. A list of related reagents is given at the end of articles.

Although most articles are devoted to a single reagent, in some cases closely related reagents are covered under one heading, e.g. Methyl Trimethylsilylacetate is discussed in the article on Ethyl Trimethylsilylacetate, and Lithium Trimethoxyaluminum Hydride in the article on Lithium Tri-*t*-butoxyaluminum Hydride.

A particular reagent can be found either directly, by going to the appropriate place in the Encyclopedia, or from the Subject Index in Volume 8. Numerous other topics, such as

types of reaction, named reactions, named reagents, general substrates or products, and specific substrates or products, are included in this index.

Volume 8 also contains a Formula Index, listing all reagents covered in the Encyclopedia.

In addition, there are two further compilations of all the reagents in Volume 8, a Reagent Structural Class Index and a Reagent Function Index. The former groups the reagents under headings such as Dienes, Hydrides, and Titanium Reagents, while the latter has headings such as Alkylating Agents, Desilylation Reagents, and Ring Expansion Agents.

The abbreviations used for journals in the references are on the front endpapers of all volumes, while the back endpapers list other abbreviations used throughout the Encyclopedia.

Flash silver surface oxide can be removed by heating in vacuum. Active surfaces can usually be ignored. Handling Storage and Precautions: The dry solid easily oxidizes when exposed to air and is very moist in a potentially deleterious. The highly corrosive sodium vapor reacts spontaneously in air, and is a severe irritant to eyes, skin, and respiratory membranes. When a case should be taken to keep the substance away from halogenated solvents, alcohols, and organic mineral acids. Flow should be quenched with a dry powder such as NaCl , Na_2CO_3 , or NaHCO_3 when CO_2 , H_2 , and other gas should be avoided. Sodium solution is best prepared by slow introduction into a flask of dry liquid, possibly containing 1% water, using care to vent liberated H_2 , and neutralizing the resulting solution with aqueous acid. Sodium stored under oil is best kept by drying freshly cut pieces with hexane and after evaporation adding to a metal beaker containing hexane.

Reaction Conditions: Sodium, along with the other commonly used alkali metals *Lithium* and *Potassium*, is an extremely powerful and selective reagent. Historically, solutions of sodium in ammonia have been used to reduce a wide variety of functional groups (see also *Sodium-Ammonia* for some of these transformations, particularly the Birch reduction of aromatic rings). These reductions are usually carried out in the presence of proton donors, normally simple alcohols or NH_3 , though occasionally these are added prior to working. Many reductions are performed with solutions of sodium in refluxing alcohol; here a large excess of sodium is often required due to its gradual decomposition to alkoxide and H_2 . It is sometimes simpler to add a mixture of alcohol and substrate to a dispersion of sodium in an inert solvent such as nitrobenzene. DMF is also occasionally employed as a solvent; solutions of sodium in

DMF behave similarly to those in ammonia. While sodium is insoluble in solvents such as DMF or THF, asphthalene is usually included and a good solution of the *Sodium Asphthalene* radical anion forms. Though the reduction potential of sodium is similar to that of sodium in other solvents (a potential of -2.5 V vs. -2.96 V in DMF¹⁰ and -2.59 V in NH_3), side reactions are often encountered, and reductions are sometimes directed to colored end groups. Other additions such as antiferromagnetic benzophenone, multi-irradiations

Have reduction potentials less negative than aliphatic ketones. Aromatic ketones and α -haloketone-substituted ketones are generally acceptable substrates for these reductions. Ketones are kinetically controlled though the thermodynamic control is not as certain as in the case of alcohols. The chemistry is determined by pyramidalization of the ketone and subsequent carbocation formation, and production of the stereoisomeric result is in most cases kinetically difficult. Study of strain-strain does allow a few general remarks to be made. Unstrained cyclohexanones usually give higher yields of alcohol rather than can be obtained with metal hydrides as by equilibrium.¹¹ Generation of an internal alcohol from bicyclic cyclohexanones often requires the use of dissolving metals, while metal hydrides can give exclusively the end product (eqs 1 and 2).¹² Bicyclo[2.2.2]heptan-2-one always provides an excess of the end product (eq 3).¹³



Sod

Sodium¹

Na

[7440-23-5]

Na

(MW 22.99)

(powerful one-electron reducing agent for most functional groups;¹ reductively couples ketones and esters to unsaturated carbon atoms;² reductively eliminates and couples halogens and other groups; can be used to generate alkoxides)

Physical Data: mp 97.8 °C; *d* 0.968 g cm⁻³.

Solubility: sol liquid NH₃; slightly sol ethereal solvents; dec in alcohols; reacts violently in H₂O.

Form Supplied in: silver-white or gray solid in brick, stick, or ingot form; more commonly as 3–8 mm spheres or as a dispersion in various inert oils.

Purification: surface oxide can be removed by heating in toluene;³ oxide impurities can usually be ignored.

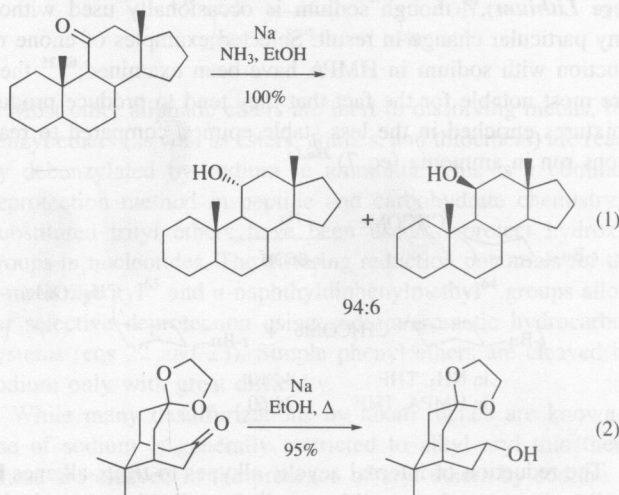
Handling, Storage, and Precautions: the dry solid quickly oxidizes when exposed to air and in very moist air is potentially flammable. The highly corrosive sodium vapor ignites spontaneously in air, and is a severe irritant to eyes, skin, and mucous membranes. Utmost care should be taken to keep sodium away from halogenated solvents, oxidants, and aqueous mineral acids. Fires should be quenched with a dry powder such as Na₂CO₃, NaCl, or NaF; water, CO₂, Halon, and silica gel should be avoided. Excess sodium is best disposed of by slow introduction into a flask of isopropanol, possibly containing 1% water, taking care to vent liberated H₂, and neutralizing the resulting solution with aqueous acid. Sodium stored under oil is best weighed by rinsing freshly cut pieces with hexane and after evaporation adding to a tared beaker containing hexane.

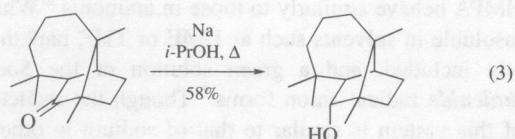
Reaction Conditions. Sodium, along with the other commonly used alkali metals **Lithium** and **Potassium**, is an extremely powerful one-electron reductant. Historically, solutions of sodium in ammonia have been used to reduce a wide variety of functional groups (see also **Sodium–Ammonia** for some of these transformations, particularly the Birch reduction of aromatic rings).⁴ These reductions are usually carried out in the presence of proton donors, normally simple alcohols or NH₄Cl, though occasionally these are added prior to workup. Many reductions are performed with solutions of sodium in refluxing alcohols; here a large excess of sodium is often required due to its gradual decomposition to alkoxides and H₂. It is sometimes simpler to add a mixture of alcohol and substrate to a dispersion of sodium in an inert solvent such as toluene. HMPA is also occasionally employed as a solvent;⁵ solutions of sodium in

HMPA behave similarly to those in ammonia.⁶ While sodium is insoluble in solvents such as DME or THF, naphthalene is usually included, and a green solution of the **Sodium Naphthalenide** radical anion forms.⁷ Though the reduction potential of this system is similar to that of sodium in other solvents (a half-wave potential of –2.5 V⁸ vs. –2.96 V in HMPA^{6b} and –2.59 V in NH₃^{1b}), side reactions are often minimized, and reductions are sometimes titrated to color end-point. Other additives such as anthracene and benzophenone result in solutions with decreased, more selective, reducing power, though this has been rarely exploited.⁸

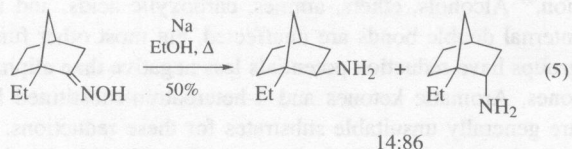
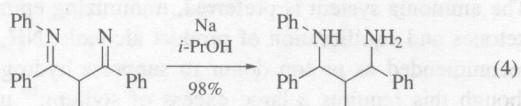
Reduction of Unsaturated Bonds. The classical reduction of ketones with sodium in alcohol, along with the mechanistically similar reduction in ammonia with added proton donors, still finds use in certain systems where the desired stereochemistry cannot be generated by metal hydrides (see also **Lithium**).^{1d–g} The ammonia system is preferred, minimizing epimerization of ketones and equilibration of product alcohols. NH₄Cl has been recommended as proton donor to suppress hydrogen transfer,⁹ though this requires a large excess of sodium;¹⁰ using several equivalents of a primary alcohol also minimizes this side reaction.¹¹ Alcohols, ethers, amines, carboxylic acids, and isolated internal double bonds are unaffected, but most other functional groups have reduction potentials less negative than aliphatic ketones. Aromatic ketones and α -heteroatom-substituted ketones are generally unsuitable substrates for these reductions.

Reductions are kinetically controlled, though the literature contains several mistaken assumptions on this point; stereochemistry is determined by pyramidalization of the ketyl and subsequent carbanion intermediates, and prediction of the stereochemical result is in most cases extremely difficult. Study of certain systems does allow a few general remarks to be made. Unhindered cyclohexanones usually give larger equatorial:axial ratios than can be obtained with metal hydrides or by equilibration.¹² Generation of equatorial alcohols from hindered cyclohexanones often requires the use of dissolving metals, while metal hydrides can give exclusively the axial product (eqs 1 and 2).¹³ Bicyclo[2.2.1]heptan-2-ones always provide an excess of the *endo*-alcohol (eq 3).^{14,15}

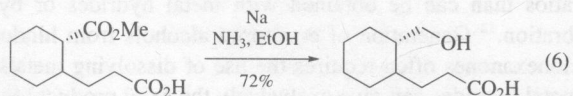




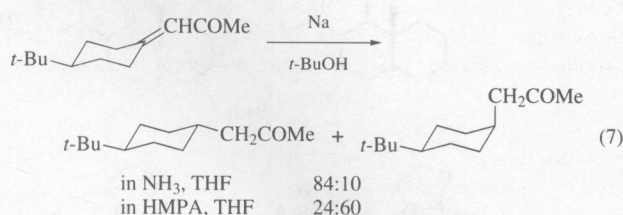
Imines are reduced to amines in good yield by sodium in alcohols, probably through a similar mechanism. In the absence of proton donors, reductive dimerization dominates.¹⁶ 1,3-Diimines, which exist as tautomeric enamino imine mixtures, are reduced to diastereomeric mixtures of diamines (eq 4).¹⁷ Allylic imines have been reduced to alkenes.¹⁸ Reduction of oximes by sodium in alcohol is particularly useful,¹⁹ since **Lithium Aluminum Hydride** can produce Beckmann rearrangements or aziridines.^{20,21} Bicyclo[2.2.1]heptan-2-one and tricyclo[2.2.1.0^{2,6}]heptan-3-one oxime reductions yield predominantly *endo*-amines (eq 5).^{21,22}



The reduction of esters to alcohols with sodium in alcohol (Bouveault–Blanc reduction)²³ has been all but supplanted by the use of metal hydrides. Where an ester must be reduced in the presence of an acid, an improved procedure run in ammonia can be used effectively (eq 6).²⁴

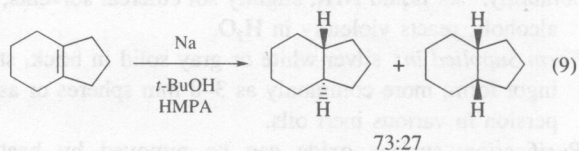
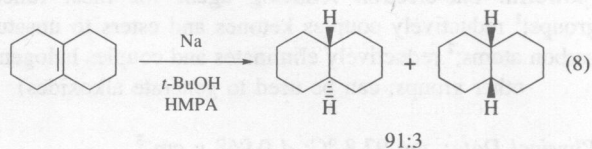


Dissolving metal reductions of α,β -unsaturated carbonyl compounds are almost always performed with lithium in ammonia (see **Lithium**),^{1d} though sodium is occasionally used without any particular change in result. Selected examples of enone reduction with sodium in HMPA have been examined;^{6b,25} these are most notable for the fact that they tend to produce product mixtures enriched in the less stable epimer, compared to reactions run in ammonia (eq 7).^{25a,1e}

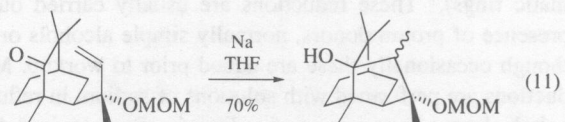
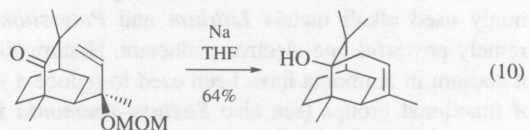


The reduction of internal acyclic alkynes to *trans*-alkenes by sodium in ammonia is well known.^{1b} Complications in reducing terminal alkynes result from deprotonation by NaNH_2 , formed

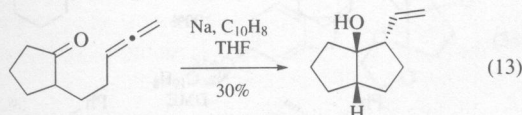
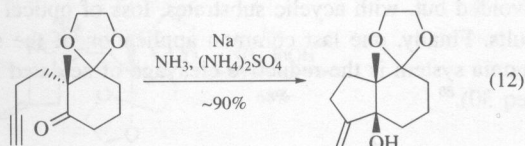
in situ. This can be exploited by addition of an equivalent of NaNH_2 ,²⁶ or overcome by addition of ammonium salts.²⁷ Medium-ring cyclic alkynes often give mixtures of *cis*- and *trans*-alkenes, resulting from partial isomerization by NaNH_2 to alkenes,²⁸ which in turn give *cis/trans* mixtures dependent on product stability and the presence or absence of proton donors.²⁹ Sodium in HMPA/*t*-BuOH has been shown to reduce alkynes;³⁰ internal monoalkenes, inert under most conditions, give near-equilibrium mixtures of alkanes with this system (eqs 8 and 9).³¹ Conjugated dienes are reduced via a *cis*-radical anion,³² while, with lithium, *trans*-dianions may play a role. Dimerization and regioisomer formation usually preclude the use of sodium, though exceptions exist.³³ A few reports of homoconjugated diene reduction have appeared.³⁴



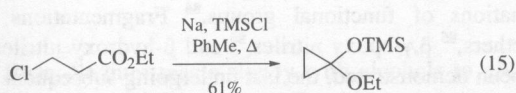
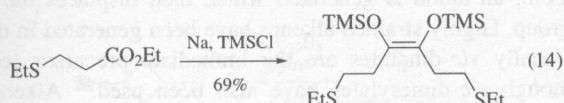
Pinacol Coupling Reactions. In the absence of proton donors, reductions of carbonyl compounds often lead to significant amounts of reductively coupled products, but the intentional pinacol coupling of ketones with sodium in inert solvents is typically a low-yielding, unselective process. Milder conditions utilize lanthanoids and low-valent transition metals, particularly titanium.³⁵ Sodium is used only in cases where no other functional groups are present.³⁶ Sodium is often employed in related intramolecular couplings with unsaturated carbon–carbon bonds, forming five- and six-membered rings regio- and (often) stereoselectively.³⁷ Ketyls cyclize onto allylic systems with *anti* displacement (eqs 10 and 11).³⁸ Transannular cyclizations have also been demonstrated.³⁹ Alkynes are cyclized similarly (eq 12),⁴⁰ usually with **Sodium Naphthalenide**.⁴¹ With allenes, the *exo* closure product is obtained (eq 13),⁴² though prolonged reaction can scramble the position of the resulting double bond.⁴³



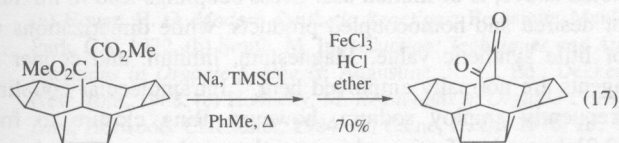
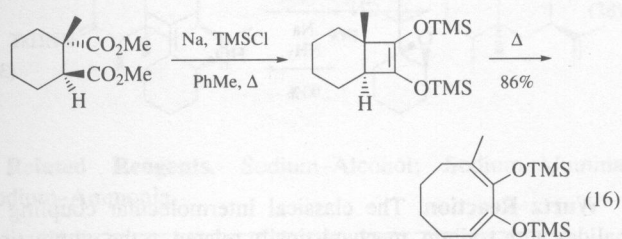
Acyloin Couplings. Reductions of esters under aprotic conditions, usually refluxing toluene or xylene, result in α -hydroxy



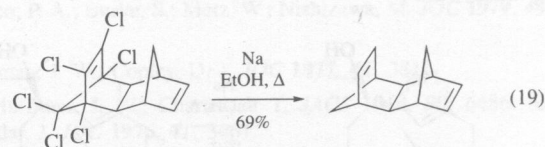
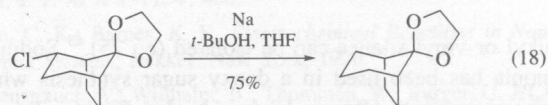
ketones, also called acyloins.² **Sodium-Potassium Alloy** alloy is also used and allows reaction at lower temperatures. Rigorous exclusion of oxygen during reaction and workup is essential. Base-catalyzed side reactions are suppressed by the coaddition of substrate and **Chlorotrimethylsilane**, so as to trap the enediolate and alkoxide products, though good yields can sometimes be obtained regardless.^{2,44} Workup is greatly simplified, and the acyloins can be freed by treatment with aqueous acid or deoxygenated methanol. Couplings can be performed on esters with leaving groups at the β -position (eq 14),⁴⁵ resulting in a useful cyclopropanone hemiacetal synthesis (eq 15).⁴⁶



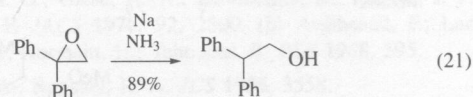
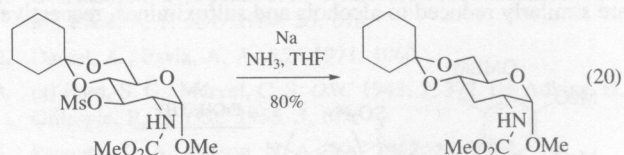
Intramolecular acyloin couplings are an enormously successful method for forming four-membered rings.⁴⁷ Highly strained products can undergo subsequent thermal ring opening (eq 16); Na/K is sometimes more effective in these cases. Hindered diesters can undergo α,α -bond cleavage prior to reduction.² Five- and six-membered rings are routinely generated, often without employing TMSCl. Larger rings, more difficult to form by other methods, are also closed in good yields,⁴⁸ including several polycyclic frameworks (eq 17).⁴⁹ Rings containing 12, 24, and 42 carbon atoms,⁵⁰ paracyclophanes, and rings containing N, O, S, and Si atoms have been formed.⁵¹



Reduction of Saturated Bonds. Typical Birch reduction conditions dehalogenate aryl, vinyl, bridgehead, and cyclopropyl halides, though side reactions are often troublesome.⁵² Alkyl fluorides are not reduced by sodium under any conditions, requiring a K/crown ether system.⁵³ Sodium in alcohol/THF is an effective substitute for Birch conditions;^{54,55} these conditions can also reduce simple alkyl halides (eq 18).^{36b} A simpler procedure employing refluxing ethanol is superior in some cases (eq 19).⁵⁶

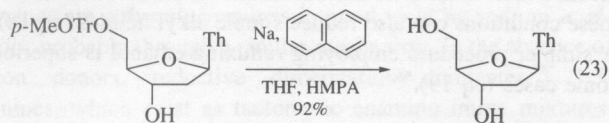
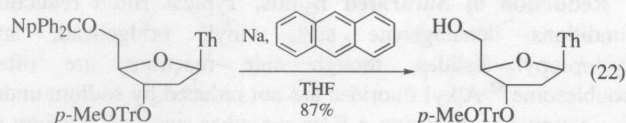


Alcohols are usually derivatized and reduced with metal hydrides, though other methods have received attention.⁵⁷ Among dissolving metal techniques, lithium or potassium in amines are most often used to hydrogenolyze various esters. Sodium in HMPA gives nearly quantitative yields of alkanes from tertiary esters.⁵⁸ Sodium in ammonia can cleave alkyl mesylates (eq 20),⁵⁹ while phosphate esters or mesylates of phenols are similarly reduced to aromatic hydrocarbons.⁶⁰ Like metal hydrides, sodium in ammonia cleaves epoxides to give the more substituted alcohols, with the exception of aryl-substituted epoxides (eq 21).⁶¹ Lithium and second-row metals, particularly calcium, are also effective for epoxide cleavages.

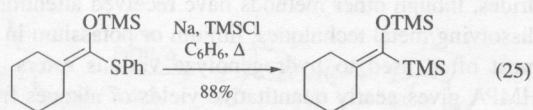
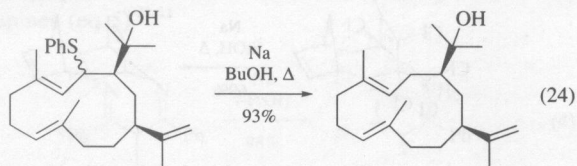


Most other aliphatic ethers are inert to dissolving metals, but benzyl ethers (as well as esters, amines, and thioethers) are readily debenzylated by sodium in ammonia. This is a common deprotection method in peptide and carbohydrate chemistry.⁶² Substituted trityl ethers have been used to protect hydroxyl groups in nucleotides. The differing reduction potentials for the *p*-methoxytrityl⁶³ and α -naphthylmethyl⁶⁴ groups allow for selective deprotection using sodium/aromatic hydrocarbon systems (eqs 22 and 23). Simple phenyl ethers are cleaved by sodium only with great difficulty.

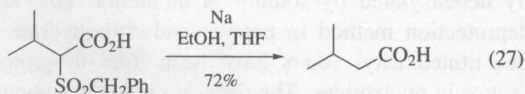
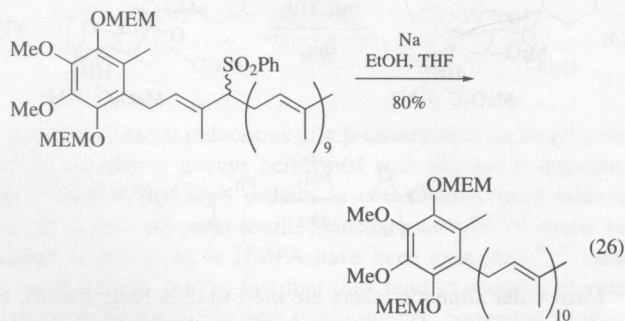
While many desulfurizations by alkali metals are known,⁶⁵ use of sodium is generally restricted to alkyl aryl thioethers. These are cleaved in the presence of aryl ethers by sodium in HMPA.⁶⁶ Phenyl thioethers are more often cleaved in refluxing alcohols (eq 24).⁶⁷ By substituting TMSCl for the proton source,



alkyl or vinyl silanes can be isolated (eq 25).⁶⁸ Sodium in ammonia has been used in a deoxy sugar synthesis where more typical reagents (*Raney Nickel*, *Nickel Boride*, *Tri-n-butyltin Hydride*) fail.⁶⁹

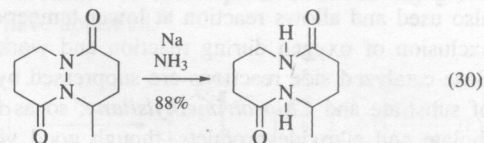
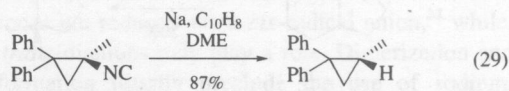
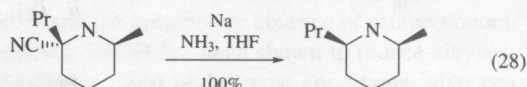


Sulfones are hydrogenolyzed by sodium in ethanol.⁷⁰ This method is again most often used where commonly preferred methods fail (eq 26),⁷¹ and includes a rare application to an α -substituted carboxylic acid (eq 27).⁷² Aryl sulfonamides are readily cleaved to amines with sodium naphthalenide and *Sodium Anthracene*.⁷³ Tosylates^{74,62} and *N*-tosylsulfoximines⁷⁵ are similarly reduced to alcohols and sulfoximines, respectively.

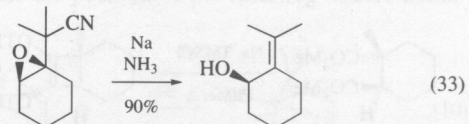
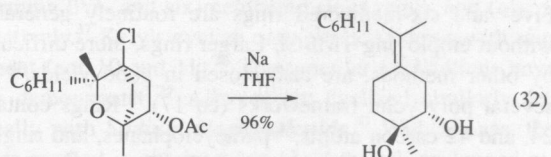
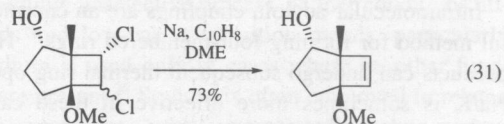


Reductive decyanation is effectively performed with sodium in ammonia.⁷⁶ This method complements *Sodium Borohydride*, which is sometimes ineffective with α -amino nitrile substrates and provides products with inversion of configuration (eq 28).⁷⁷ An alternative method employing sodium or preferably potassium in HMPA/*t*-BuOH also smoothly removes nitriles.⁷⁸ Isocyanides are reduced to hydrocarbons, providing an effective deamination method (eq 29).⁷⁹ Rearrangements are largely

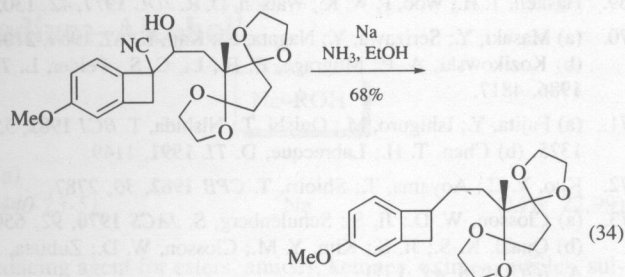
avoided but, with acyclic substrates, loss of optical activity results. Finally, one last common application of the sodium/ammonia system is the reductive cleavage of acylated N-N bonds (eq 30).⁸⁰



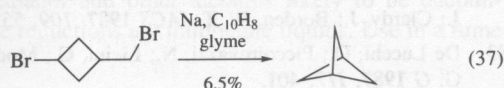
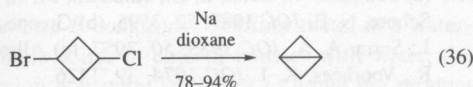
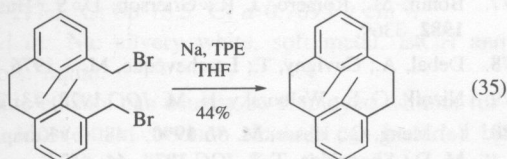
Reductive Eliminations. When a leaving group is situated adjacent to a reducible functionality, elimination results. It is generally agreed that at the site of the initially reduced carbon atom, an anion is generated which then displaces the leaving group. Highly strained alkenes have been generated in this way. Usually *vic*-dihalides are the immediate precursor (eq 31),⁸¹ though *vic*-dimesylates have also been used.⁸² Alkenes have also been generated from *vic*-dinitriles⁸³ and more exotic combinations of functional groups.⁸⁴ Fragmentations of β -chloro ethers,⁸⁵ β,γ -epoxy nitriles,⁸⁶ and β -hydroxy nitriles⁸⁷ have also been demonstrated, the last undergoing subsequent double bond reduction (eqs 32–34).



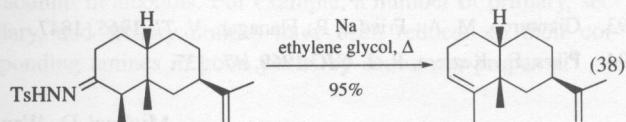
Wurtz Reaction. The classical intermolecular coupling of halides with sodium, mechanistically related to the eliminations noted above, is of limited use. Cross couplings lead to mixtures of desired and homocoupled products, while dimerizations are of little synthetic value. Magnesium, lithium, and copper reagents are normally employed here.⁸⁸ Intramolecular couplings frequently employ sodium, however. Ring closure to form [2.2]phanes is effective when tetraphenylethylene (TPE) is used catalytically (eq 35).⁸⁹ Greatest utility is found in the formation



of cyclopropanes (eq 36),⁹⁰ and to a lesser extent cyclobutanes (eq 37),⁹¹ where **Zinc** is preferred.



Use as a Base. Sodium reacts slowly with alcohols to give solutions of alkoxides. While sodium alkoxides are far more commonly generated by **Sodium Hydride**, or obtained commercially, the older method is still occasionally used. The protic Bamford-Stevens reaction uses sodium to generate alkoxides from **Ethylene Glycol**, present as solvent.⁹² Sodium methoxide can be substituted, but the original conditions are usually employed. Regioselectivity can be a problem; while the more substituted regioisomer usually predominates, prediction is difficult.⁹³ Rearrangements of cationic intermediates also limit its use, though many successful examples of this reaction do exist (eq 38).⁹⁴



Related Reagents. Sodium-Alcohol; Sodium-Alumina; Sodium-Ammonia.

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Sodium-Alcohol¹

Na-ROH

(Na)

[7440-23-5]

Na

(MW 22.99)

(reducing agent for esters, amides, ketones, oximes, nitriles, sulfonamides, aromatic hydrocarbons, certain alkenes, ethers, and carbon-halogen bonds; moderately strong base)

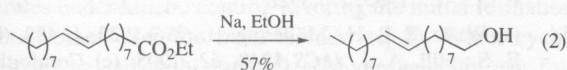
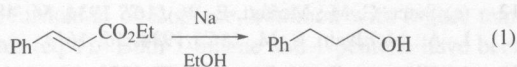
Physical Data: Na: mp 97.5 °C; bp 880 °C; *d* 0.97 g cm⁻³. EtOH: mp -117.3 °C; bp 78.5 °C; *d* 0.7893 g cm⁻³.

Form Supplied in: Na: silvery white, soft metal. EtOH and other alcohols: liquid.

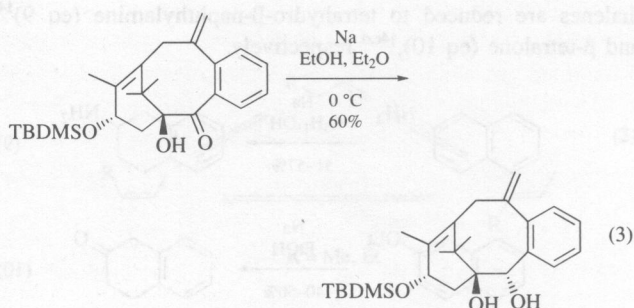
Drying: absolute ethanol can usually be employed without further drying. Most other common alcohols can be dried by storing over anhydrous calcium sulfate followed by distillation.

Handling, Storage, and Precautions: **Sodium** metal is a water-reactive, flammable solid. In case of contact with water, the heat of the reaction is usually sufficient to ignite the product hydrogen. Ethanol and other alcohols likely to be encountered in these reductions are flammable liquids. Use in a fume hood.

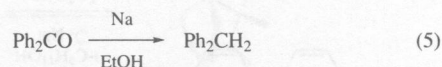
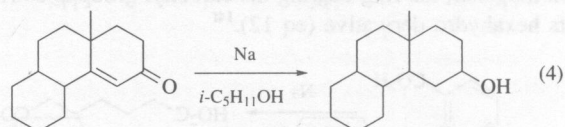
Reduction of Esters and Carboxamides. Though often replaced by the use of more modern hydride reagents, the Bouveault-Blanc reduction has long been known to convert esters to alcohols by refluxing the former reagents with sodium in alcohols.² For example, ethyl hydrocinnamate is converted to hydrocinnamyl alcohol in good yields (eq 1).² Numerous examples of reductions of mono-³ and diesters⁴ can be found in the literature. The major improvement in the procedure over the years has been the use of stoichiometric amounts of ester, alcohol, and toluene or xylene added to sodium in xylene.⁵ Treatment of unsaturated esters with sodium in alcohols reduces conjugated double bonds² but not unconjugated alkenes (eq 2).⁶ Less common have been reductions of carboxamides to amines by sodium in alcohols. For example, a number of primary, secondary, and tertiary amides have been reduced to their corresponding amines in good yields by sodium in propanol.⁷



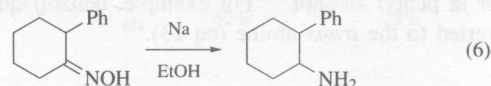
Reduction of Ketones and Derivatives. Aliphatic ketones and phenones are readily converted to alcohols by sodium in alcohols,⁸ as illustrated by the thermodynamically controlled reduction shown in eq 3, which forms part of a recently described synthesis of taxol and its analogs.^{8d}



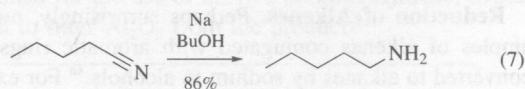
Reduction by sodium in alcohols of α,β -unsaturated ketones affords saturated alcohols (eq 4),⁹ while similar reductions of diaryl ketones give methylene derivatives (eq 5).¹⁰



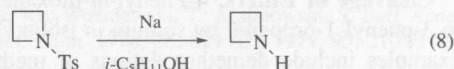
Oximes are conveniently converted to amines by sodium in alcohols.¹¹ For example, the oxime of 2-phenylcyclohexanone is reduced by sodium in ethanol to the corresponding amine in quantitative yield (eq 6).^{11b} The use of higher molecular weight alcohols has been reported to afford better yields of products.^{11d}



Reduction of Nitriles. Aliphatic nitriles are also reduced to amines in satisfactory yields by sodium in *n*-butyl alcohol^{12a} or ethanol and toluene (eq 7).^{12b}

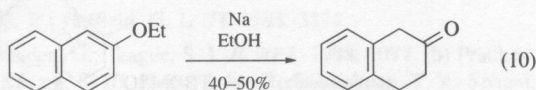
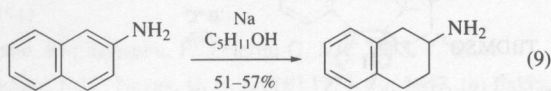


Reduction of Sulfonamides. Both aliphatic and aromatic sulfonamides are converted to sulfinic acids and amines by sodium in isopentyl alcohol.¹³ This reduction has been employed in the preparation of azetidine (eq 8).^{13b}

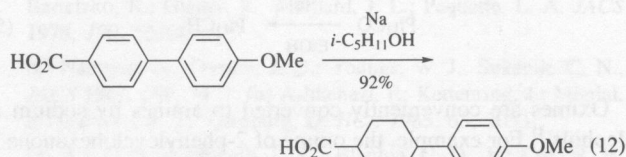
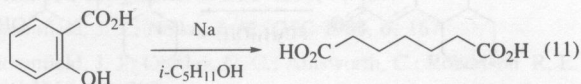


Reduction of Aromatic Hydrocarbons. Naphthalene and higher aromatic hydrocarbons, as well as certain amino, ether, and carboxyl derivatives, are reduced to more saturated derivatives by sodium in numerous alcohols.^{1a,14} Thus while naphthalene itself is converted by sodium in ethanol and benzene to the 1,4-dihydro derivative,^{14b} β -naphthylamine and β -alkoxynaph-

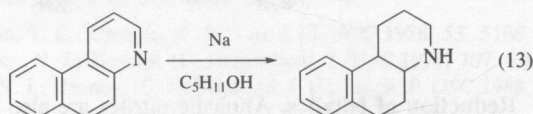
thalenes are reduced to tetrahydro- β -naphthylamine (eq 9)^{14a} and β -tetralone (eq 10),^{14c,d} respectively.



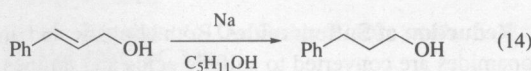
Interestingly, sodium/isopentyl alcohol reduction of salicylic acid gives pimelic acid (eq 11).^{14e} In the case of biphenyl substituted with a carboxyl group on one ring and a methoxy group on the other, the ring bearing the carboxyl group is converted to its hexahydro derivative (eq 12).^{14f}



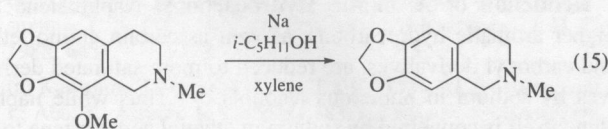
Pyridine derivatives are also reduced by sodium in ethanol¹⁵ or in pentyl alcohol.^{11b} For example, benzo[*f*]quinoline is converted to the *trans*-amine (eq 13).^{11b}



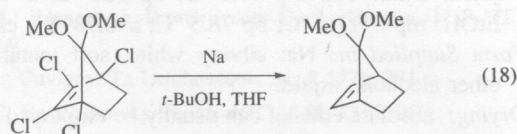
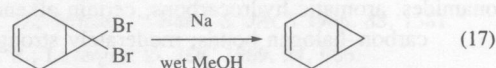
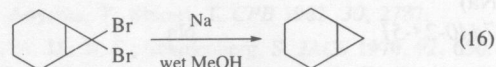
Reduction of Alkenes. Perhaps surprisingly, numerous examples of alkenes conjugated with aromatic rings have been converted to alkanes by sodium in alcohols.^{1a} For example, cinnamyl alcohol is conveniently reduced by this method (eq 14).¹⁶



Cleavage of Ethers. 4-Phenyl-*m*-dioxane has been reduced to 3-phenyl-1-propanol by sodium in isobutyl alcohol.¹⁷ Similar examples include demethoxylations of methyl aryl ethers (eq 15)^{18a,b} and debenzylations of benzyl derivatives of certain sugars.^{18c}



Reduction of Carbon-Halogen Bonds. *gem*-Dibromides are reduced by sodium in wet methanol to the parent hydrocarbons (eqs 16 and 17).¹⁹ Both vinylic and allylic chlorides, but not methyl ether moieties, are similarly reduced by sodium in *t*-butyl alcohol and THF (eq 18).²⁰



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Sodium-Alumina



(Na)
[7440-23-5] Na (MW 22.99)
(Al₂O₃)
[1344-28-1] Al₂O₃ (MW 101.96)

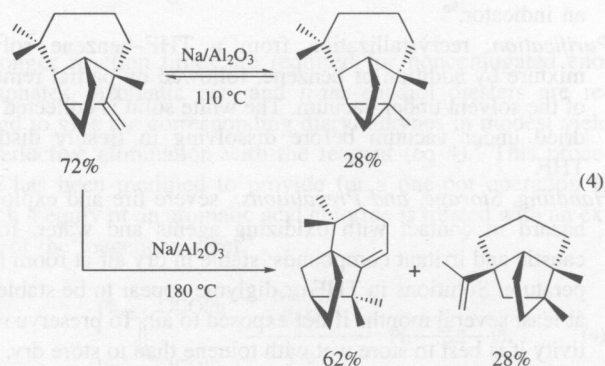
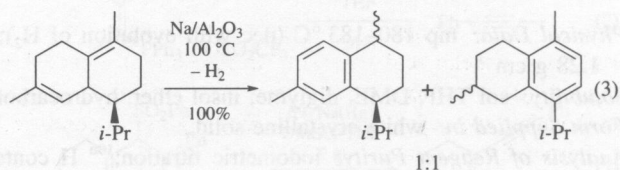
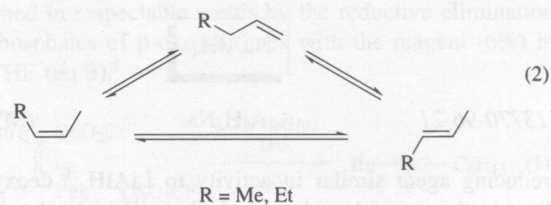
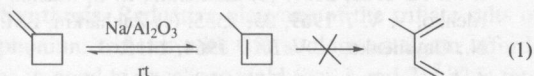
(isomerization of alkenes;¹ isomerization of amines;² a form of high surface area sodium metal³)

Physical Data: sodium: mp 97.8 °C; *d* 0.968 g cm⁻³. Alumina: *d* 3.97 g cm⁻³.

Preparative Method: basic **Alumina** is dried at 150–200 °C and vigorously stirred with **Sodium** metal under an inert atmosphere until cool. The 2–10% sodium on alumina mixtures (as typically used for alkene isomerization) are free flowing, non-pyrophoric solids ranging from bright to dark gray; the color intensity markedly increases with increasing metal content.^{1,4-6}

Handling, Storage, and Precautions: sodium metal reacts violently with water to produce flammable H₂ gas. High sodium-containing Na/Al₂O₃ catalysts may be pyrophoric. In case of fire, do not expose to water, CO₂, or vaporizable liquids. The activity of the catalyst is lost upon exposure to air or moisture.

Alkene Isomerization. Isomerization of alkenes may be accomplished under mild conditions. Thus methylenecyclobutane is converted to methylcyclobutene in nearly quantitative yield, avoiding the formation of isoprene, common with higher temperature routes (eq 1).⁴ Both 1-butene and 1-pentene have been isomerized to the internal alkene with this catalyst.^{5,7} The system operates under kinetic control, favoring the initial formation of the *cis*-isomer over the *trans*-isomer (eq 2). When cyclic dialkenes are treated with Na/Al₂O₃, dehydrogenation can follow the reversible C=C bond shift (eq 3).¹ More forcing conditions can cause skeletal rearrangement (eq 4).¹



Miscellaneous Uses. This catalyst has also been used to racemize optically active benzyl amines.² Na/Al₂O₃ has also been used as a sodium metal source in the large scale preparation of sodium cyclopentadienide.³ Recently, this method has been abandoned for the use of oil-free **Sodium Hydride**, avoiding the need to filter Al₂O₃ from the product.⁸

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Sodium Aluminum Hydride



[13770-96-2]

AlH₃Na

(MW 54.01)

(reducing agent similar in activity to LiAlH₄;¹ deoxygenative dimerization of carbonyls and alcohols;^{11a} hydroalumination of alkenes and alkynes^{11b})

Physical Data: mp 180–183 °C (dec with evolution of H₂); *d* 1.28 g cm⁻³.

Solubility: sol THF, DME, diglyme; insol ether, hydrocarbons.

Form Supplied in: white crystalline solid.

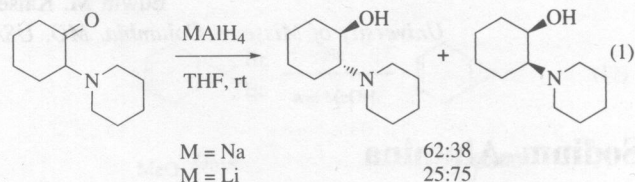
Analysis of Reagent Purity: iodometric titration;^{10b} H content determined by gas evolution analysis; Al content determined by EDTA–Zn(OAc)₂ back titration at pH 4 using dithizone as an indicator.^{9a}

Purification: recrystallization from a THF–benzene solvent mixture by addition of benzene, followed by partial removal of the solvent under vacuum. The white solid is collected and dried under vacuum before dissolving in freshly distilled THF.

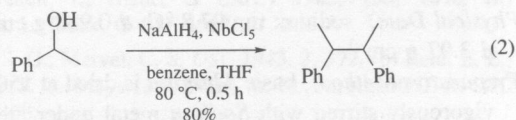
Handling, Storage, and Precautions: severe fire and explosion hazard in contact with oxidizing agents and water, forms caustic and irritant compounds; stable in dry air at room temperature. Solutions in THF or diglyme appear to be stable for at least several months if not exposed to air. To preserve reactivity it is best to store wet with toluene than to store dry. Use in a fume hood.

Functional Group Reductions. This reagent reduces aldehydes, ketones, carboxylic acids, esters, and acid chlorides to give alcohols. Amides, nitriles, and aliphatic nitro compounds give amines. Aromatic nitro compounds yield azo compounds. Yields are usually within 10% of those reported for **Lithium Aluminum Hydride**.¹ NaAlH₄ is about 10–11 times less reactive than LiAlH₄ in the reduction of ketones.² Heterogenous reductions of esters in diethyl ether, benzene, toluene, or heptane give good yields of the alcohols.^{1a,3} Hydrogenolysis of alkyl halides occurs at a rate considerably slower than with LiAlH₄.^{1,4a,b} Aromatic iodides and bromides are readily reduced in THF but diglyme is a better solvent for chlorides.^{4c} Ethers and double and triple bonds are normally stable to this reagent. Under controlled conditions, the reaction with esters, dialkylamides, and aromatic nitriles can provide aldehydes in good yields.⁵ Aliphatic nitriles proceed mainly to the amines with only 15–25% yield of the aldehydes. Best yields are obtained by inverse addition of the hydride at low temperatures. Certain lactones can be partially reduced.^{6a} Phthalic anhydrides are sluggishly converted to the lactones and substituent effects on regioselectivity have been studied.^{6b} Quaternary pyridinium iodides are reduced to piperidines.⁷ Reduction of *N*-cyclopropylimines gives the cyclopropylamines as well as the *n*-propylamines resulting from ring cleavage.⁸

Stereoselective Reductions. NaAlH₄ gives a slightly smaller extent of axial addition to 4-*t*-butylcyclohexanone than is observed for LiAlH₄ (88% and 92%, respectively).⁹ The stereochemical features of a number of ketone reductions by this reagent have been examined.^{9,10} Greater degrees of stereoselectivity are generally found with LiAlH₄. In the case of cyclic α-amino ketones, larger amounts of *trans*-isomers are produced compared to LiAlH₄ (eq 1).^{10d-f}



Deoxygenative Dimerization Reactions. In the presence of NaAlH₄/NbCl₅, aromatic carbonyl compounds undergo deoxygenative dimerization to yield alkenes (56–99%).^{11a} Purely aliphatic carbonyls give trace to low yields of alkenes. Allylic and benzylic alcohols form symmetrical coupling products (eq 2). Allylic rearrangements occur in some cases. Under these conditions, epoxides can be deoxygenated to give the corresponding alkenes.



Hydrometalation. Internal alkynes are converted to (*Z*)-alkenes with high stereoselectivities (>20:1) using the NaAlH₄/NbCl₅ system.^{11a} Terminal alkenes and internal alkynes are reduced rapidly and in high yield by NaAlH₄ in the presence of a catalytic amount of **Dichlorobis(cyclopentadienyl)titanium**.^{11b} The reduction of 2-alkyn-1-ols by NaAlH₄ via a cyclic alanate provides β- or γ-substituted allyl alcohols, depending on the solvent and the electronic character of the substituent.¹²

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Sodium Amalgam

Na(Hg)

[11110-52-4]

Na

(MW 22.99)

(used in the preparation of alkenes and alkynes; to reductively cleave C–S and N–O bonds; for the reductive cleavage of quaternary phosphonium and arsonium salts; selective dehalogenation of aryl halides; also for the reduction of a variety of other functional groups)

Physical Data: the consistency and mp vary with the sodium content; 1.2% sodium is a semisolid at room temperature and melts completely at 50 °C; 5.4% sodium melts above 360 °C. **Solubility:** sodium amalgams are decomposed by water but more slowly than sodium.

Form Supplied in: crushed solid; limited commercial availability.

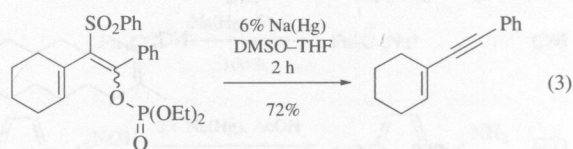
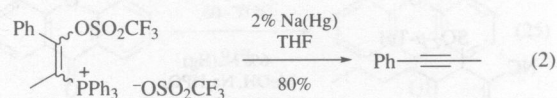
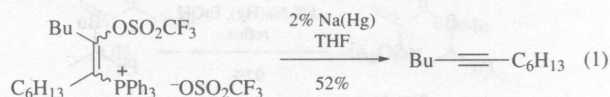
Analysis of Reagent Purity: the amalgam can be analyzed for sodium by titration with 0.1 N sulfuric or hydrochloric acid.

Preparative Methods: several procedures for the preparation of sodium amalgam have been reported.^{1–4} Amalgams containing 2–6% sodium are the most commonly employed for synthetic work. The safest and most convenient procedure for the preparation of 2% sodium amalgam is the addition of **Mercury(0)** to ribbons of **Sodium** metal.^{5,6} No external heating is required with this protocol. The resulting solid can be crushed and stored indefinitely in a tightly stoppered container.

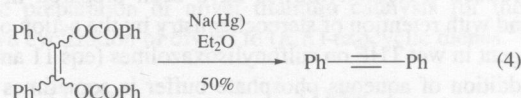
Handling, Storage, and Precautions: moisture sensitive; keep tightly closed.

Alkyne Synthesis. Reductive cleavage of the triflate salts of vinyl phosphonium triflates with 2% sodium amalgam affords pure alkynes in good to excellent yield (eqs 1 and 2).⁷ This represents a significant improvement in yield and purity over the

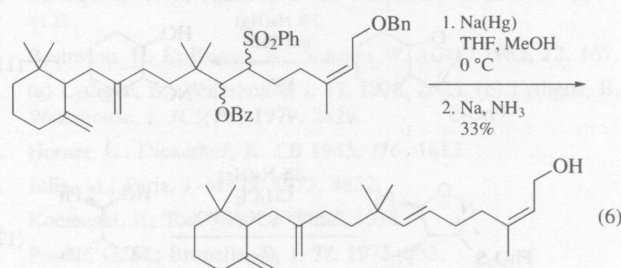
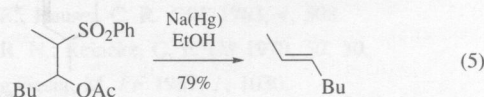
method involving thermal cleavage of acyl ylides. The highest yields are obtained when one group is aryl (eq 2). Alkynes are also obtained in respectable yields by the reductive elimination of enol phosphates of β -oxo sulfones with the reagent (6%) in DMSO–THF (eq 3).⁸



Longer reaction times are required for nonconjugated enol phosphates. Aromatic *cis*- and *trans*-enediol diesters are reported to give the corresponding diaryl alkynes in modest yield by reductive elimination with the reagent (eq 4).⁹ This procedure has been modified to provide for a one-pot operation in which 4 equiv of an aromatic acyl chloride is treated with an excess of the reagent in ether.⁹



Alkene Synthesis. The preparation of *trans*-alkenes from the reaction of β -alkoxy or acyloxy sulfones with sodium amalgam has been reported (eq 5).¹⁰ Trisubstituted and tetrasubstituted precursors generally give disappointing results. Stereoselective introduction of the double bond in a total synthesis of diumycinol was accomplished with this method (eq 6).¹¹ This protocol is effective when other standard conditions fail.



Desulfurization.^{12–17} This reaction has perhaps found the widest use of the reagent. The value of sulfides, sulfoxides, and sulfones in organic synthesis is increased by the ease with which

Avoid Skin Contact with All Reagents