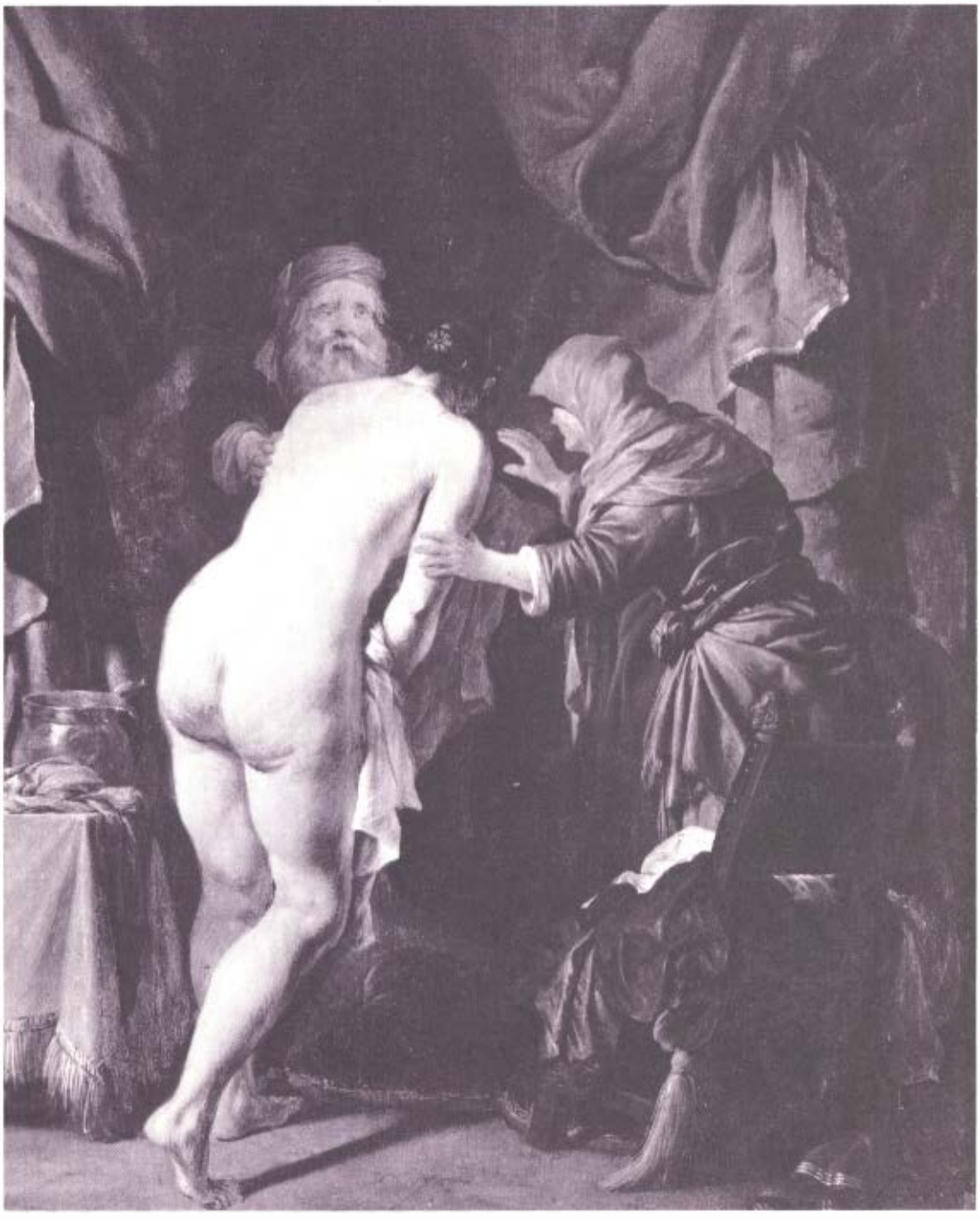
Aldrichimica Acta

Volume 13, Number 1, 1980



Hydroxylamine-*O*-sulfonic Acid. **See page 3.**
Chiral Starting Materials and Reagents. **See page 13.**

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Aldrichimica Acta

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About Our Cover:

This is a most unusual painting, in subject, in color and in its history.

It depicts Sarah bringing Hagar to the aged Abraham (Genesis *16*, 1-3), a subject rarely used by baroque artists. It is a small panel ($12\,^1/_2 \times 9\,^3/_4$ inches) of unusual color - delicate greens and reds. It was painted by Salomon de Bray in 1650. It is interesting to trace the model of the naked Hagar through the ages. De Bray probably copied the main figure of the *Allegory of Fertility* by Jacob Jordaens (Fig. 1), who had copied it from a figure by Moeyaert (Fig. 2), who must have taken his idea from a figure of Aphrodite by Praxiteles. Transmissions of visual ideas, such as this one from the antique through a pre-Rembrandtist and Jacob Jordaens to our Hagar, are probably quite common, but seldom so obvious and well documented.

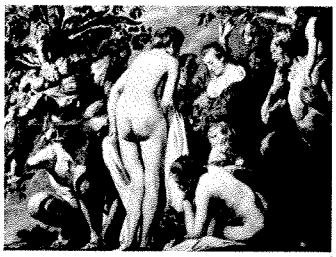


Fig. 1

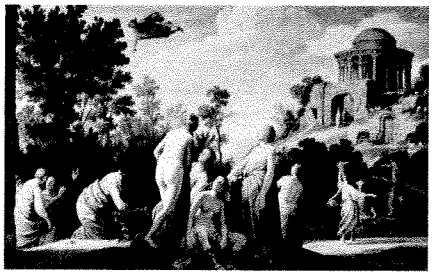


Fig. 2

Our chemist-collector had known this painting for many years, as it had belonged to one of the great private collectors in England, Dr. E.S. Schapiro, who had loaned it and ten other Biblical works to an exhibition, "The Bible through Dutch Eyes" in Milwaukee, of which our chemist had been the guest curator. Dr. Schapiro passed away recently and left his entire collection to the Hermitage in Leningrad. However, the Hermitage was not willing to pay the high estate taxes due, and so the executors had to sell some of the paintings, this one among them.

Are you interested in our Acta covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

Also, many paintings reproduced on our Acta covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Hydroxylamine-*O*-sulfonic acid — a versatile synthetic reagent

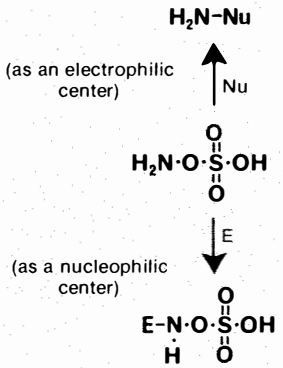
Raymond G. Wallace†
School of Chemistry
Brunel University
Uxbridge, Middlesex UB8 3PH
Great Britain

Synopsis

Hydroxylamine-*O*-sulfonic acid **(HOSA)** has only recently become widely commercially available despite the fact that **it has** proved to be a valuable synthetic **reagent** in preparative organic chemistry. **Unfortunately**, however, information **regarding** the use of HOSA in organic synthesis has remained scattered in the literature, and it is to focus attention on the versatility and potential of this reagent that this information has been brought together now in the form of a short review article.

Important among the areas of application of HOSA are amination and reductive deamination reactions, nitrile and oxime formation, and the preparation of amides and diazo compounds. These and other reactions, including the use of HOSA for the synthesis of heterocycles such as oxaziridines, diaziridines, pyrroles, isothiazoles, benzisoxazoles, benzodiazepines, isothiazolo- and pyrazolopyridines, and imidazolinones and related derivatives are discussed in the review. Many of these preparations can be carried out in high yield.

Hydroxylamine-*O*-sulfonic acid, $NH_2 \cdot OSO_3H$ (abbreviated to HOSA in this article) has become in recent years commercially available. Although much fruitful chemistry has been carried out using HOSA, to this author's knowledge, there has been no systematic review in English* of its use as a synthetic reagent. It is a chemically interesting compound because of the ability of the nitrogen center to act in the role of both nucleophile and electrophile, dependent on circumstances, and thus it has proved to be a reagent of great synthetic versatility.



Besides being directly involved in reactions, it may serve as an *in situ* source of other chemical entities (*e.g.*, imene) which then undergo reaction with a given substrate. Reference will be made from time to time to these various modes of reaction. The uses of HOSA as a reagent are organized below according to the different synthetic transformations that it can bring about.

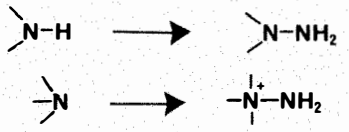
*For a short review in Japanese see ref. 1.

Probably by far the most well known and explored reactions of HOSA are amination reactions, illustrating electrophilic attack by HOSA, with amination on nitrogen being the most important, although a significant number of aminations on both carbon and sulfur have been reported. Amination on phosphorus also occurs.

AMINATION

(a) At a nitrogen atom

(i) Preparation of mono- and disubstituted hydrazines and trisubstituted hydrazinium salts



Monosubstituted hydrazines can be prepared in yields of the order of 50% by treatment of a primary amine with HOSA in aqueous solution in the presence of base (eq. 1).[2-5] Similarly, secondary amines react to give 1,1-disubstituted hydrazines (eq. 2).[4,5]

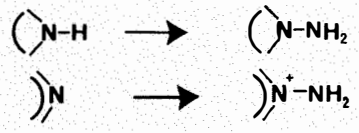
An alternative route for mono- or disubstituted hydrazines uses an aqueous solution of the amine and a ketone, or the

†On secondment from the Cancer Research Campaign's Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

corresponding Schiff's base, instead of the amine alone and involves diaziridine ring formation (*vide infra*) which avoids the use of a considerable excess of amine to suppress further reaction of the hydrazine product and has additional advantages (for a discussion see reference 6 and references cited therein).

1,1,1-Trisubstituted hydrazinium salts are formed when tertiary amines are treated with HOSA under basic conditions in aqueous or alcoholic media (eqs. 3,4).[4,5,7]

(ii) Masked hydrazines - amination on the nitrogen heteroatom of nitrogen heterocycles



Many nitrogen heterocycles can be aminated on nitrogen using HOSA. These include azetidine,[8] pyridine,[4,5] quinoline,[4,5] pyridazine,[9] pyrimidine,[7] pyrazine,[9] tetrazole,[10] indole,[11,12] benzimidazole,[12,13] triazine,[14] benzoxazole,[15] and purine[12,16] ring systems (eqs. 5-16). (The pyrimidine ring system, however, will often undergo ring opening and rearrangement reactions as alternative reaction pathways:[9] a specific example of this is given under miscellaneous reactions.) Here, as in the synthesis of the simple hydrazines, the nitrogen of the HOSA acts as an electrophilic center in the reaction.

In the case of the 1-aminopyridinium cation,[4,5] 1-aminoindole,[11] and 1,2-diaminobenzimidazole[13] especially, the method constitutes an important preparative procedure since the reaction either fails with other reagents (pyridine) or the HOSA synthesis provides a more straightforward route to the compounds in question (indole, benzimidazole). 1-Aminobenzotriazole[14] forms a convenient benzyne precursor.

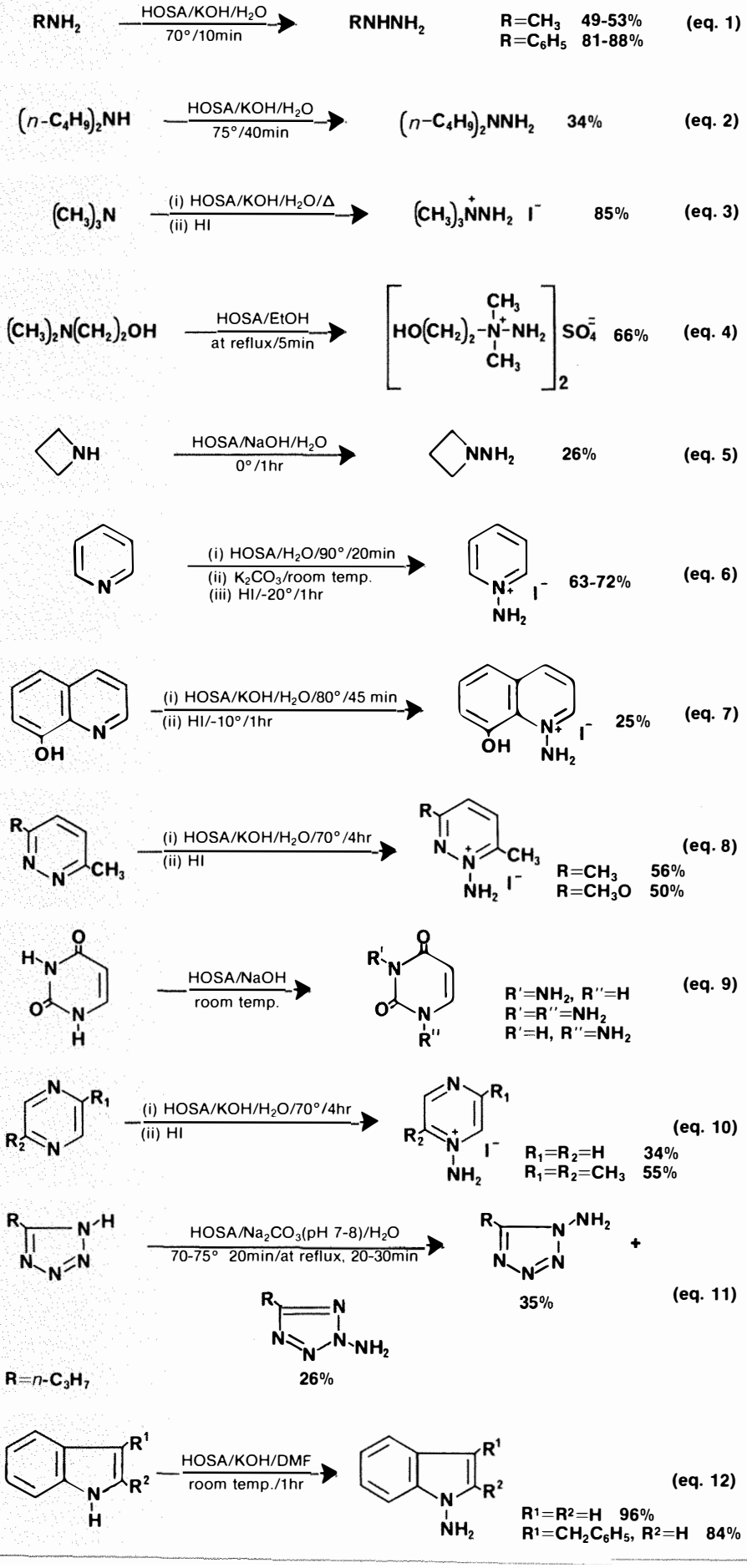
(iii) Preparation of 2-tetrazenes

Piperidine and pipercolines react with HOSA in aqueous solution, in the presence of sodium hydroxide, to give 1,1,4,4-tetrasubstituted 2-tetrazenes (eq. 17).[17] Presumably, the simple hydrazine is initially formed and is subsequently oxidized to the tetrazene.

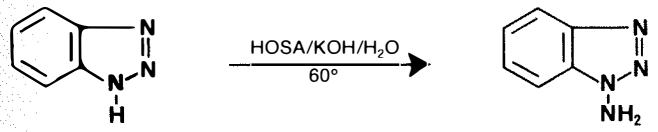
(b) At a carbon atom

HOSA will aminate on aliphatic, aromatic and heterocyclic carbon atoms under a variety of conditions.

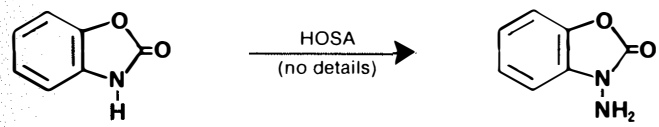
(i) Aliphatic carbon



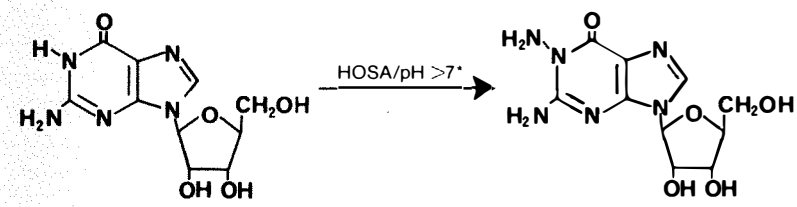
(eq. 13)



(eq. 14)

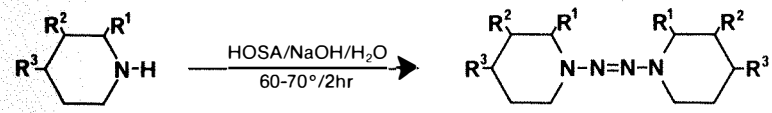


(eq. 15)

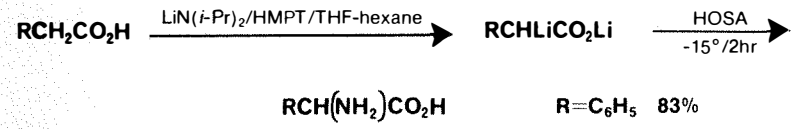


(eq. 16)

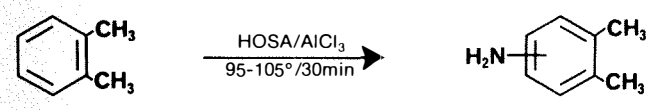
*Note: pH 2-4 gives C-8 amination



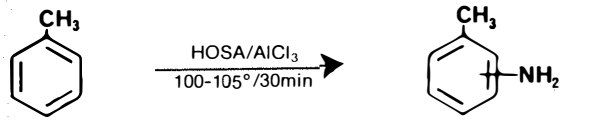
(eq. 17)



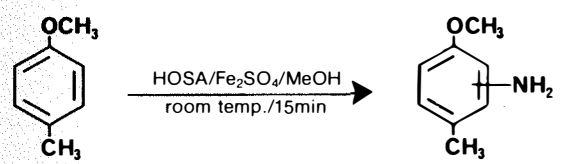
(eq. 18)



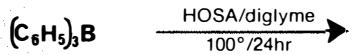
(eq. 19)



(eq. 20)



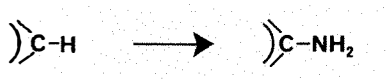
(eq. 21)



(eq. 22)

One of the most successful of these procedures is the elegant one-step synthesis of α-amino acids from carboxylic acids. The acid is lithiated in a mixed solvent system and afterwards treated with HOSA (eq. 18)[18] to give the α-amino acid. HOSA will also aminate active methylene compounds as is demonstrated in the synthesis of substituted pyrroles[19] from β-keto esters and β-diketones.

(*ii*) *Aromatic carbon*



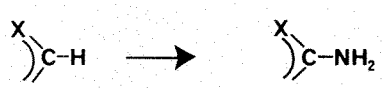
Two main methods have been employed to bring about direct amination in aromatic systems using HOSA. In both cases the yields tend to be on the low side.

The first employs aluminum chloride as a catalyst and has been fairly extensively investigated by Keller[20] and Kovacic.[21] There appears to be a number of points of variance between the work of the two authors. The precise aminating species is not known. Examples from both authors' work are given below (eqs. 19,20).[20,21]

The second method is a homolytic amination procedure developed by Minisci and his co-workers,[22] whereby what is thought to be a protonated amino radical is generated in a redox system (H_2N-$\cdot OSO_3H/Fe^{++}$) at room temperature and this then attacks an aromatic substrate. Yields of between 10 and 40% of monoaminated product are reported (eq. 21). (In many instances the yields are quantitative with respect to the aromatic substrate actually consumed.) In certain cases the reaction shows a degree of stereospecificity.

A third method,[23] from the very recent literature, is based on H.C. Brown's procedure for the conversion of alkenes *via* the organoborane to aliphatic amines (*vide infra*). If an aryl organoborane is substituted for the alkyl borane in the reaction (the paper gives triphenylborane as an example — prepared from phenylmagnesium bromide and boron trifluoride) an arylamine is produced (eq. 22). The disadvantage of the method is that, unlike trialkyl boranes, which utilize two of the three alkyl groups in amine formation, triphenylborane uses only one phenyl group and thus the overall yield with regard to amination on the aromatic ring is not high.

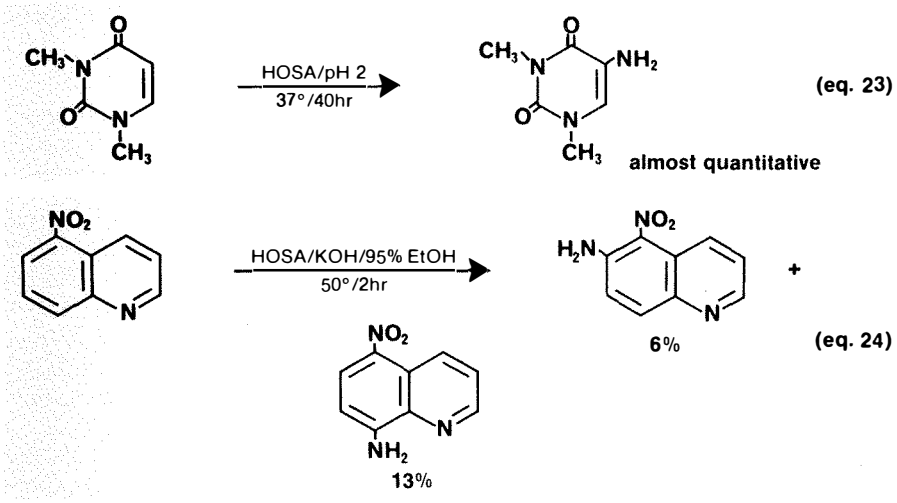
(*iii*) *Heterocyclic carbon*



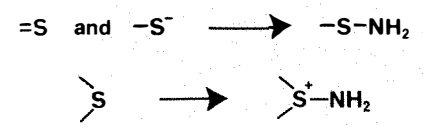
Certain heterocycles will react with HOSA to give a C-substituted amino derivative. For instance, 1,3-dimethyl-

uracil reacts with HOSA at pH 2 over 40 hours to give the C-amino product in almost quantitative yield (eq. 23).[24] Guanosine (eq. 16) aminates at the 8-position[16] at pH 2-4 (70°) and 5-nitroquinoline (*cf.* 8-hydroxyquinoline) aminates at the 6- and 8-positions under basic conditions (eq. 24).[25]

That the mechanism of some of these reactions may be one of addition followed by elimination is suggested by the fact that quinazolines, unsubstituted in the 4-position, react with HOSA at 60-65° over 5-10 minutes to give *N*-(3,4-dihydro-4-quinazolinyl)hydroxylamine-*O*-sulfonic acids, which can be isolated in good yield (eq. 25).[26] However, prolonged treatment with HOSA (70°, 4 hours) gives principally the 4-aminoquinazoline and no dihydro compound. (Interestingly, benzimidazoles and *ortho*-disubstituted benzenes are also products of the reaction under these conditions).[25]



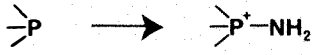
(c) At a sulfur atom



Amination of sulfur in a variety of organic situations can be carried out using HOSA. Thus thiols(ones),[27] thioacids,[28] thioamides,[28,29] dithioacids[28] and thioethers[30] undergo amination to give the corresponding hydrosulfamines and hydrosulfonium salts (eqs. 26-30). The yields for the reactions are generally good and, as with most HOSA transformations, the experimental procedure is relatively simple.

Sulfilimines, in particular, have proved to be very useful intermediates in organic synthesis.[31]

(d) At a phosphorus atom



Triphenylphosphine, when treated with HOSA in methanol, gives triphenylphosphiminium hydrogen sulfate (eq. 31) in 69% yield.[32]

REDUCTIVE DEAMINATION

Two methods of bringing about the transformation $RNH_2 \rightarrow RH$ using HOSA are available: an indirect method *via* the sulfonamide[33] and a direct route[34] which has appeared in the literature only recently.

Reductive deamination refers to the transformation of an amine to a product of lower oxidation level (in the sense proposed by Robinson) and involves the net replacement of an amino group by hydrogen.

In the indirect route,[33] a primary aliphatic or aromatic amine is treated with sulfonyl chloride (typically benzene-, *p*-toluene- or methanesulfonyl chloride) in dry pyridine and the mixture warmed on a steam bath. The sulfonamide, which is isolated, is dissolved in NaOH and then treated with HOSA and the reaction mixture distilled to give the alkane or arene. Yields of product are usually high (eq. 32).

Doldouras and Kollonitsch[34] have shown that there is no need to proceed *via* the sulfonamide, since the primary amine will react directly with 2-3 molar equivalents of HOSA, in the presence of

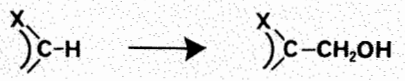
base, at 0°, to give the deaminated product in yields in excess of 50% (eq. 33). The authors have shown that the reaction works for a variety of structural types including amines containing other functionalities, and claim that it is a selective and general method. They have coined the name 'hydrodeamination' for the process and furthermore have illustrated how it may be extended to the conversions $RNH_2 \rightarrow RD$ and RT.

In both methods a common monosubstituted diimide (RN=NH) is proposed as an intermediate (their mode of formation differing) which readily decomposes to RH and nitrogen.

REDUCTION

HOSA alone, or in conjunction with other reagents, provides under basic conditions a source of diimide which will reduce double bonds. Thus, HOSA with cyclohexanone gives 1,1-dihydroxyazocyclohexane, an unstable substance, which, if allowed to decompose at room temperature (which it does rapidly by way of diimide) in the presence of quinone or of azobenzene, yields hydroquinone and hydrazobenzene respectively.[35] HOSA and hydroxylamine sulfate together form an *in situ* source of diimide capable of selectively hydrogenating conjugated multiple bonds (eqs. 34, 35).[36] Using HOSA alone, Appel and Büchner[37] give examples of the reduction of both conjugated and nonconjugated multiple bonds but the yields tend to be lower (eq. 36).

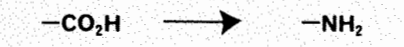
HYDROXYMETHYLATION



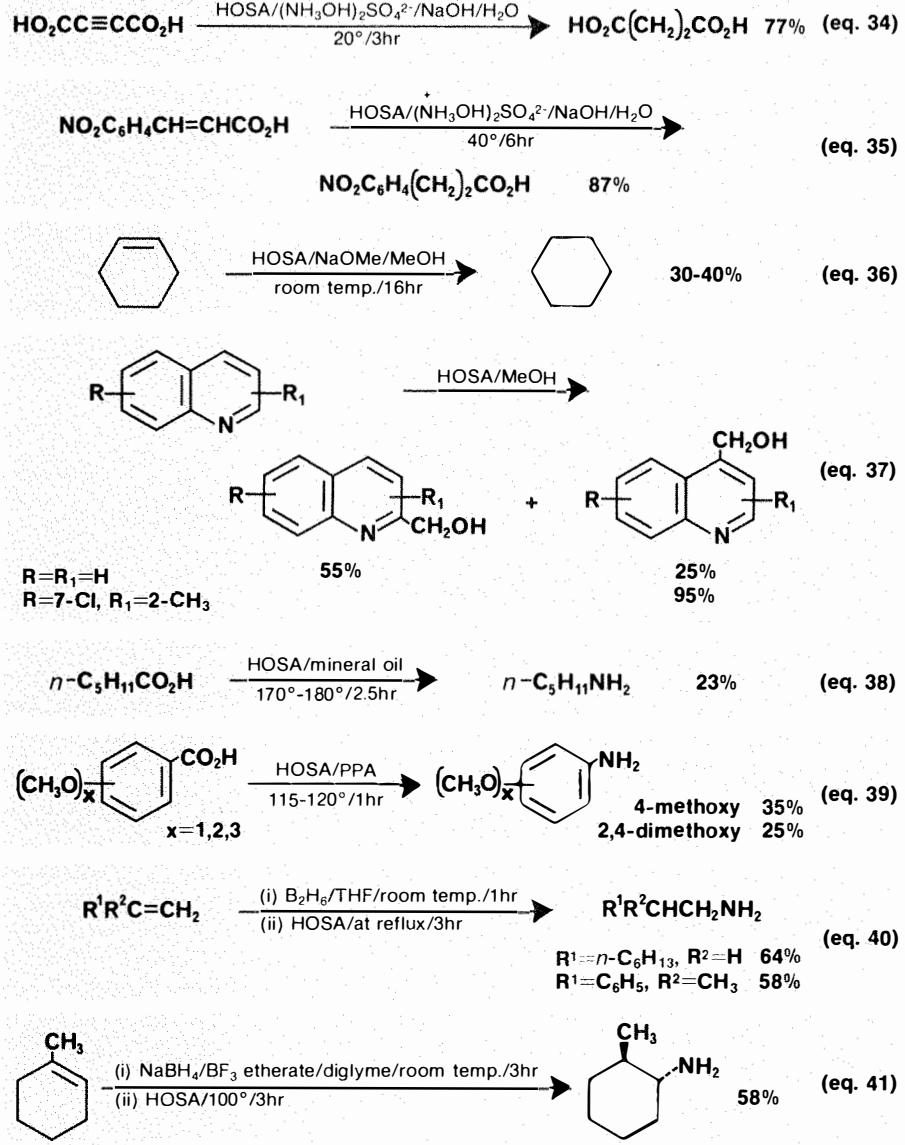
Quinolines can be hydroxymethylated in the 2- and/or 4-position using HOSA in methanol (eq. 37).[38] The discovery arose when a desired amination on nitrogen using the standard HOSA method could not be achieved owing to insolubility of some quinolines in the aqueous medium and, as a result, the solvent was changed to methanol. The reaction has been found to be general for quinolines substituted in the carbocyclic ring and having either a 2- or 4-position (or both) vacant.

FUNCTIONAL GROUP TRANSFORMATIONS:

Loss of carbon



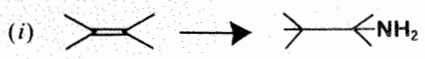
Numerous attempts have been made[39,40] to prepare amines in high yield by the reaction of carboxylic acids or their derivatives with HOSA. The best results to date have been yields of the order of 20-30% and have been obtained by heating the acid (or its



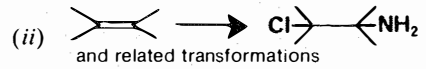
anhydride) with HOSA in mineral oil at 160-180° (eq. 38)[39] or polyphosphoric acid at 115-125° (eq. 39).[40] However, the conditions for this transformation clearly still need to be optimized.

Addition to double bonds

Alkenes

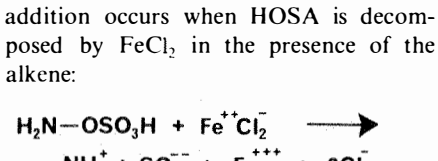


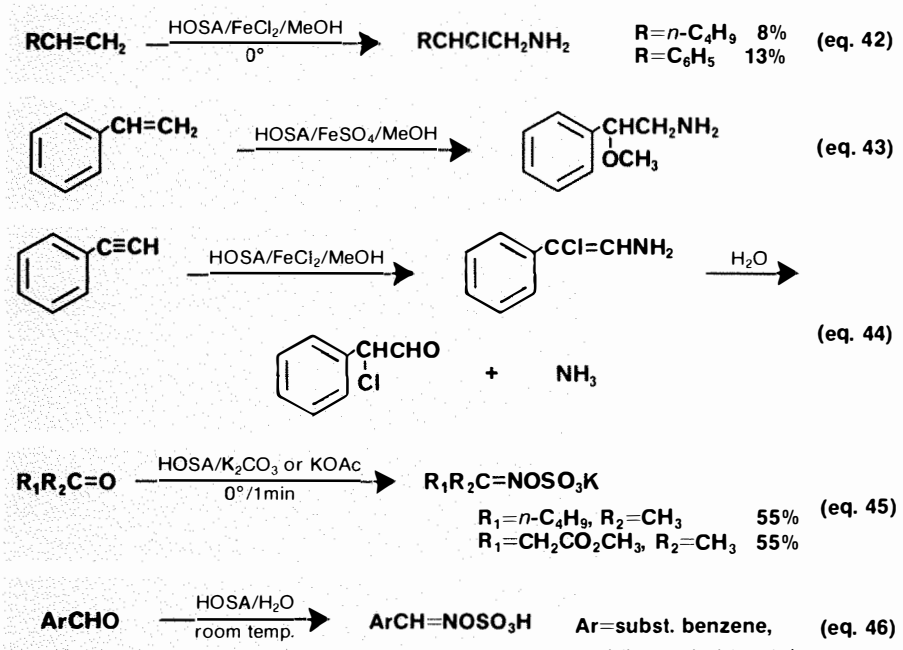
H.C. Brown has developed a simple one-step conversion of alkenes into primary amines *via* the corresponding organoborane using HOSA (eq. 40).[41] The method is applicable to a wide variety of alkenes, and in a later paper,[42] he has shown that it can be applied to relatively hindered alkenes with equal success by conducting the reaction in diglyme, in which HOSA is soluble, rather than in tetrahydrofuran as in the earlier work (eq. 41). In both cases the organoborane is prepared *in situ* — either by the addition of diborane to the alkene or by the addition of boron trifluoride etherate to the alkene and sodium borohydride in diglyme. The reaction is highly stereospecific as is demonstrated in the conversion of norbornene and α-pinene to the isomerically pure *exo*-norbornylamine and isopinocampheylamine, respectively.[42] Occasionally a rearranged amination product is observed.[43]



and related transformations

In a related but mechanistically quite different process, the metal salt redox system of Minisci (*cf.* amination on aromatic carbon — method two) is used to bring about the addition of the elements NH_2 and Cl across a double bond.[44,45] The addition occurs when HOSA is decomposed by $FeCl_2$ in the presence of the alkene:





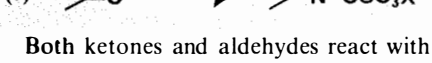
*R.G. Wallace, unpublished observations.

Examples are given in eq. 42. It would appear that the amino group attaches itself to the least-substituted carbon atom. The addition differs from the organoborane method in not being stereospecific.

If addition is carried out in methanolic solution with $FeSO_4$ instead of $FeCl_2$, an amino ether is produced (eq. 43)[44] and if sodium azide is also present an azido amine is formed.[45]

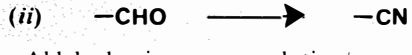
Phenylacetylene with $FeCl_2$ yields α-chlorophenylacetaldehyde by hydrolysis of the corresponding intermediate enamine (eq. 44).[44]

Carbonyl compounds

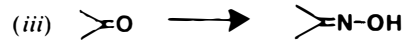


Both ketones and aldehydes react with HOSA to give oxime-*O*-sulfonic acids and salts (eqs. 45, 46).[46,47] In the case of ketones and some aldehydes, these derivatives can be isolated and are well defined, reasonably stable, crystallizable solids. They can be prepared in good yield and undergo a variety of further reactions. This transformation illustrates the alternative role of the HOSA nitrogen as nucleophile.

The condensation reaction to give the oxime-*O*-sulfonic acid or salt forms a common first stage in a number of related and synthetically very useful transformations.



Aldehydes, in aqueous solution/suspension, can be smoothly converted in high yield into nitriles (of the same carbon number) with HOSA.[26,47] The precise conditions depend on the nature of the aldehyde (details are given in eqs. 47-49), the important factor being for them to be sufficiently rigorous to bring about the elimination of sulfuric acid from the intermediate oxime-*O*-sulfonate.

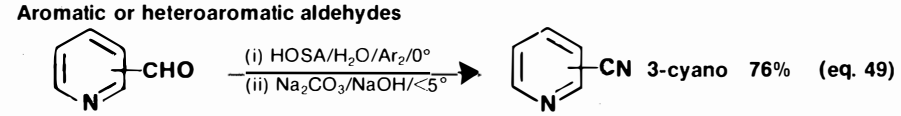


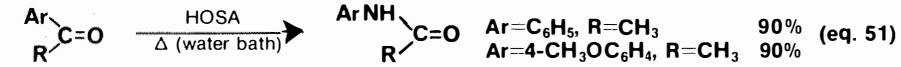
Aliphatic ketones react exothermically when warmed together with HOSA in a water bath to give the corresponding oxime in very good yield (eq. 50).[48] The reaction is accompanied by the loss of nitrogen.

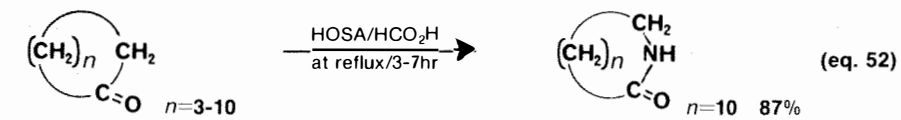
Aliphatic aldehydes

Aromatic or heteroaromatic aldehydes

Aromatic or heteroaromatic aldehydes





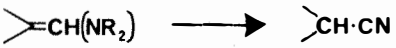


Aryl alkyl ketones, under the above conditions (eq. 51), yield N-aryl aliphatic amides, again in good yields.[48]

According to Sherk *et al.*,[48] diaryl ketones do not react under these conditions, but Ho[49] has reported the formation of amides in tetrahydrofuran. Schmidt- and Beckmann-type mechanisms are proposed for these rearrangement reactions, the precise details of which have not been resolved.[48,49]

In a very recent extension of this synthetic transformation, Olah and Fung[50] have shown that alicyclic ketones can be converted to their corresponding lactams, in high yield, by heating the ketone and HOSA under reflux in formic acid for several hours (eq. 52). Benzophenone, under similar conditons, gives benzanilide in 68% yield.[50]

Enamines

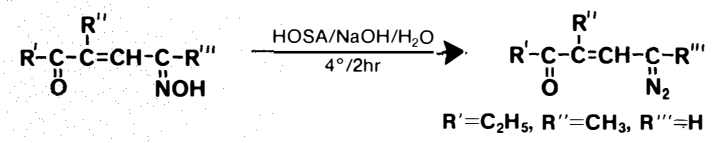


An additional nitrile synthesis using HOSA has recently been reported.[51] This time the precursor is an enamine. The method is extremely useful since enamines can be prepared readily from a variety of active methylene compounds and ketones. The enamine and HOSA are stirred together for 1 hour at room temperature, whereby the nitrile is obtained in good yield (eq. 53).

Forster reaction

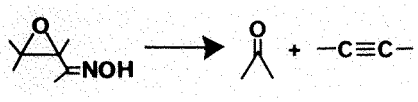
Oximes react with HOSA in aqueous base to give diazo compounds.[52] Thus,

fluorenone oxime gives diazofluorene in 60% yield and benzophenone oxime gives diphenyldiazomethane (30%). The reaction also works well for fully conjugated α,β-unsaturated 1,4-ketoximes (eq. 54).[53]

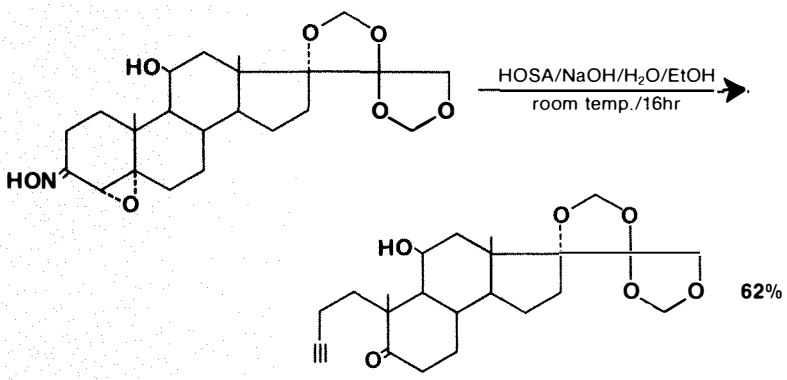


(eq. 54)

Fragmentation reactions



In a sagacious extension of the diazo functionality formation reaction just described, Wieland, Kaufmann and Eschenmoser[54] have demonstrated in the field of steroidal chemistry the facile conversion of an α,β-oxido oxime to an alkynone (eq. 55). A further example and a discussion of the mechanism of the reaction is given in a later paper.[55]

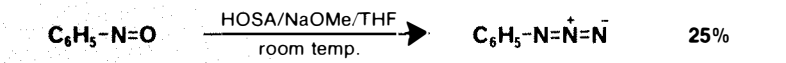


(eq. 55)

Miscellaneous

(i) −N=O ⟶ −N=N⁺=N⁻

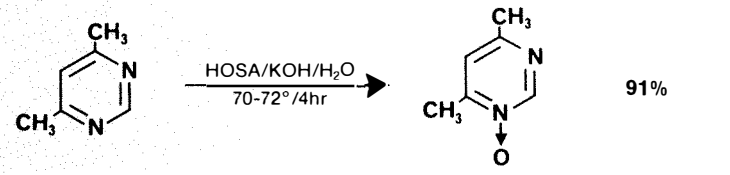
Nitrosobenzene will react with HOSA in tetrahydrofuran in the presence of base to give phenyl azide (*cf.* Forster reaction) (eq. 56).[56]



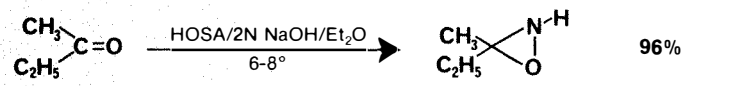
(eq. 56)

(ii) N-Oxide formation

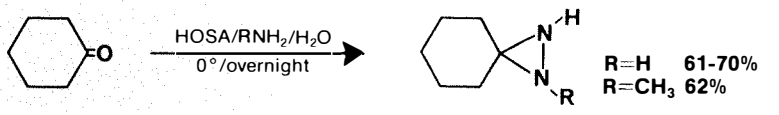
Certain 4-substituted pyrimidines[9] and condensed pyrimidines (quinazolines)[26] react with HOSA to give N-oxides. For example, 4,6-dimethylpyrimidine, with the potassium salt of HOSA in aqueous methanol over 4 hours at 70°-72°, gives 4,6-dimethylpyrimidine-1-oxide (eq. 57).[9] A mechanism involving addition of HOSA, followed by ring opening and then recyclization and, finally, loss of sulfur trioxide and ammonia is proposed for the reaction.[9]



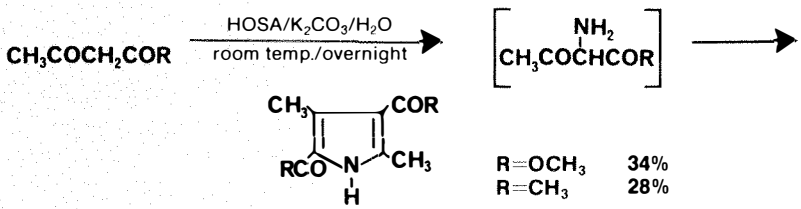
(eq. 57)



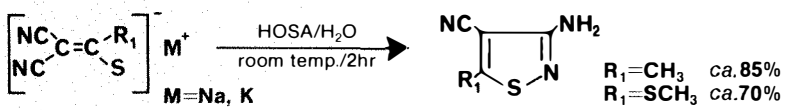
(eq. 58)



(eq. 59)



(eq. 60)



(eq. 61)

HETEROCYCLE FORMATION

(a) Cyclization reactions

Oxaziridines

The oxaziridine ring system can be prepared by the reaction of HOSA with an aliphatic ketone[57,58] or benzaldehyde[59] in 2*N* NaOH at 6-8°. Thus, 3-ethyl-3-methyloxaziridine is obtained in 96% yield (eq. 58)[57] from 2-butanone. The oxaziridine is stable only at very low temperature. More stable oxaziridines are generally obtained by acylating the unsubstituted oxaziridine *in situ*.[59]

Diaziridines

Related to the preparation of oxaziridines and probably another of the most widely explored areas of HOSA chemistry has been the synthesis of diaziridines. Both simple[60] and complex diaziridines such as those with steroidal[61] and multifused[62] ring structures have been described. Principal references are given in reviews by Schmitz[63,64] who notes that by 1964, fifty or so diaziridines had been prepared by the HOSA method.

The diaziridine is formed by reaction of HOSA with ketone/ammonia mixtures, Schiff's bases or a mixture of a carbonyl compound and a primary amine. A typical synthetic procedure, described in *Organic Syntheses*,[65] is illustrated in eq. 59. The diaziridines may easily be oxidized to diazirines.

The pyrrole system

Tamura *et al.*[19] have described a simple one-step method for the preparation of tetrasubstituted pyrroles. A β-diketo compound is treated with HOSA in aqueous potassium carbonate solution overnight to give a symmetrically substituted pyrrole (yields 28-34%, eq. 60). Pyrroline is formed in low yield when HOSA is treated with NaOMe in methanol in the presence of 1,3-butadiene.[66] The 1,4-addition of imene ($\underline{\text{N}}$H) to the diene is invoked in this reaction.

Isothiazoles

Dicyanothioalkene salts* (eq. 61, these

*The yields from monocyano compounds are very low.

can easily be prepared in yields of over 70% by the thioacylation of malononitrile by esters of dithiocarboxylic, thionocarboxylic, xanthic or trithiocarbonic acids at room temperature) react with HOSA in aqueous solution to give 3-aminoisothiazoles.[67,68] The yield of crude reaction product is generally good but isolation of the pure isothiazole may in some cases present technical difficulties.

Benzisoxazoles

Kemp and Woodward[69] have described how benzisoxazole can be prepared in 95% yield when salicylaldehyde is combined with HOSA in water, followed by treatment with sodium bicarbonate for 1 hour at room temperature (eq. 62). A similar preparation was reported eleven years after the publication of Kemp and Woodward's paper, by Suwiński,[70] who seems to have been unaware of the former authors' work. The reaction involves nucleophilic attack by the HOSA nitrogen. The preparation of Kemp and Woodward is suited to large-scale reaction.

Benzodihydro-[1,2]-diazepines

δ-Amino aromatic aldehydes (see eq. 63) can be cyclized in low yield using HOSA to give diazepines.[71] The major product of the reaction, however, is the aromatic nitrile (*vide ante*). The yields of diazepines, nevertheless, can be increased by increasing the nucleophilicity of the nitrogen atom of the aniline function (see eq. 63) and/or by employing mesitylsulfonylhydroxylamine in place of HOSA in the reaction (yields up to 76%).

The proposed mechanism for the cyclization involves a ring expansion step; an additional benzodiazepine ring synthesis, which is a direct ring expansion of a preformed starting material, is described a little later.

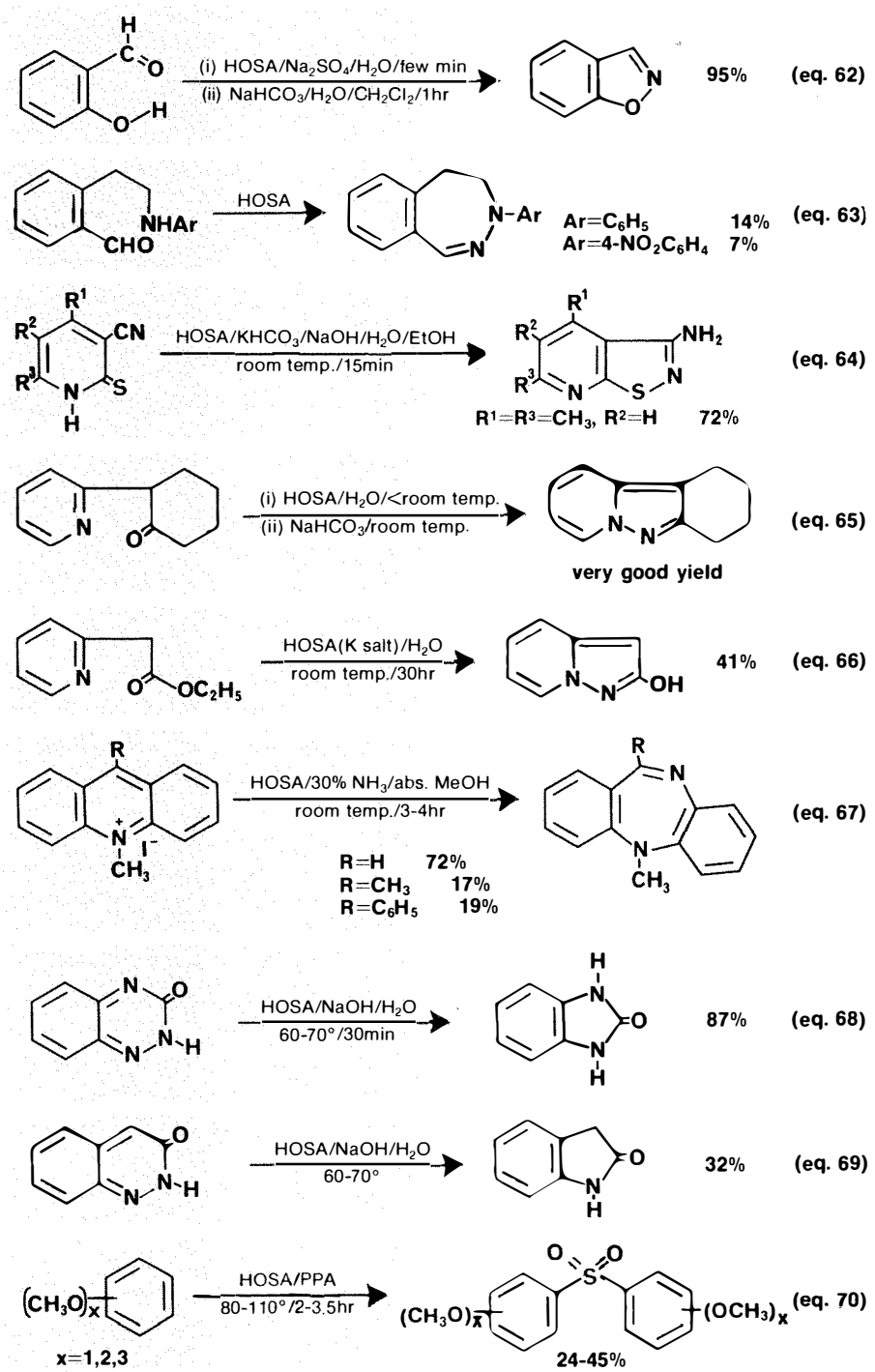
Isothiazolopyridines

In an extension of the isothiazole synthesis described above, 3-cyanopyridine-2-thiones are found to cyclize on treatment with HOSA in the presence of base to give 3-aminoisothiazolo[5,4-*b*]pyridines (eq. 64).[27] The yields in this reaction are good.

Pyrazolopyridines

Pyridines with a β-carbonyl functionality in the 2-position undergo ring closure with HOSA to give pyrazolo[1,5-*a*]-pyridines (eqs. 65,66)[70,72] in good yield. The reaction would seem to occur by electrophilic attack of the HOSA on the carbonyl function to give a derived oxime-*O*-sulfonate, with subsequent electrophilic attack of the oxime nitrogen on the nitrogen of the pyridine ring.

(b) Ring expansion



Dibenzo-[1,4]-diazepines

Treatment of *N*-methylacridinium derivatives with HOSA in absolute methanol containing 30% ammonia for 3-4 hours at room temperature results in an expansion of the heterocyclic ring. The resulting 5-methyldibenzo[*b,e*]-(1,4)-diazepines[73] are obtained in variable yield (eq. 67).

(c) Ring contraction

Imidazolin-2-ones and their benzo derivatives

1,2,4-Triazin-3-ones, when treated with HOSA in aqueous alkali at 70°, undergo a ring contraction reaction to give imidazolin-2-ones in high yield.[74] Thus, 5,6-diphenyl-1,2,4-triazin-3-one gives 4,5-diphenylimidazolin-2-one (68%), 1,2,4-benzotriazin-3-one gives benzimidazolin-2-one (87%, eq. 68) and phenanthro[9,10-*e*]-[1,2,4]triazin-3-one (requiring aqueous/ethanolic NaOH) gives 1,3-dihydrophenanthro[9,10-*d*]imidazol-2-one (74%). *N*-Aminotriazines are considered to be intermediates in these ring contractions.

Oxindole

Cinnolin-3-one, under similar conditions to those above, reacts with HOSA

to give oxindole in 32% yield (eq. 69).[74]

MISCELLANEOUS

Most of the preceding reactions described have involved the incorporation of the nitrogen of the HOSA in the reaction product. One reaction which differs from all of these is that between aromatic ethers and HOSA in polyphosphoric acid. Here, sulfur is incorporated and the product is a diaryl sulfone (eq. 70).[75] It is suggested that HOSA is cleaved to give H_2SO_4 and it is further reaction of this that gives rise to the sulfone.

CONCLUSIONS

HOSA has proved to be a reagent of diverse synthetic utility, its multifarious uses having been amply illustrated in the foregoing paragraphs. Such versatility is a consequence of the inherent ability of HOSA to act as both a nucleophile and electrophile and also to provide an *in situ* source of other chemical entities, factors referred to at the beginning of this article. These properties have led to its exploitation in such a variety of situations.

Clearly there is scope for its application in further organic transformations, and in particular, it must have a further part to play in new heterocyclic syntheses.

ACKNOWLEDGMENT

I wish to thank the Cancer Research Campaign for financial support.

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About the Author

Dr. Wallace is a research scientist working for the Cancer Research Campaign. He obtained his B.Sc. degree from Southampton University in 1968 and subsequently carried out his Ph.D. research at the School of Pharmacy, Portsmouth Polytechnic. His main interests lie in the area of heterocyclic chemistry and in particular he is concerned with the synthesis of hypoxic cell radiosensitizers for use in cancer therapy. He holds a Visiting Research Fellowship at Brunel University.

Aldrich offers HOSA and many of the reagents cited by Dr. Wallace:

"Please Bother Us."

by Jyra Baas.

Last year, Professor G.R. Wyatt of the Department of Biology at Queen's University wrote to me suggesting that we make 7-ethoxy-6-methoxy-2,2-dimethylchromene (Ethoxy-Precocene). "The substance has activity as a 'precocene' or specific cytotoxic agent for the corpus allatum of insects, which stops the production of the juvenile hormone and thus brings about precocious metamorphosis and prevents reproductive maturation. . . . we have found it to be highly effective in the 'chemical allatectomy' of African migratory locusts. We find that 1 mg applied to newly emerged adult female locusts completely blocks reproductive maturation, including the juvenile hormone-dependent synthesis of yolk protein, which is a central subject of our research."

Ethoxy-Precocene seems a very exciting compound, related to the anti-juvenile hormones Precocene I and II, which we have been making for some time. And so we made it.

It was no bother at all, just a pleasure to be able to help.

Chiral Starting Materials and Reagents

An Outline of Recent Synthetic Applications

William A. Szabo
and
Helen T. Lee
Aldrich Chemical Company, Inc.
Milwaukee, Wisconsin 53233

Format and Scope

In recent years the chemical literature has reflected the growing popularity of chiral starting materials and reagents for the construction of optically active organic molecules.[1] We present below a broad overview of some of this literature in outline form, arranged according to an arbitrary system of chemical classes. It is hoped that this format will provide the reader with an appreciation for the wide variety of readily available, optically active compounds which have been successfully employed in contemporary organic synthesis.

Space limitations require that we confine our examples to those starting materials and reagents (used in stoichiometric[2] quantities) whose chirality is incorporated intact into the product molecule and/or is used to direct the stereochemical outcome of a synthetic step. We must apologize to the many authors whose work could not be accommodated in a survey of this length.

Categories of Synthetically Useful, Optically Active Starting Materials and Reagents

I. Natural Products
  A. Containing Nitrogen
    1. Alkaloids
    2. α-Amino Acids
  B. Non-nitrogenous
    1. Sugars
    2. Terpenes
    3. α-Hydroxy Acids

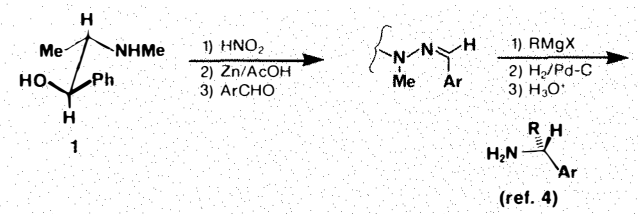
II. Synthetic Products
  A. Primary Amines
  B. Alcohols
  C. Miscellaneous

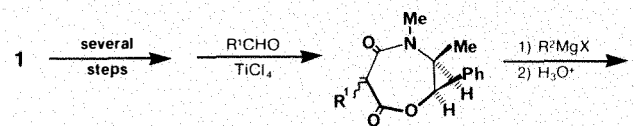
Chiral[3] Starting Materials and Reagents: Recent Synthetic Applications

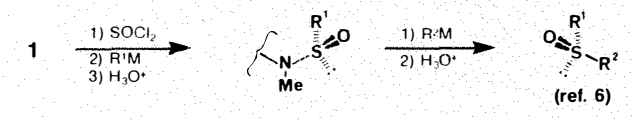
I. Natural Products
  A. Containing Nitrogen

I. Alkaloids

(-)-Ephedrine (**1**):

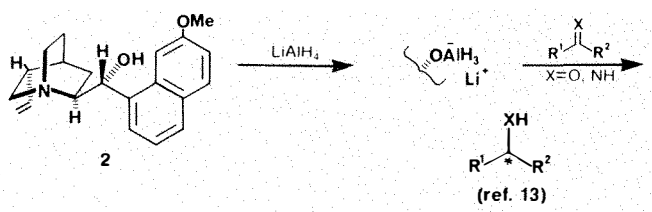






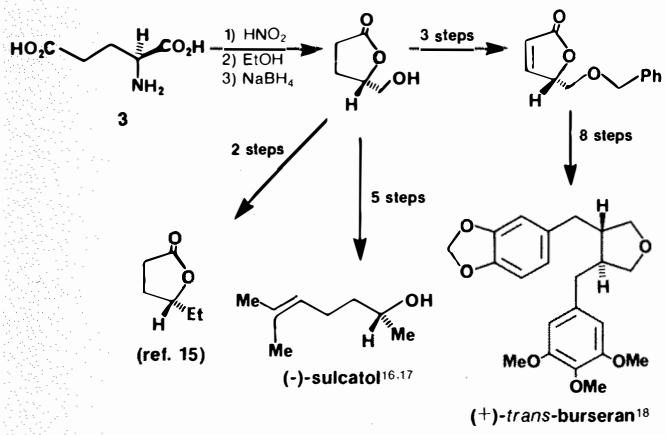
Also: preparation of chiral, isotope-labeled ATP,[7] α-substituted ketones and carboxylic acids,[8] *O,S*-dialkyl phosphoramidothioates,[9] and a carbonyl masking group.[10] The enantiomeric (+)-ephedrine has recently been used for the synthesis of (*S*)-(+)-4-methyl-3-heptanone, an alarm pheromone.[11,12]

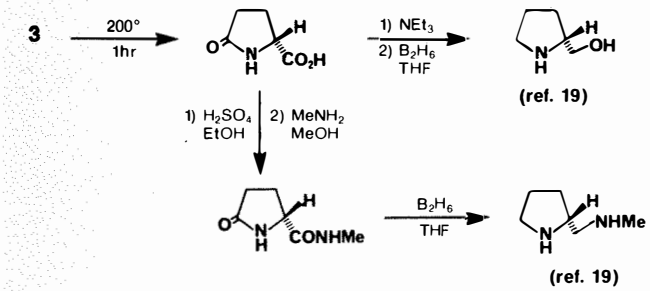
Quinine (**2**):



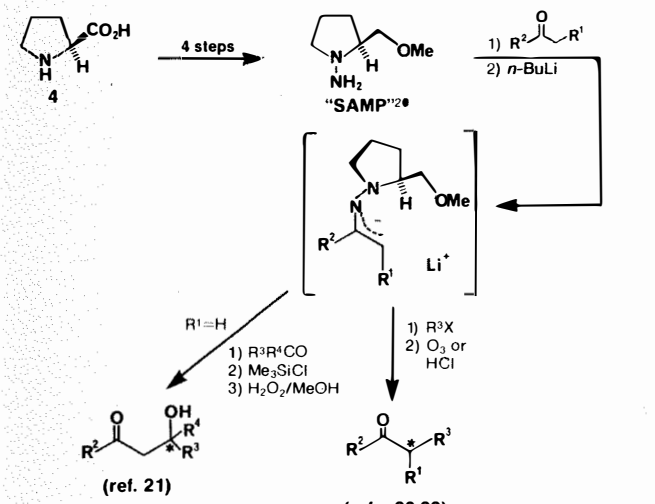
2. α-Amino Acids

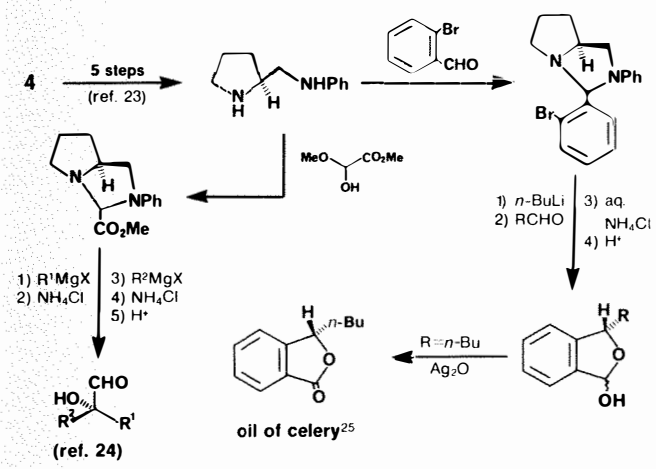
L-(+)-Glutamic acid (3):[14]





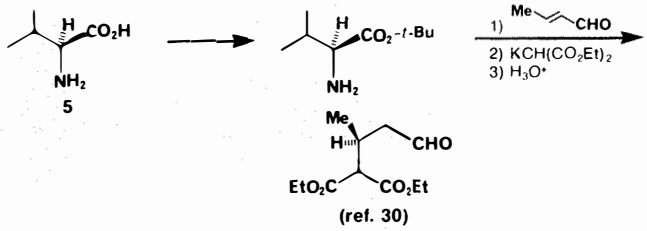
L-(-)-Proline (4):





Also: preparation of chiral α-hydroxy acids,[26] α-amino acids,[27] alkyl methylphenylphosphinates,[28] and prolyl dipeptides.[29]

L-(+)-Valine (5):



D-(+)- and L-(-)-Cystine: studies on the total synthesis of streptogramin antibiotics.[31]

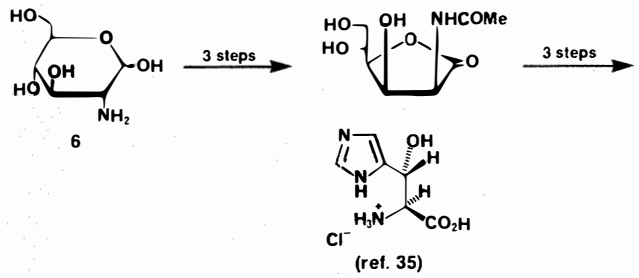
L-(+)-Leucine: preparation of (-)-ipsenol, an active component of a bark beetle aggregation pheromone.[32]

L-(+)-Serine: synthesis of (-)-deoxoprosopinine and (-)-deoxoprosophylline, the unnatural enantiomers of two *Prosopsis* alkaloids.[33]

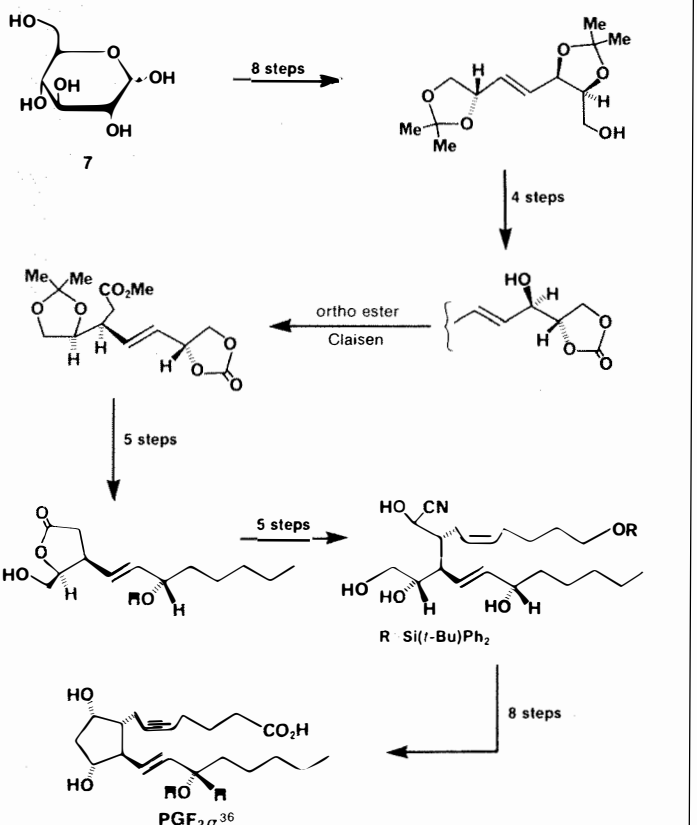
B. Non-nitrogenous (*parent systems*)

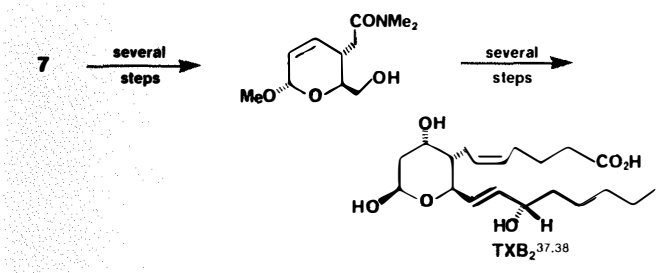
1. Sugars[34]

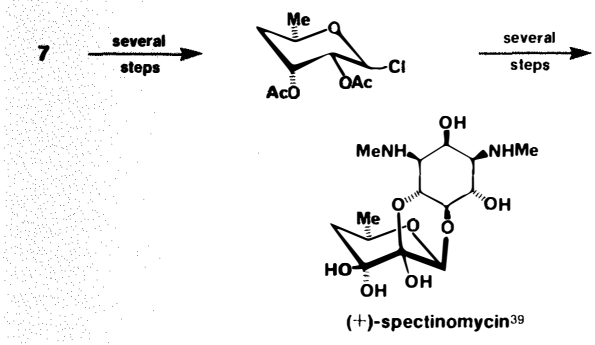
D-(+)-Glucosamine (6):



D-(+)-Glucose (7):

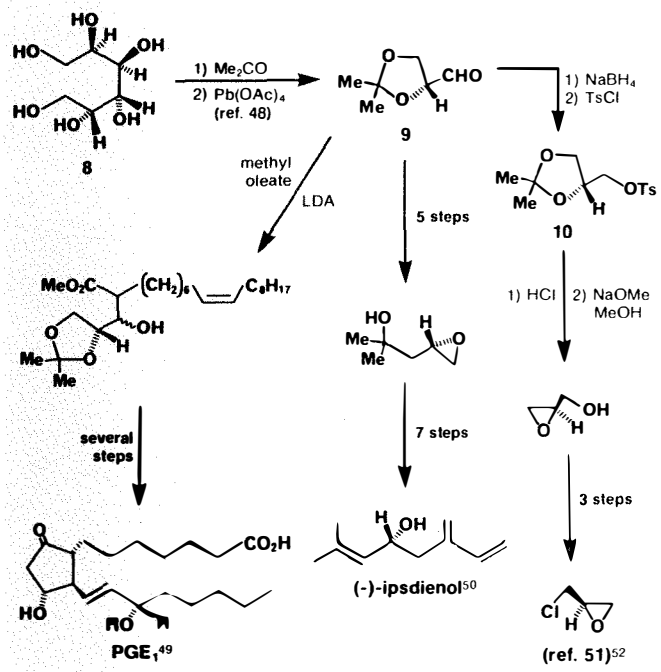






Also: recent total synthesis of anisomycin,[40] (+)-furanomycin,[41] pentenomycin,[40] canadensolide,[42] cerulenin,[43] tetrahydrocerulenin,[44] and (-)-α-multistriatin;[45] and synthesis of macrolide fragments[46] and a variety of chiral pyranones.[47]

D-Mannitol (**8**):



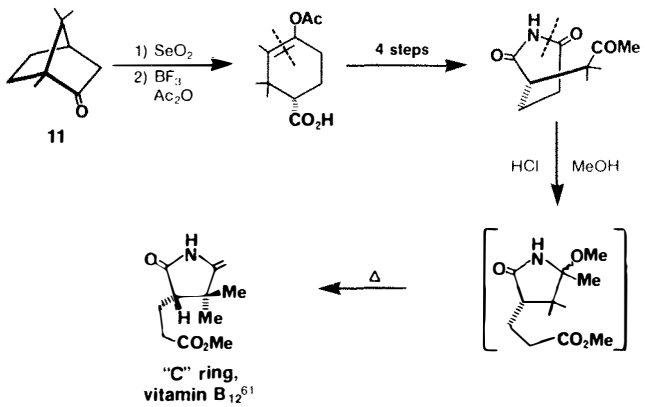
Also: preparation of chiral cryptands,[53] (-)-α-multistriatin,[54] and a variety of chiral epoxides,[55] amino alcohols,[56] and benzodioxans[57] of medicinal interest.

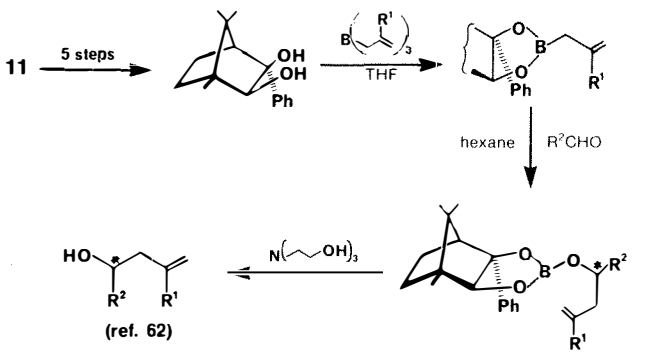
General: preparation of optically active macrocyclic polyethers (*e.g.*, from D-altrose, D-galactose, D-glucose, L-iditol, D-mannitol, D-mannose, and L-threitol)[58] and reducing agents (prepared from a variety of O-protected sugars and $LiAlH_4$[59] or $NaBH_4$[60]).

2. Terpenes

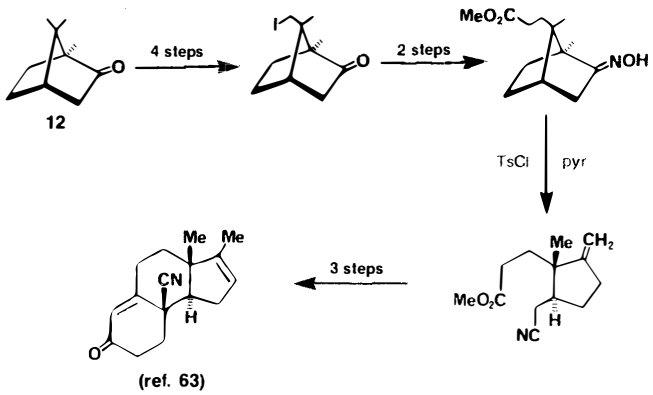
a. Type 

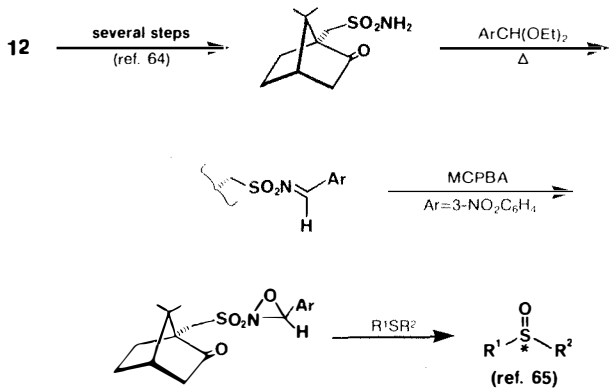
(+)-Camphor (**11**):





(-)-Camphor (**12**):



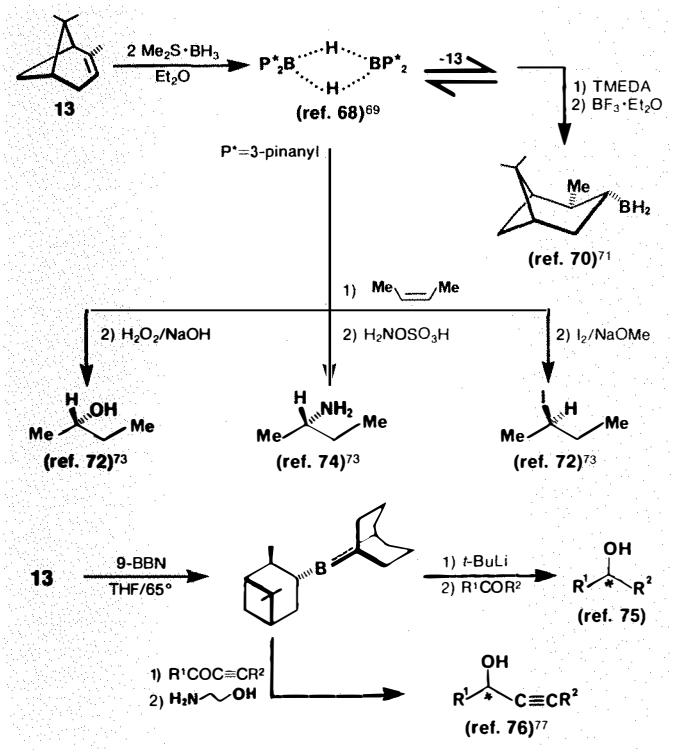


(-)-Borneol: synthesis of cyclopropanes *via* chiral carbenoids.[66]

(-)-Camphene: synthesis of nojigiku, an alcohol found in Japanese chrysanthemum.[67]

b. Type 

(+)-α-Pinene (**13**):

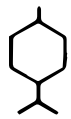


Also: synthesis of chrysanthemic acid derivatives[78] and (+)-*trans*-verbenol, a component of bark beetle pheromone.[79]

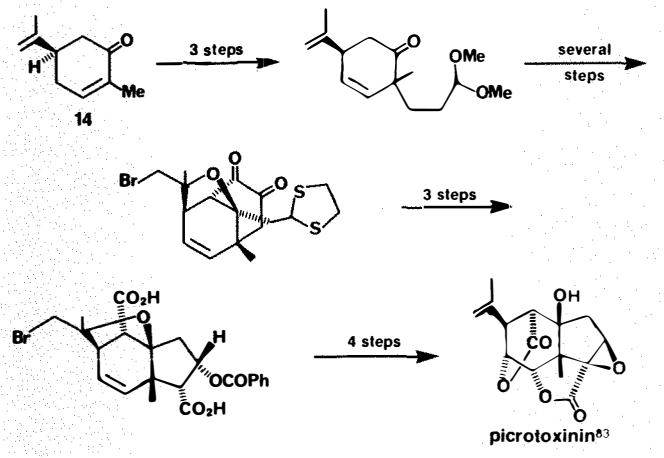
(-)-Nopol: preparation of structural analogs of thromboxane A_2.[80]

(-)-3-Pinanecarboxylic acid: preparation of a chiral oxidizing agent.[81]

(-)-β-Pinene: synthesis of (+)-grandisol, the major component of a male boll weevil pheromone.[82]

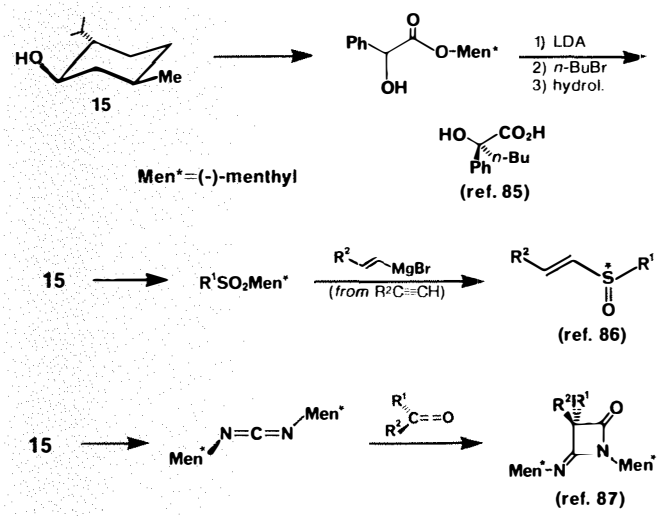
c. Type 

(-)-Carvone (**14**):



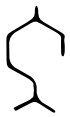
Also: synthesis of (-)-4,11-epoxy-*cis*-eudesmane, the major component of a termite defense secretion.[84]

(-)-Menthol (**15**):

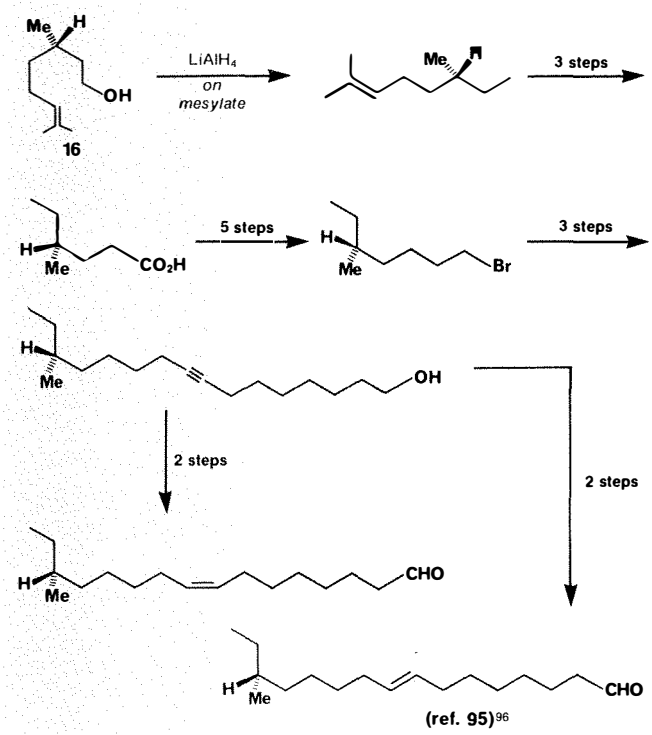


Also: use of menthyl *esters* for the synthesis of optically active β-sulfonyl sulfoxides,[88] sulfoximines,[89] chrysanthemic acids (*via* chiral carbenoids),[90] and (+)-disparlure;[91] asymmetric crossed aldol reactions;[92] and photocycloadditions to produce optically active oxetanes.[93]

(*R*)-(+)-Limonene: synthesis of (*R*)- and (*S*)-*p*-mentha-1,8-dien-4-ol, one of which (not disclosed) is a component of several essential oils and an insect attractant.[94]

d. Type 

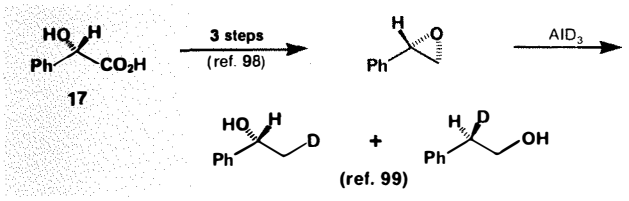
(-)-Citronellol (**16**):



(+)-Citronellol: synthesis of (-)-α-multistriatin.[97]

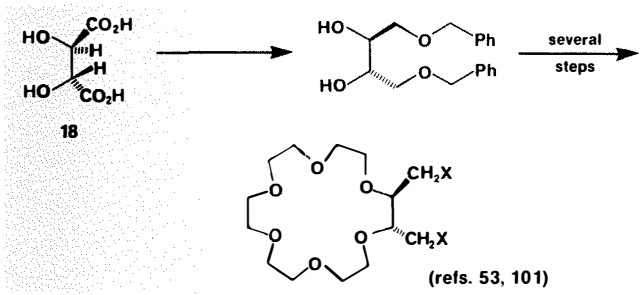
3. α-Hydroxy Acids

(+)-Mandelic acid (**17**):



Also: preparation of deuterated, optically active 2-phenylethanols and phenylethanes.[100]

(+)-Tartaric acid (**18**):

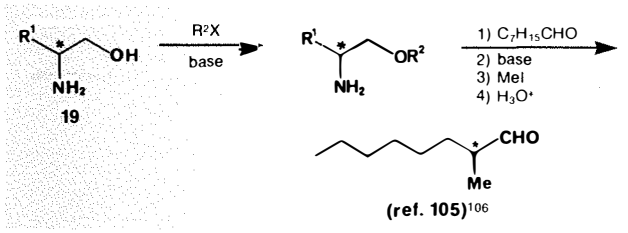


Also: synthesis of prostaglandin intermediates,[102] (+)-disparlure,[103] and optically active 1-benzyloxy-3,4-epoxy-2-butanol, a useful synthon for the preparation of a variety of asymmetric molecules.[104]

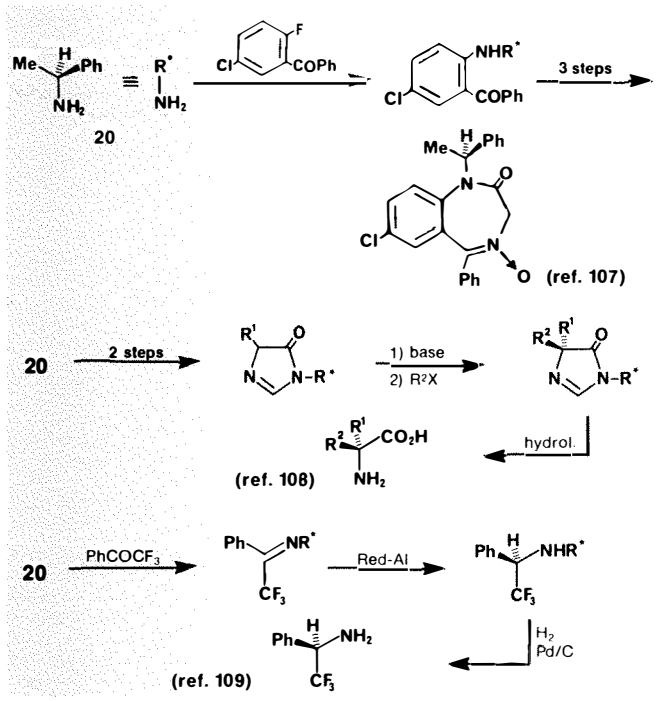
II. Synthetic Products

A. Primary Amines

Ethanolamines (**19**):



(-)-α-Methylbenzylamine (**20**):



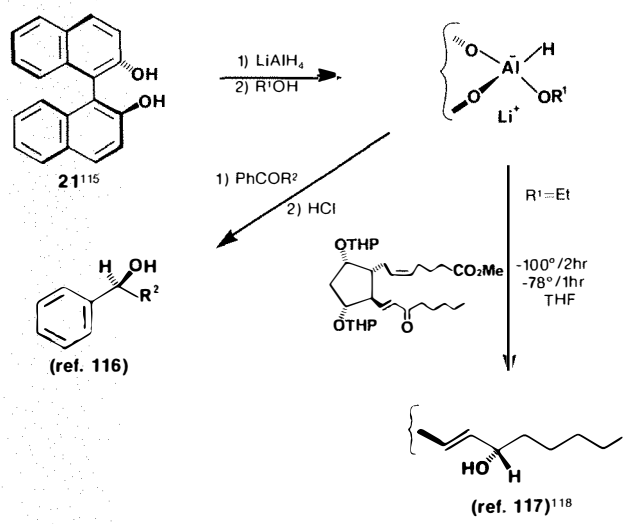
Also: synthesis of stereoisomers of 4-methylcyclophosphamide,[110] optically active aspartic acid[111] and serine[112] (*via* chiral aziridines), and a complex (with $LiAlH_4$) for the asymmetric reduction of ketones.[113] Note that many of the transformations described above have also been effected with the (*R*)-(+)-enantiomer of **20**.

(*R*)-(-)-2-Amino-1-butanol: asymmetric alkylation of cyclohexanone.[114]

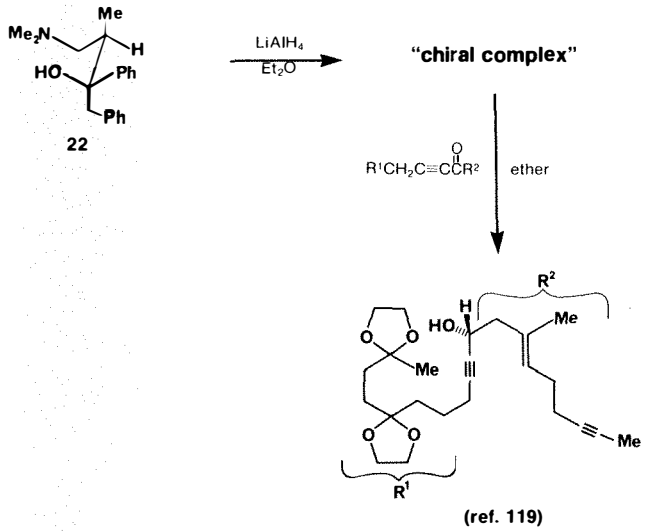
(+)-2-Amino-1-phenyl-1,3-propanediol: preparation of (-)-4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline [see Section IIC].

B. Alcohols

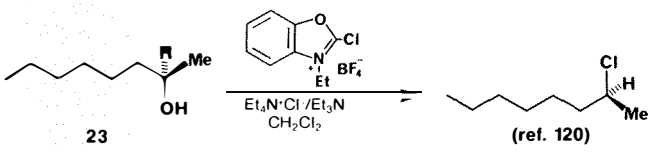
(-)-2,2′-Dihydroxy-1,1′-binaphthyl (**21**):



(+)-4-Dimethylamino-3-methyl-1,2-diphenyl-2-butanol (**22**):



(-)-2-Octanol (**23**):



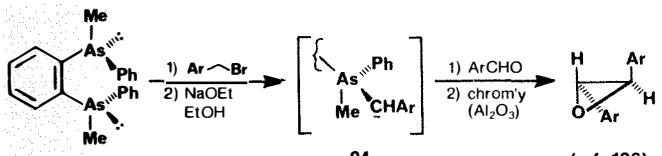
(*S*)-(+)-3-Hydroxy-2-methylpropanoic acid: synthesis of the ionophore antibiotic calcimycin,[121] (*R*)- and (*S*)-muscone,[122] and α-tocopherol.[123]

(*S*)-(-)-2-Methyl-1-butanol: synthesis of *S*-enantiomers of several *Trogoderma* sex pheromone components.[124]

Chiral benzyl alcohols: preparation of optically active β-phenylpropionic acids.[125]

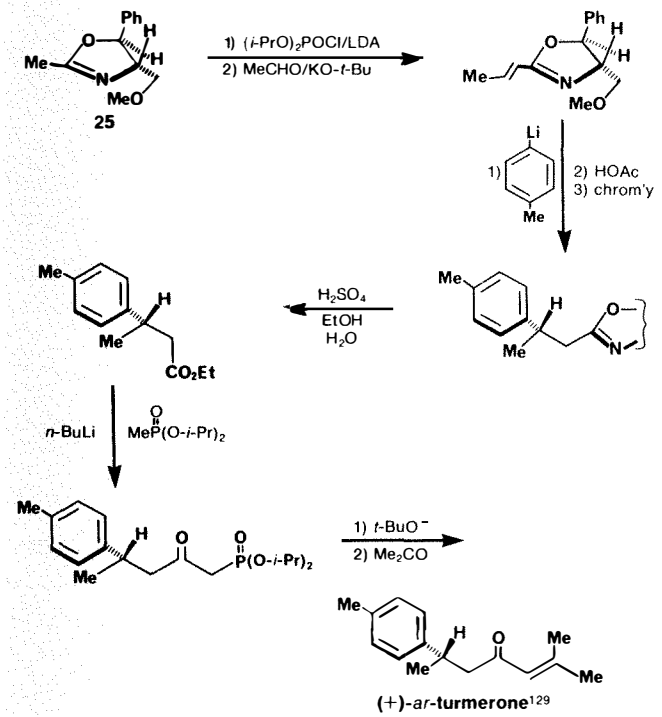
C. Miscellaneous

Arsonium ylides (**24**):



24 **(ref. 126)**

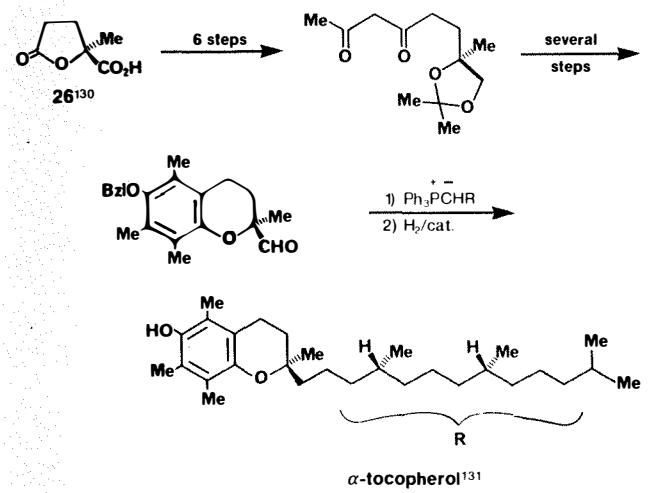
(-)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline (**25**):[127,128]



25

(+)-*ar*-turmerone[129]

(-)-2-Methyl-5-oxotetrahydro-2-furoic acid (**26**):

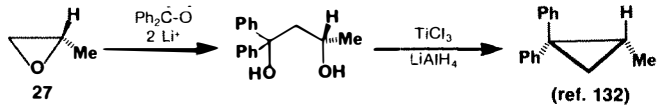


26[130]

α-tocopherol[131]

Also: synthesis of (*S*)-(-)-frontalin, an aggregation pheromone component.[130]

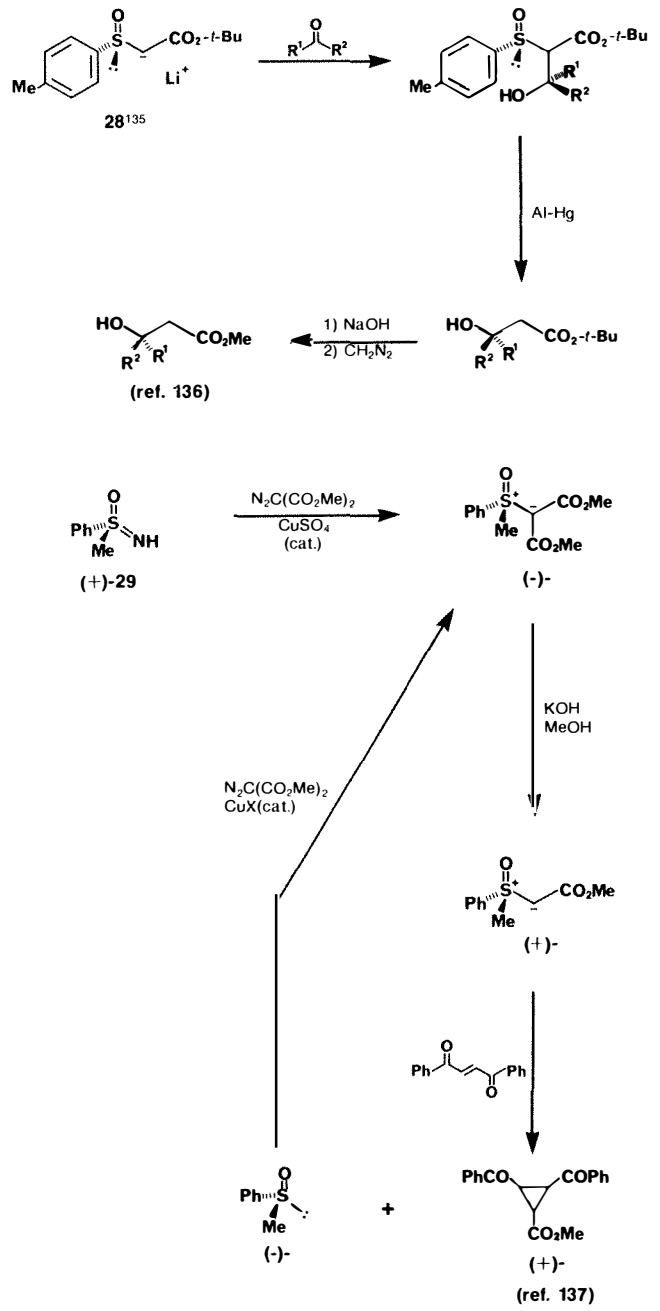
(-)-Propylene oxide (**27**):



27 **(ref. 132)**

(+)-Propylene oxide: synthesis of (*R*)-(+)-recifeiolide, a fungal macrolide.[133]

Sulfur reagents (**28,29**):[134]



28[135]

(ref. 136)

(+)-**29**

(-)-

(+)-

(-)-

(+)-

(ref. 137)

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About the Authors

William A. Szabo received his Ph.D. degree in organic chemistry from the University of Florida in 1974. He did postdoctoral work with Professor Max Tishler at Wesleyan University prior to joining Aldrich in 1976. Dr. Szabo's interests span synthetic and medicinal chemistry, especially the areas of new reagents, synthetic strategy, and drug design.

Helen T. Lee received her Ph.D. degree in synthetic medicinal chemistry from the University of Michigan in 1978 (Professor Joseph H. Burckhalter). She joined Aldrich in 1979 after completing postdoctoral work on the synthesis of oligonucleotides at the Michigan Cancer Foundation. Dr. Lee's research interests include general organic synthesis and the synthesis of biologically active compounds.

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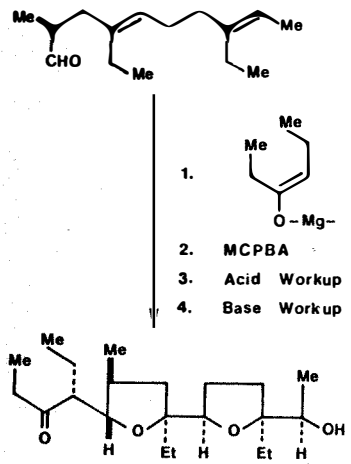


10) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 259 (1979); T. Fukuyama, C.-L.J. Wang, and Y. Kishi, *ibid.*, **101**, 260 (1979); T. Fukuyama, K. Akasaka, D.S. Karanewsky, C.-L.J. Wang, G. Schmid, and Y. Kishi, *ibid.*, **101**, 262 (1979); Y. Kishi, *Lectures in Heterocyclic Chemistry, Vol. 5*, HeteroCorporation, Provo, Utah, 1980.
11) C.T. Buse and C.H. Heathcock, *J. Am. Chem. Soc.*, **99**, 8109 (1977).
12) R.W. Kilb, C.C. Lin, and E.B. Wilson, Jr., *J. Chem. Phys.*, **26**, 1695 (1957).
13) D.R. Herschbach and L.C. Krisher, *ibid.*, **28**, 728 (1958).
14) A.A. Bothner-By, C. Naar-Colin, and H. Guenther, *J. Am. Chem. Soc.*, **84**, 2748 (1962).
15) G.J. Karabatsos, *ibid.*, 89, 1367 (1967).
16) We consider this a case where it would be feasible to extend the chain from left to right, but not from right to left; thus the upper right diastereomer is not enantiomeric with the lower left.
17) H.B. Henbest and R.A.L. Wilson, *J. Chem. Soc.*, 1958 (1957).
18) K.B. Sharpless and R.C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).
19) M.R. Johnson, T. Nakata, and Y. Kishi, *Tetrahedron Lett.*, 4343 (1979); M.R. Johnson and Y. Kishi, *Tetrahedron Lett.*, 4347 (1979).
20) This work was done by Dr. I. Hasan.
21) This work was done by Dr. R.W. Freerksen.
22) The total synthesis of narasin was achieved by Dr. S. Hatakeyama and Mr. M.D. Lewis.

About the Author

Yoshito Kishi was born on April 13, 1937, in Nagoya, Japan. He received the B.S. degree from Nagoya University in 1961, and the Ph.D. degree (Professors Yoshimasa Hirata and Toshio Goto) from the same institution in March 1966. During the period from 1966 through 1969 when he was an Instructor in the Department of Chemistry at Nagoya University, he took a leave of absence to conduct research at Harvard University as a Postdoctoral Fellow with Professor Robert B. Woodward (1966-1968). Upon returning to Nagoya, he was promoted to the position of Associate Professor in the Department of Agricultural Chemistry which he held from 1969 through 1974. Since July 1974, he has been a Professor of Chemistry at Harvard University.

Dr. Kishi has achieved the total synthesis of numerous complex natural products including *Cypridina* luciferin, *Latia* luciferin, echinulin and neoechinulin, tetrodotoxin, sporidesmins, gliotoxins, penam and cephem, octahydrohistrionicotoxin, saxitoxin, mitomycins, lasalocid A, monensin, austamide, gephyrotoxin, narasin and rifamycin S.

His awards include the 1967 Award of the Chemical Society of Japan, the 1972 Asahi Press Award, the 1973 Chunichi Press Award, and the 1980 ACS Award for Creative Work in Synthetic Organic Chemistry. Dr. Kishi has been invited to deliver plenary lectures in his field at numerous U.S. and international conferences. He is a member of the American Chemical Society, the Chemical Society of Japan, The Chemical Society (London) and the Swiss Chemical Society. He has been awarded a Guggenheim Fellowship for 1980.

Lab Notes

Suction filtration of certain solids frequently results in the inconvenience of plugged filter-paper pores.

A dependable and inexpensive solution to this problem involves placing a circular piece of wire gauze (approx. 17 mesh, composed of 0.016-in. wire) between the Buchner funnel and the filter paper. The diameter of the wire gauze should be such that the outer ring of funnel holes is in direct contact with the filter paper, enabling the paper to be seated properly.

The wire gauze serves to distribute the suction more evenly over the filter paper, allowing ease of filtration without embedding the solid in the filter paper and plugging the pores.

Diane Grob Schmidt
Graduate Student
University of Cincinnati
Cincinnati, Ohio 45221

Editor's note:
In an earlier issue of *Aldrichimica Acta* (Vol. 11, Number 4, 1979, p 62) J. A. Peter's lab note suggested the use of zeolite NaA pellets for eliminating water and ethanol in commercial chloroform or carbon tetrachloride. Aldrich offers 4A molecular sieves which can be used for this purpose.

I always read your "Lab Notes" column for ideas and suggestions that I might use in the Chemistry Department stockroom or laboratories. There have been many very good and useful letters over the years. Now I would like to submit an idea that is right in step with the growing trend of conservation or "putting everything to full use."

Since DOT regulations have forced you to make beautiful, sturdy boxes to ship chemicals in, our custodian, Nicholas Szymanski, decided these boxes were much too nice to be thrown away. He makes attractive bird houses out of them at a minimum of cost and effort. (We also save all of the vermiculite packing material for oil spills, insulation and other shipping uses.) Thus we utilize everything we receive from Aldrich.

Aldrich Wooden Shipping Box
Bird House

1. Cut slant from front of box to back so rain will run off roof.
2. Drill a $1^1/_4$-in. hole 3 in. from top (any bigger will allow undesirable birds to enter). Place wooden peg 1 in. below hole.
3. Cut roof from scrap lumber 1 in. larger than box, nail guides on inner surface to secure roof.
4. Cut scrap lumber to fasten house to tree or pole and nail to back of box.
5. Leave natural or use stain.

Sylvia M. Clarke
Chemistry Stores Manager
Chemistry Department
State University College
Fredonia, New York 14063

Single crystals for X-ray diffraction studies are often grown by vapor diffusion of a poorer solvent into a solution of the compound of interest, however the choice of a solvent system is often elusive. In order to minimize the amount of sample (and shelf space) necessary to find a suitable system, I have found that sealed disposable pipettes placed in snap-cap one-dram vials work well. In more detail, a Pasteur pipette is broken at the wide end, at a length slightly less than the height of the vial to be used. The sharp edge of the soft glass is easily sealed with a Bunsen burner, leaving a sample well with a polished opening. This is placed in the one-dram vial which contains the volatile solvent (approx. $^1/_3$ full). The sample solution is added to the well and the vial is capped and placed aside where it will not be disturbed. This system is so small that many vapor diffusion chambers can be simultaneously set up.

If a larger diffusion chamber is desired, I have found that a 200-ml Berzelius beaker and a small (70 x 50mm) crystallization dish (or a #11 rubber stopper) work well. In this case a small (30ml) beaker containing the sample solution is placed inside the Berzelius beaker which is charged with the second solvent. The lip of the Berzelius beaker is smeared with vacuum grease and the inverted crystallization dish is placed on top (or it can be stopped with the rubber stopper). This chamber is advantageous in that it is narrow and doesn't take up much shelf space and at least one other chamber can be stacked on top of it. It is also a very good solvent chamber for TLC.

Robert Nathan Katz
Postdoctoral Research Associate
Department of Chemistry
Columbia University
New York, N.Y. 10027

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red-and-white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Ywa Bader.

After the last catalog, #19, was published in 1978, hundreds of chemists wrote and talked to me about our apparent thoughtlessness in deleting the "Classes of Compounds" section which had been in our catalogs for many years.

We had made a study and had found that only a small proportion of our customers use that section, and so we had taken it out of our catalog and printed it separately, to send to every chemist requesting it. We included a postpaid card in the front of the catalog, for our customers' convenience in ordering the separate supplement, but who looks at postcards?

In our new catalog, just published, we placed that postcard in the very center of the catalog, in the hope that *now* it just couldn't be missed, but again, a number of chemists have wondered why we have not included that section. Just send us the postcard — or any postcard requesting it — and we will send you that supplement.

However, remember that this supplement lists only the compounds in our Catalog/Handbook, not those in our Library of over 23,000 compounds. If you would like a computer printout of *all* compounds of a given class in both the Catalog/Handbook and the Library, we will be happy to send you that specific printout at no charge.

Answering those many chemists was no bother at all, just a pleasure to be able to help.

Recent Developments in the Chemistry of Natural Products[1]

Yoshito Kishi
Department of Chemistry
Harvard University
12 Oxford St.
Cambridge, MA 02138

For the past ten years we have been studying the total synthesis of various natural products. We have emphasized particularly polyfunctional, complex, rather unstable natural products such as tetrodotoxin,[2] sporidesmins,[3] gliotoxin,[4] saxitoxin,[5] and mitomycins.[6] However, about five years ago we decided to add a new topic to our research program; namely, the study of acyclic chemistry. More specifically, we were interested in synthesizing polyketide-derived natural products from acyclic precursors. There are various polyketide-derived natural products which await the synthetic chemist's quest; for example, macrolide antibiotics, ansamycin antibiotics, polyether antibiotics, and so on. We decided to consider polyether antibiotics[7] as our primary synthetic target for the following reasons. First, at the time this project was started, we had never heard of any synthetic studies on polyether antibiotics. Second, polyether antibiotics present a formidable challenge to the synthetic chemist. Four representative polyether antibiotics are listed in Table 1.[7] There are 17 asymmetric centers present in monensin, for example, which means that in principle 131,072 stereoisomers exist for this antibiotic. In the case of lonomycin, the number of possible stereoisomers exceeds 8 million! The total number of isomers for these antibiotics will be infinite if constitutional isomers are counted. Thus, to achieve the total synthesis of one of these antibiotics, it is very important to have a high degree of stereo-, regio-, and chemoselectivity for each step of the synthesis. Third, polyether antibiotics present almost perfect cases for testing principles or synthetic methods for controlling stereo-, regio-, and chemoselectivity in acyclic systems.

In order to propose a sensible and workable scheme for a synthesis, we need to know the answers to three questions:

1) What might be the expected major product for each step of the proposed synthesis?
2) What might be the expected degree of stereo-, regio-, or chemoselectivity?
3) In cases where the selectivity is found not satisfactorily high, what might be the method to improve it?

Judging from experience gained over the past five years, we are now convinced that these three questions can be answered reasonably well even in acyclic systems, and hence syntheses using acyclic compounds can be executed in a stereo- and regiocontrolled manner effectively.

Going back to the synthesis of polyether antibiotics, we did not hesitate in choosing lasalocid A as our first target molecule. At the time this project was begun, we did not have enough confidence to propose the synthesis of complex molecules from a con-

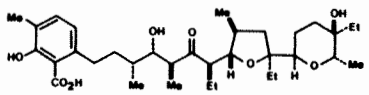
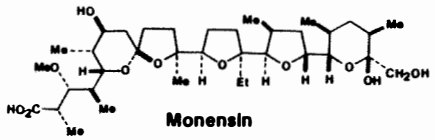
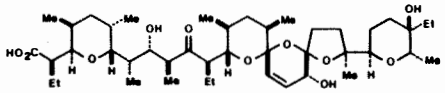
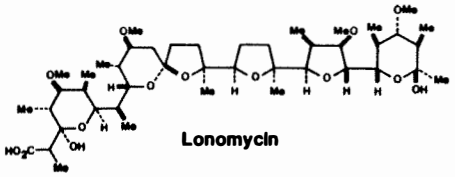
Dr. Yoshito Kishi (left) receiving the ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Irwin Klundt, vice-president of Aldrich.

formationally flexible acyclic precursor. Therefore, we decided to start with a relatively simple molecule. Lasalocid A is one of the simplest polyether antibiotics in terms of the number of asymmetric centers — *only* 10 asymmetric centers exist — yet it has three important functional groups, β-hydroxy ketone, tetrahydrofuran, and tetrahydropyran, commonly found in other naturally occurring polyether antibiotics. Therefore, the synthesis of lasalocid A will be the cornerstone for the synthesis of polyether antibiotics in general. Fortunately the total synthesis of lasalocid A was successfully carried out:[8] the key intermediate isolasalocid ketone was synthesized by three different routes.[9] We were particularly pleased with the route starting with the vinyl ketone, shown in the lower half of Scheme 1. In this synthesis, the isolasalocid ketone was synthesized in 11 steps, including protecting and deprotecting steps, from the vinyl ketone in about 20% overall yield by using only acyclic precursors. The most remarkable aspect of this synthesis is that in terms of stereo-, regio- and chemoselectivity, even the worst step had a product ratio of 10:1.

Encouraged by the successful synthesis of lasalocid A, we then moved to monensin. Again, a very successful conclusion[10] certainly provided more confidence toward this type of approach in organic synthesis. More important, however, during studies for the synthesis of the left half of monensin, we felt able, at least to some extent, to answer the three questions raised previously.

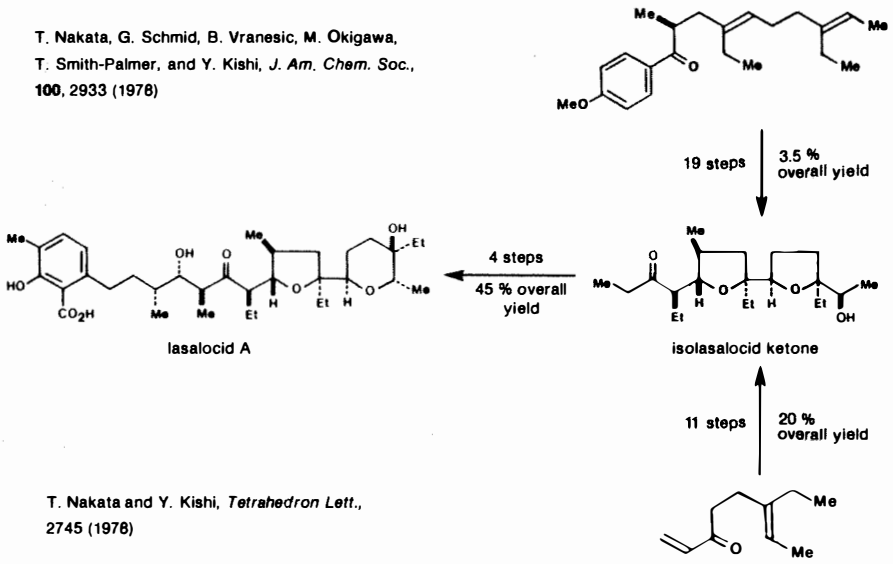
Based on Professor Heathcock's[11] and also our own[8] studies on crossed aldol reactions, we originally considered that the left half of monensin might be synthesized by two crossed aldol reactions as indicated in Scheme 2. Indeed, this was the way we had first synthesized the left half of the antibiotic. However, we were not satisfied since the stereoselectivity of the second crossed

Table 1

Polyether Antibiotics	Number of Asymmetric Centers	Possible Stereoisomers
 Lasalocid A	10	1,024
 Monensin	17	131,072
 Narasin	19	524,288
 Lonomycin	23	8,388,608

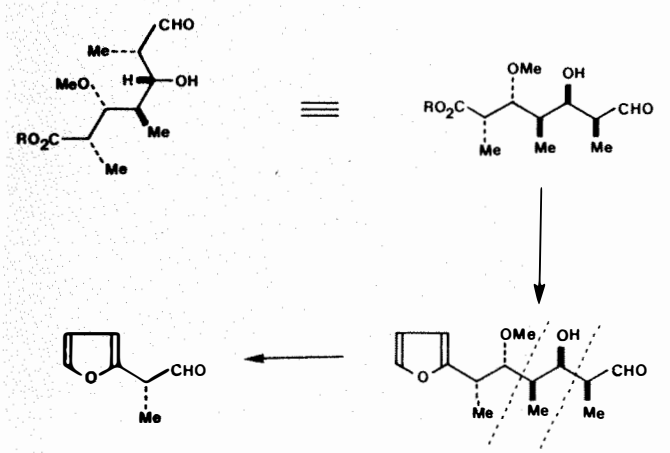
Scheme 1

T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, **100**, 2933 (1978)

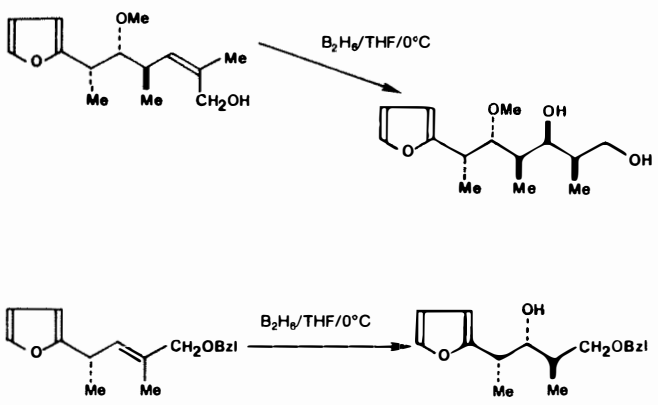


T. Nakata and Y. Kishi, *Tetrahedron Lett.*, 2745 (1978)

Scheme 2

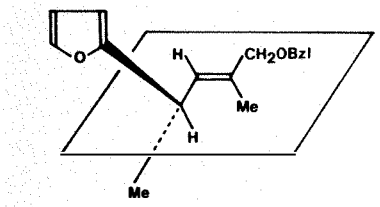


Scheme 3



aldol reaction was only a ratio of 1.8:1 at best. After numerous unsuccessful experiments, we finally discovered a satisfactory method. That was the hydroboration shown in Scheme 3, the stereoselectivity of which was a ratio of 8:1 and 12:1, respectively.

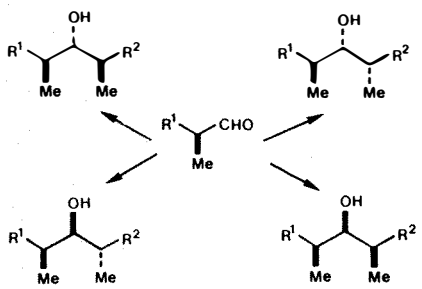
The origin of the remarkable stereoselectivity observed might be related to the conformational preference at the sp^3 and sp^2 centers of the allylic alcohols. According to the pioneering investigations by Wilson,[12] Herschbach,[13] Bothner-By,[14] and others, the preferred conformation of this type of compound is assumed to be eclipsed. Among the three possible eclipsed conformations, the one shown below is assumed most preferred because of the least steric



crowding. Hydroboration is expected to take place from the less hindered side to yield the observed product. The observed phenomena are similar, in a very broad sense, to examples where Cram's rule is applied. Indeed, based on a consideration of the preferred conformation of the carbonyl compounds, some efforts toward the rationalization of Cram's rule have been made by Karabatsos.[15] However, the situation with carbonyl compounds is complicated by the fact that the stability difference among the three eclipsed conformations is relatively small and also that the carbonyl groups are strongly polarized. On the other hand, the situation of the olefinic compounds is simpler, and hence a straightforward analysis based on this picture is possible. We would like to demonstrate the usefulness of this concept with the following example.

The partial structural unit, R^1-CH(Me)CH(OH)CH(Me)-R^2, is often found in important natural products. The three asymmetric centers of this unit give rise to four possible diastereomers[16] as shown in Scheme 4, all of which are known to be partial structures of polyether, ansamycin, or macrolide antibiotics. We have been interested in developing stereo- and regioselective methods for synthesizing these four structural units from the indicated aldehyde, which is readily available in optically active and racemic forms. Through the studies of the monensin synthesis, it has already been shown that the two diastereomers shown in the lower half of Scheme 4 can be synthesized by hydroboration or crossed aldol reactions.

Scheme 4



A proposal for controlling the stereochemistry of the two remaining diastereomers is shown in Scheme 5. Considering the preferred, eclipsed conformation discussed previously, it might be possible to invert the stereochemical outcome of hydroboration by using a polar functional group on group R^1. Thus, the diastereomer shown on the upper left of Scheme 4 would be produced. By changing the stereochemistry of the olefinic bond of the starting material, the diastereomer shown on the upper right of Scheme 4 should be formed. To this end, it should be mentioned that a highly stereoselective synthesis of *cis*-allylic alcohols necessary for these studies, from the indicated aldehydes, has been developed in our laboratories.[10]

In order to examine the aforementioned possibility, we synthesized *trans*- and *cis*-allylic alcohols with R^1=CH_2OH, CH_2OMe, CH_2SMe, or CH_2NMe_2 and studied the stereochemical outcome of hydroboration, using borane complex with tetrahydrofuran, dimethylamine or dimethyl sulfide in various solvents. We uniformly observed that the major product is the one belonging to the diastereomer shown on the lower left of Scheme 4. Under these circumstances, we decided to study the epoxidation reaction, the results of which are summarized in Table 2.[17] The high stereoselectivity observed for the two

Scheme 5

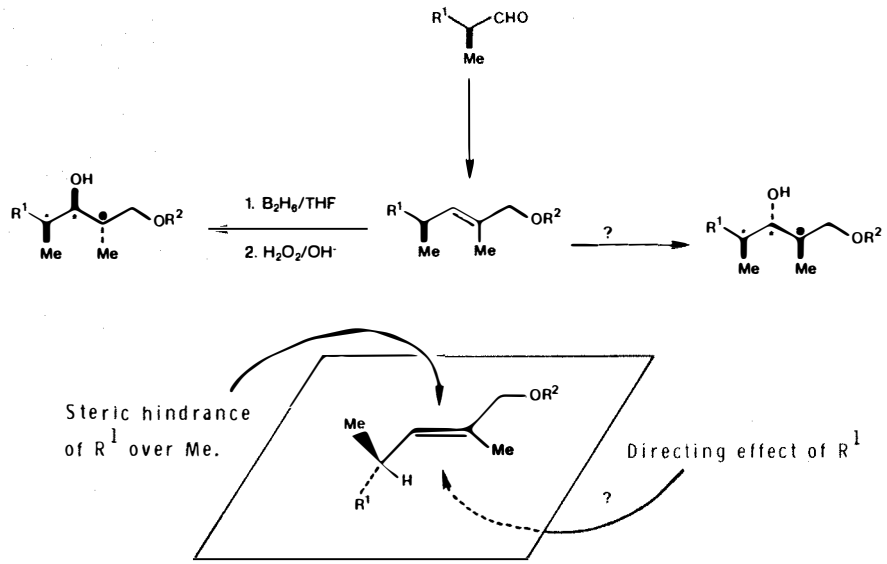
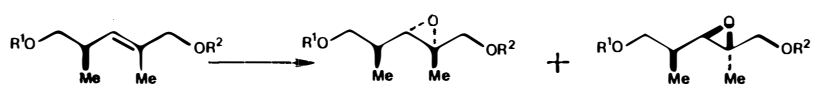
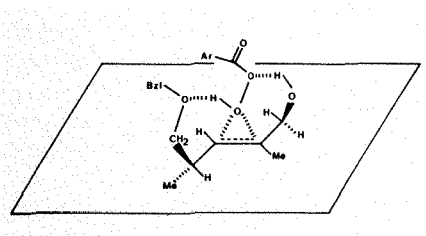


Table 2



R^1	R^2	Ratio (A : B) MCPBA/CH_2Cl_2/0°C	Ratio (A : B) t-BuO_2H/VO(acac)$_2$/C_6H_6/RT
H	H	> 25 : 1	> 25 : 1
H	$C_6H_5CH_2$	6 : 1	> 25 : 1
$C_6H_5CH_2$	H	> 25 : 1 ←	4 : 3
$C_6H_5CH_2$	$C_6H_5CH_2$	1 : 1 (RT)	too slow to measure

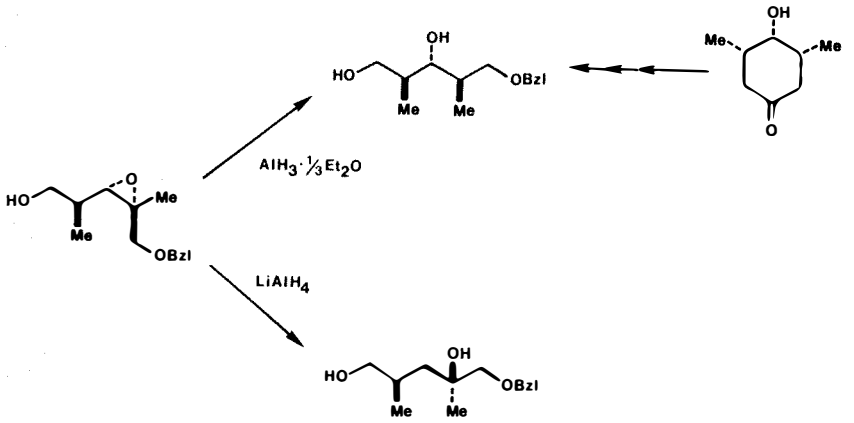
compounds listed on the top two lines is well explained by applying the directing effects recognized by Henbest[17] and Sharpless[18] to the aforementioned preferred, eclipsed conformation of the substrates (*cf.* Scheme 5). The high stereoselectivity observed for the compound listed on the third line, under the conditions indicated by an arrow, was explained by a cooperative effect depicted below. Very similar results were observed for the



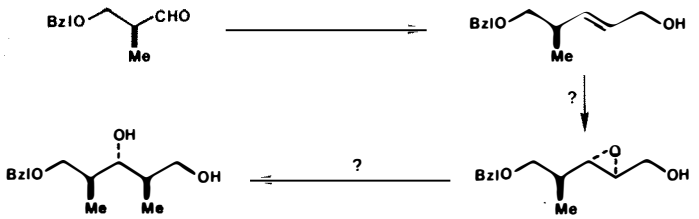
cis-allylic alcohol as well. The stereochemistry assignment of the epoxides was made mainly by chemical methods. For example, the stereochemistry of the major epoxide derived from the *cis*-allylic alcohol was determined by chemical correlation with the cyclohexanone derivative as shown in Scheme 6. Although the aluminum hydride reduction of the epoxide gave the alcohol corresponding to the upper left diastereomer in Scheme 4 as the major product, this procedure was not satisfactory in terms of regio- and stereoselectivity. To overcome this problem, we considered the possibility depicted in Scheme 7. Namely, we hoped that the ring-opening reaction of the epoxide might take place more regio- and stereoselectively. As expected, we could realize a complete regio- and stereospecific ring-opening reaction of the epoxide with lithium dimethylcuprate. The major reason for the observed regiospecificity seems due to the steric hindrance toward the incoming reagent, since the ring-opening reaction of the epoxide shown in the lower half of Scheme 8 gave a mixture of two possible products.

Let us now turn our attention to the stereoselectivity of the epoxidation reaction of the nor- series. The degree of the stereoselectivity of the nor-allylic alcohol shown in Scheme 9 was very low compared with the example discussed before, which is shown again in the lower half of Scheme 9 for comparison purposes. At first glance, the results were very surprising, but we soon realized that they could be explained in terms of the stability difference among the three eclipsed conformations shown in Scheme 10. In the case of R=Me, the conformation **A** is expected to be the most preferred by far, because of considerable steric compression due to the R and methyl

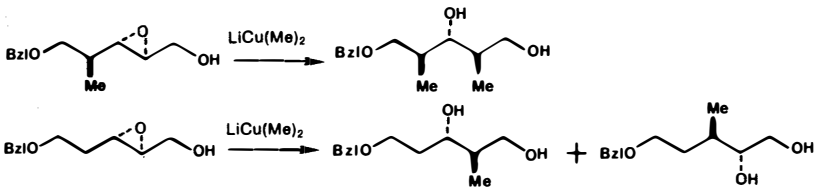
Scheme 6



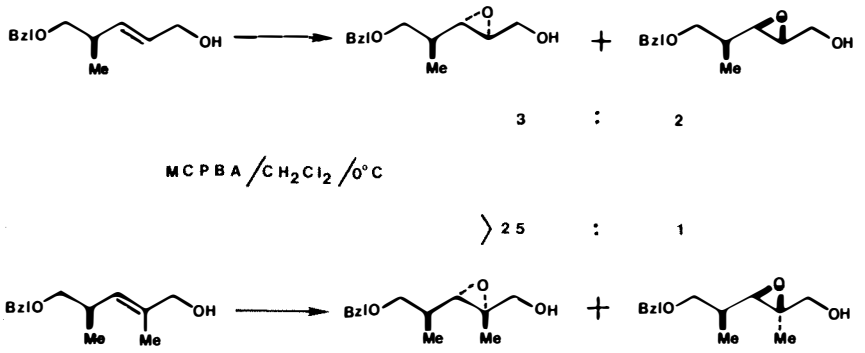
Scheme 7



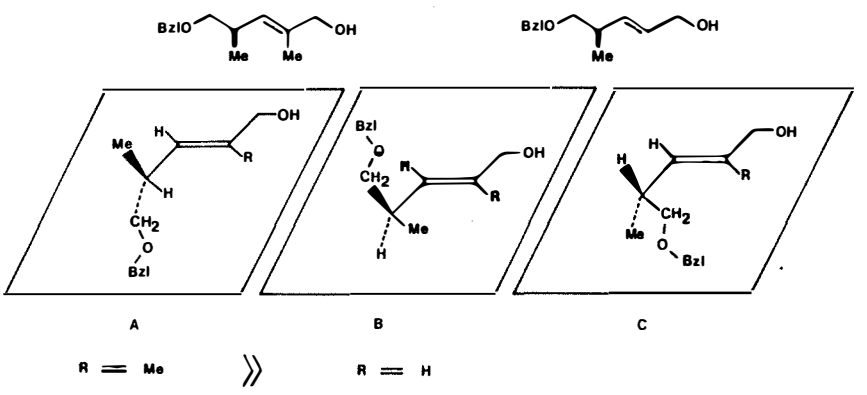
Scheme 8



Scheme 9



Scheme 10



or benzyloxymethyl groups in the conformations **B** or **C**. On the other hand, in the case of R=H, the steric compression due to the R and methyl or benzyloxymethyl groups will be small, hence the stability difference among the three conformations will be small. This could be reflected in the poor stereoselectivity.

Given the explanation above, there are two very obvious methods to be considered to improve this poor stereoselectivity. One is the epoxidation reaction of the nor-*cis*-allylic alcohol shown in Scheme 11. As expected, the alcohol gave a single epoxide, based on NMR analysis of the crude product. In Scheme 12, a complete regio- and stereospecific transformation of the epoxide to the upper right and left diastereomers in Scheme 4, respectively, is summarized.[19]

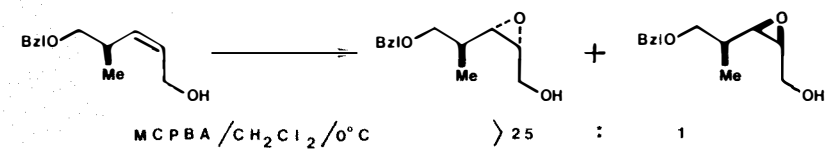
The second possible method to improve the poor stereoselectivity is depicted in Scheme 13. In this scheme, the substituted **X**, desirably bulky, will make one eclipsed conformation preferred over the other two, hence we can expect a highly stereoselective epoxidation. After epoxidation, the C-**X** bond should be replaced by the C-H bond with retention of its stereochemistry. A current literature search made the choice of **X**=$SiMe_3$ seem obvious. To test this possibility, the allylic alcohol with the trimethylsilyl group was stereospecifically synthesized (see Scheme 14). As expected, epoxidation did take place cleanly, and then the carbon-silicon bond was replaced by the carbon-hydrogen bond on treatment with fluoride anion. The overall stereospecificity was excellent; no signals due to other diastereomers were detected in the NMR spectra of the crude product.[20] Thus, it was now possible to synthesize the four diastereomers shown in Scheme 4 in a stereo- and regiocontrolled manner.

Now let us examine the application of the methods we have just discussed.

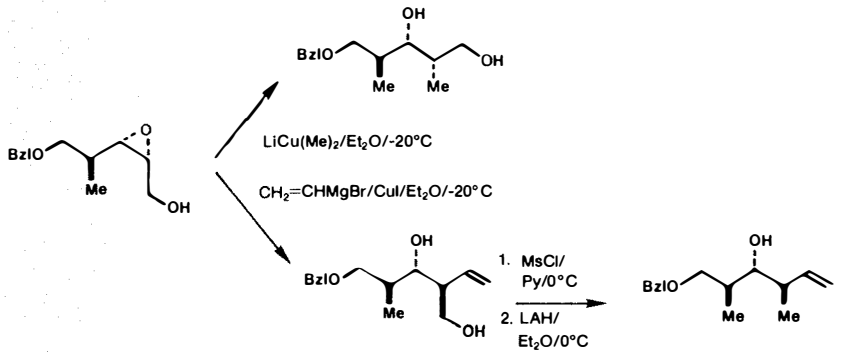
One specific example we would like to discuss briefly is the total synthesis of the polyether antibiotic narasin.[7] In narasin, there are 19 asymmetric centers in addition to one *cis*-olefinic bond. This means that control of more than 1 million stereoisomers is necessary, in principle, to synthesize the antibiotic from acyclic precursors. The first step of our retrosynthesis was the crossed aldol reaction shown in Scheme 16. The feasibility of this type of crossed aldol reaction was well demonstrated in our lasalocid A and monensin syntheses.

The retrosynthesis of the right half from its open form is shown in Scheme 17. Stereocontrolled intramolecular ketaliza-

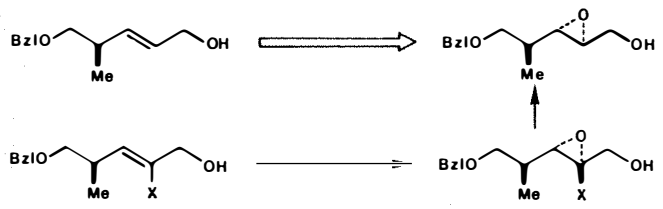
Scheme 11



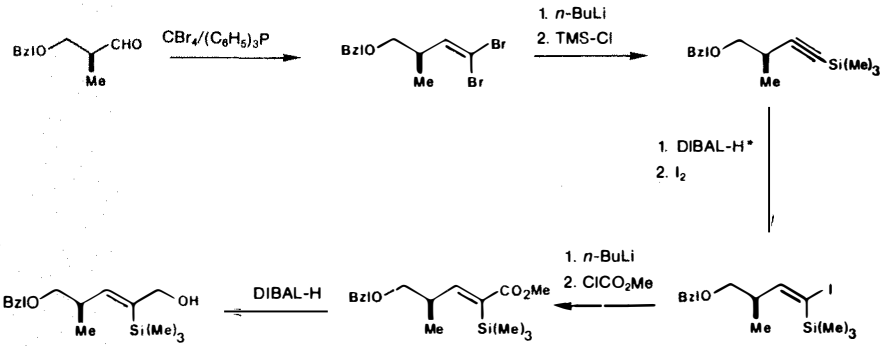
Scheme 12



Scheme 13

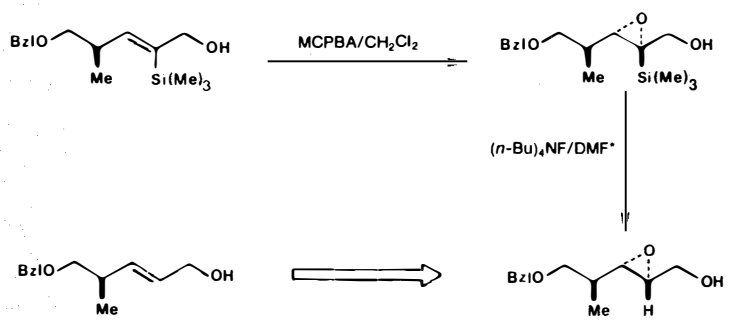


Scheme 14



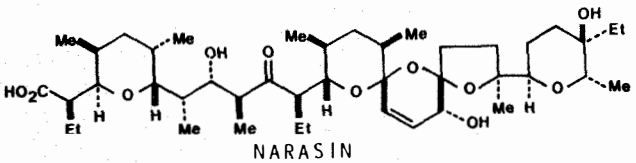
* *cf.* K. Uchida, K. Utimoto, and H. Nozaki, *J. Org. Chem.*, **41**, 2215 (1976)

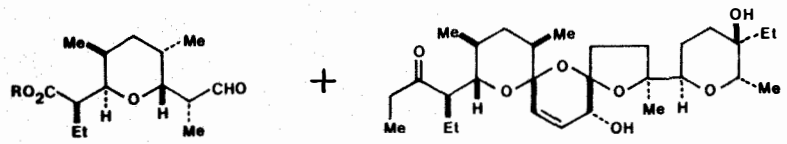
Scheme 15



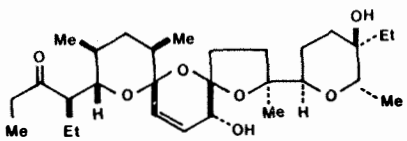
* *cf.* T. H. Chan, P. W. K. Lau, and M. P. Li, *Tetrahedron Lett.*, 2667 (1976)

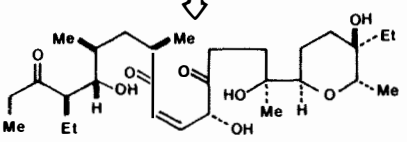
Scheme 16

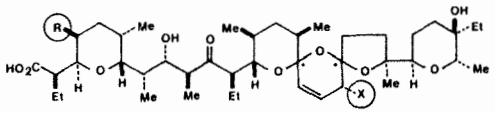




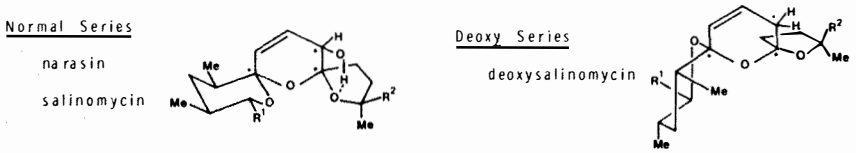
Scheme 17







NARASIN	R = Me,	X = OH
SALINOMYCIN	R = H,	X = OH
DEOXYSALINOMYCIN	R = H,	X = H

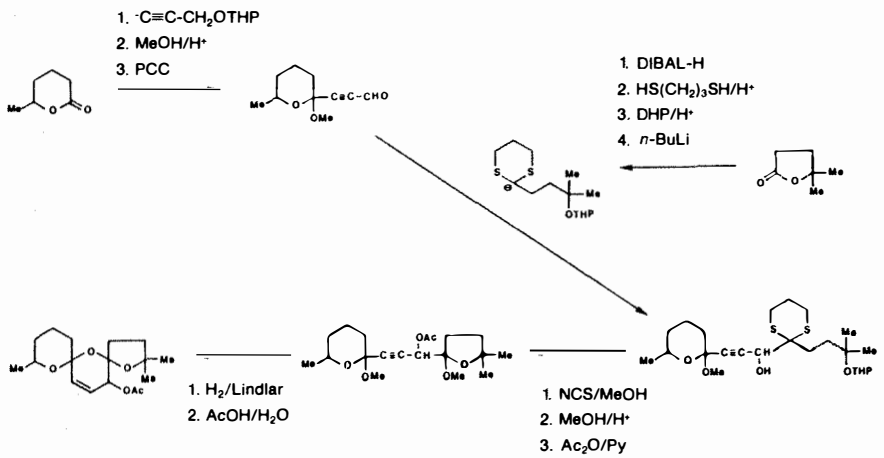


tion under thermodynamically controlled conditions, somewhat similar to the proposed retrosynthesis, was one of the key steps of our monensin synthesis. However, the present case is more complicated than the monensin case, since the relative stability of the desired and undesired stereoisomers with respect to two spiro ketal centers is obscure. In relation to this problem, it is important to mention the relative stereochemistry at the two spiro ketal centers of narasin, salinomycin, and deoxysalinomycin; namely, it is known that narasin and salinomycin have the same relative stereochemistry, while that of deoxysalinomycin is different. The dipole-dipole interaction of the two carbon-oxygen bonds in the narasin and salinomycin series seems to be thermodynamically unfavorable. Nonetheless, a review of the extraction procedure of these antibiotics makes it hard to believe that narasin or salinomycin would have thermodynamically unfavorable relative stereochemistry. We believed that the indicated hydrogen bond stabilization would override a seemingly unfavorable dipole-dipole interaction at the bisspiro center of the narasin and salinomycin series. Indeed, we could recently demonstrate that this was the case. Analysis of the stereoview of the bisspiro center of narasin clearly indicated the possibility that the allylic alcohol group could stereoselectively be introduced by kinetically controlled reduction of the corresponding α,β-unsaturated ketone.

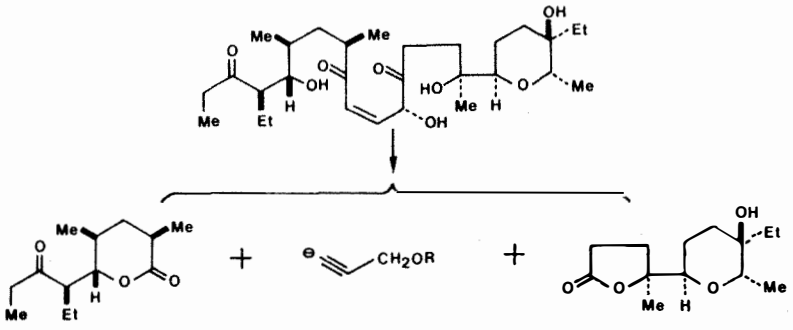
Regarding the possible synthetic route of the open form and its cyclization to the bisspiro ketal, an efficient method shown in Scheme 18 was developed by using the model system.[21] It is important to protect the allylic alcoholic group to avoid the aromatization to a furan.

Supported by successful results in the model system, the open form of the right half can now be disconnected into three segments as seen in Scheme 19. The lactone of the right side is structurally very similar

Scheme 18



Scheme 19



to lasalocid A ketone, which has already been synthesized in our laboratory (see Scheme 20).[8] Indeed, the synthesis of this lactone was straightforward.

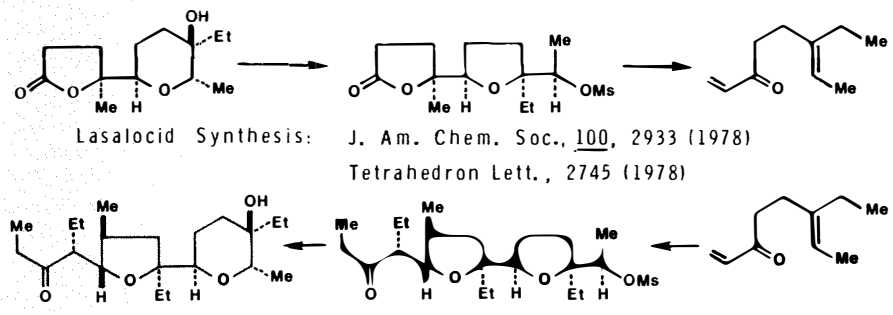
It seemed that the tetrahydropyran ring of the left half of narasin might be constructed from the properly functionalized 1,5-diol system as depicted in Scheme 21. There are two options available for this disconnection, but we chose the one shown at the left. The reason for this decision should be obvious when one recognizes the structural similarity between the left and middle segments; these segments share the same five carbon atoms indicated by asterisks in the following structures.

Relying on the methods discussed previously, a straightforward retrosynthesis of these segments can be envisioned. In the upper half of Scheme 22, a retrosynthesis of the left segment is summarized. The first disconnection utilized the hydroboration method. To continue the disconnection along this line, a hydroxyl group must be put temporarily at the methylene carbon. In the actual synthesis, this type of hydroxyl group used as a handle can smoothly be removed by mesylation, followed by hydride reduction, in excellent overall yield. There are two options available for this purpose, but we chose the diastereomer shown in the right hand corner of the second line for the following reason. The stereoselectivity of method B — epoxidation followed by cuprate reaction — is extremely high, while the stereoselectivity of method A — hydroboration — is a range of 12~4:1, depending on substrates. In the lower half of Scheme 22, a retrosynthesis of the middle segment — note the structural similarity between the middle segment Prelog-Djerassi lactonic acid — is summarized, which is nearly identical to the one shown for the left segment.

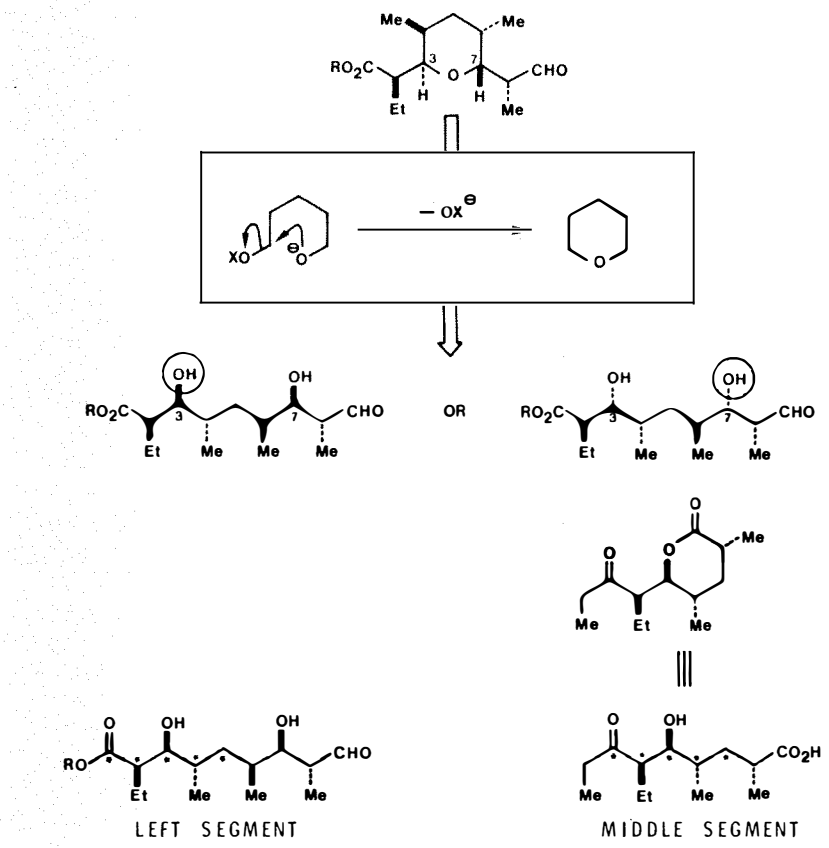
Following the proposed schemes, we have recently completed a stereocontrolled total synthesis of narasin,[22] although improvements on some steps are still needed. For example, at the present moment, the cyclization reaction to construct the tetrahydropyran ring is not satisfactorily effective enough, but we are very optimistic about improving this step.

In closing, I would like to take this opportunity to express my sincere appreciation to all of my former and present group members. Needless to say, it would be impossible to carry out any single synthesis to its successful completion without their commitment, enthusiasm, and devotion to chemistry. Financial support from the National Institutes of Health (NS 12108) and the National Science Foundation (CHE 7806296) is gratefully acknowledged.

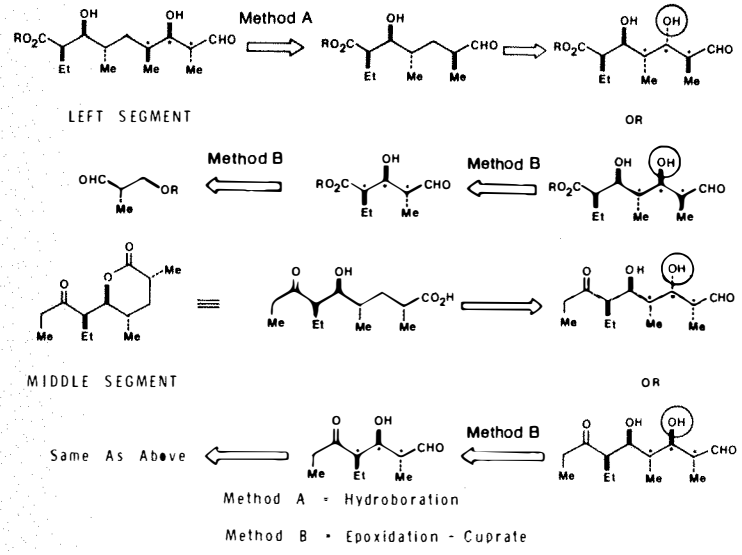
Scheme 20



Scheme 21



Scheme 22



Hydrazine — Rocket Fuel to Synthetic Tool

Henry W. Schiessl
Olin Corporation
Chemical Research Building
275 Winchester Ave.
New Haven, CT 06511

I. INTRODUCTION

Hydrazine, NH_2NH_2, is the simplest diamine and is unique in its class because of the N-N bond. It was first prepared by Curtius in 1887, though many of its derivatives were already known by then. Subsequently, Raschig[1] made it by the oxidation of ammonia with hypochlorite *via* the intermediate formation of chloramine as the aminating agent (eq. 1a and 1b).

$$NH_3 + NaOCl \longrightarrow NH_2Cl + NaOH \quad \text{(eq. 1a)}$$

$$NH_3 + NH_2Cl + NaOH \longrightarrow N_2H_4 + NaCl + H_2O \quad \text{(eq. 1b)}$$

To this day, it is still prepared commercially by the oxidation of ammonia, either with hypochlorite or with hydrogen peroxide.[2] Production capacity in the U.S.A. (1980) is about 38 million lbs; capacity in Europe and Japan brings the total to nearly 80 million lbs. In the U.S.A., it is available in an anhydrous form as well as in aqueous solutions of 64-, 54.4- and 35-wt. % N_2H_4. Catalyzed hydrazine solutions are also produced for specialized applications. Among the hydrazine salts, the sulfate, chloride and bromide are commercial products. The simple alkyl derivatives, monomethylhydrazine and 1,1-dimethylhydrazine are also produced on a large scale.

Hydrazine found its first significant application during World War II as a fuel component for the German rocket-powered ME-163 fighter plane. As such, it has since played an important role in U.S.A. space and military applications; however, its chemical uses now far surpass its use as a fuel. The areas in which hydrazine and its derivatives have found applications include:

- Fuels - in aerospace and fuel cells,
- Corrosion inhibitors and antioxidants,
- Scavenger of dissolved oxygen in hot water and boiler systems,
- Agricultural pesticides and plant-growth regulators,
- Polymers - as monomers, cross-linking agents, chain extenders, stabilizers and foaming agents,
- Dyes and photography,
- Pharmaceuticals,
- Metal reduction to form mirrors, noble metal catalysts, etc.,
- Hydrogenation of organic functional groups,
- Explosives, and others.

Several books[3,4] and reviews[5-9] have been written on the chemistry of hydrazine.

II. CHEMICAL AND PHYSICAL PROPERTIES

Hydrazine is a colorless, fuming liquid (m.p. 2.0°C, b.p. 113.5°C) with an ammoniacal odor. It dissolves in polar solvents such as water, alcohols, ammonia, and amines. The melting-point diagram for the hydrazine-water system indicates compound formation at 64 wt. % N_2H_4, the so-called hydrazine hydrate, $N_2H_4 \cdot H_2O$, with a melting point of -51.7°C. At 1 atm, hydrazine and water form a high-boiling azeotrope (120.5°C, 58.5 mole % N_2H_4).

The salient properties that determine the chemistry as well as the applications of hydrazine can be grouped under the following headings:

Endothermic	Reductant
Base	Oxidant
Difunctional	Nucleophile

The use of hydrazine as a fuel in rocketry and in fuel cells depends in large measure on its endothermic nature (+12.1 kcal per mole). However, anhydrous hydrazine is thermally quite stable (250°C) and not at all shock-sensitive. Certain metals (molybdenum, iridium) and oxides (iron oxide) significantly lower the decomposition temperature and must be avoided when working with high-strength hydrazine solutions. Hydrazine vapors are somewhat more hazardous. Explosive limits in air are 4.7-100 vol. %. Certain diluents (nitrogen, helium, water vapor) reduce the explosive range considerably.[10] Anhydrous hydrazine has a flash point of 52°C; the 64% aqueous solution, 72°C; and below a concentration of 40%, there is no flash point.

Hydrazine is a base, slightly weaker than ammonia. Basicity decreases with alkyl substitution,[11] but the nucleophilicity of the substituted nitrogen increases, so that further alkylation occurs on the substituted nitrogen to give 1,1-dialkylhydrazines (**1**) and 1,1,1-trialkylhydrazinium salts (**2**).

R_2NNH_2 (**1**) R=alkyl $R_3\overset{+}{N}NH_2\ X^-$ (**2**)

Salts are also formed with organic and inorganic acids. From hydrochloric acid, for example, it is possible to make both the monohydrochloride and the dihydrochloride (eq. 2).

$$N_2H_4 \xrightarrow{HCl} N_2H_5^+\ Cl^- \xrightarrow{HCl} N_2H_6^{++}\ 2Cl^- \qquad \text{(eq. 2)}$$

Salts with the $N_2H_6^{++}$ cation exist only in the solid state or in highly concentrated acid solutions. Hydrazinium salts are generally white, crystalline solids stable at room temperature. Oxidizing anions such as nitrate and perchlorate lead to instability. With the exception of monohydrazinium sulfate, the common salts are fairly soluble in water. The hydrochloride and hydrobromide are excellent soldering fluxes.[12] These salts are often convenient sources of "anhydrous" hydrazine. With essentially no vapor pressure, they do not pose the inhalation toxicity hazard of hydrazine itself, although precautions must be taken against dust inhalation.

With alkali metals, anhydrous hydrazine acts as a proton donor to form the hydrazide anion (eq. 3). These metal

$$2Na + 2N_2H_4 \longrightarrow 2Na^+ + 2N_2H_3^- + H_2 \qquad \text{(eq. 3)}$$

hydrazides have received only passing attention,[13-17] no doubt due to their sensitivity to water and air. The hydrazide ion, however, is more nucleophilic than is hydrazine itself and will undergo reactions that hydrazine will not, for example, addition across nonactivated olefinic bonds.[16]

Hydrazine and its salts are good reducing agents as indicated by their standard redox potentials (eqs. 4 and 5).[18] Clearly,

$$N_2H_4 + 4OH^- \longrightarrow N_2 + 4H_2O + 4e^- \qquad \text{(eq. 4)}$$

$E^\circ = +1.16v.$

$$N_2H_5^+ \longrightarrow N_2 + 5H^+ + 4e^- \qquad \text{(eq. 5)}$$

$E^\circ = +0.23v.$

hydrazine is a much better reducing agent in alkaline solution than in acid. Hydrazine is isoelectronic with hydroxylamine and also with hydrogen peroxide and can act as an oxidizing agent (eqs. 6 and 7).[18]

$$N_2H_4 + 2H_2O + 2e^- \longrightarrow 2OH^- + 2NH_3 \qquad \text{(eq. 6)}$$

$E^\circ = +0.1v.$

$$N_2H_5^+ + 3H^+ + 2e^- \longrightarrow 2NH_4^+ \qquad \text{(eq. 7)}$$

$E^\circ = +1.275v.$

Although they are thermodynamically favorable, especially in acid solution, there are few examples of such reactions, indicating that they are perhaps kinetically limited for lack of an appropriate catalyst.

III. INORGANIC REACTIONS

Hydrazine reacts with oxygen to form nitrogen and water (eq. 8). This is the basis

$$N_2H_4 + O_2 \longrightarrow N_2 + 2H_2O \qquad \text{(eq. 8)}$$

for its use as a corrosion-control agent in boilers and hot-water heating systems, by scavenging dissolved oxygen in the water. Theoretically, equal parts by weight of hydrazine and oxygen react; however, systems protected with hydrazine are normally operated with a slight residual excess. The reaction is somewhat slow at lower temperatures; therefore, catalyzed compositions to overcome this deficiency are on the market. The same reaction occurs in the hydrazine fuel cell operating on air,[19] as well as in bipropellant rocket systems using liquid oxygen as the oxidizer.

Hydrazine reduces many metal ions to lower valence states or to the metals themselves, depending on reaction conditions. Audrieth[4] has reviewed the older literature covering the following metals:

Antimony	Iron	Platinum
Arsenic	Lead	Polonium
Bismuth	Manganese	Selenium
Cerium	Mercury	Silver
Chromium	Molybdenum	Tellurium
Cobalt	Nickel	Tin
Copper	Osmium	Vanadium
Gold	Palladium	

In aqueous, acidic solution, chromate is reduced to the Cr(III) stage (eq. 9).[20] Under basic conditions, the reaction proceeds with precipitation of chromium(III)

$$4HCrO_4^- + 3N_2H_5^+ + 13H^+ \longrightarrow 4Cr^{+3} + 3N_2 + 16H_2O \qquad \text{(eq. 9)}$$

hydroxide, providing an effective means for removing chromate from waste waters such as those arising in chrome-plating and metal-treating operations.[21]

Hydrazine is useful for the electroless plating on metal or nonmetallic surfaces of such metals as copper,[22,23] nickel,[24] stainless steel[25] and silver.[26] Finely divided powders of cobalt,[27] gold,[28] selenium[29] and silver[30] can be prepared by reduction of the salts with hydrazine. Mercury compounds can be removed and recovered from waste waters by hydrazine reduction and separation.[31] Noble metal catalysts such as platinum[32] and palladium[33] are prepared by reduction with hydrazine to form finely dispersed or colloidal particles. Mo(VI) is reduced by hydrazine to Mo(V) and Mo(III);[34] vanadium(V) to (III)[35] and uranium(VI) to (IV), a procedure potentially useful in the extractive metallurgy of uranium[36] as well as in the recovery of spent nuclear fuel.[37] Silicon metal may be etched by aqueous hydrazine for use in integrated circuitry[38] or in solar cells.[39]

At elevated temperatures and pressures (such as in steam boilers), hydrazine *oxidizes* iron to form a magnetite surface (eq. 10) and *reduces* ferric oxide (rust), also to magnetite (eq.11).

$$3Fe + 4N_2H_4 + 4H_2O \longrightarrow Fe_3O_4 + 8NH_3 \qquad \text{(eq. 10)}$$

$$6Fe_2O_3 + N_2H_4 \longrightarrow 4Fe_3O_4 + N_2 + 2H_2O \qquad \text{(eq. 11)}$$

Carbon dioxide and carbon disulfide react with hydrazine to give carbazic acid (**3**) and dithiocarbazic acid (**4**), respectively.

$NH_2NHCOOH$ (**3**) $NH_2NHCSSH$ (**4**)

These compounds undergo many of the typical reactions of hydrazine (acylation, hydrazone formation, etc.) as well as those of organic acids (for example, ester formation). They are, therefore, valuable intermediates in the synthesis of numerous derivatives, especially in the preparation of heterocyclics such as oxadiazoles and thiadiazoles.

Sulfur dioxide and hydrazine react in alcoholic solution to form insoluble hydrazinium sulfite, $(N_2H_5)_2SO_3$. With thionyl chloride, and calcium oxide as HCl acceptor, hydrazine gives the calcium salt of hydrazinemonosulfinic acid (eq. 12), an

extremely strong reducing agent.[40]

$$2SOCl_2 + 2N_2H_4 + 3CaO \longrightarrow \quad \text{(eq. 12)}$$
$$Ca(NH_2NHSO_2)_2 + 2CaCl_2 + H_2O$$

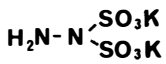
The corresponding hydrazinesulfonic acids and their salts are prepared in a number of ways. The monosulfonic acid **5**

$$H_2N\text{-}NH\text{-}SO_3H$$
5

is formed from hydrazine and SO_3. Dihydrazinium sulfate and chlorosulfonic acid in pyridine yield the symmetrical hydrazinedisulfonic acid **6** as the pyridine

$$N_2H_5^+ + 2ClSO_3H \longrightarrow \quad \text{(eq. 13)}$$
$$HO_3SNH\text{-}NHSO_3H + 2HCl + H^+$$
6

salt (eq. 13). The unsymmetrical di-(**7**) and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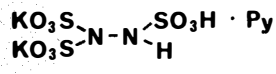
the trisulfonic acids (**8**) have been prepared as potassium or pyridine salts. The final member of this series, the hydrazinetetrasulfonic acid (**9**), is best prepared by anodic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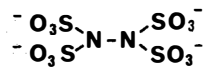

9

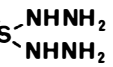
oxidation of salts of imidodisulfonic acid, $N(SO_3)_2^{-3}$.[41] Ammonolysis of **9** gives hydrazine (eq. 14). As is typical of com-

$$(9) + 4NH_3 \longrightarrow \quad \text{(eq. 14)}$$
$$N_2H_4 + 4NH_2SO_3^-$$

pounds with the -NH-NH- group, *sym*-hydrazinedisulfonic acid (**6**) can be oxidized by KOCl to the -N=N- derivative, in this case the yellow, insoluble and very explosive potassium salt of azodisulfonic acid (**10**).

$$KO_3SN = NSO_3K$$
10

Sulfuryl halides and hydrazine form sulfuryl hydrazide (**11**), a compound stable to aqueous alkali but subject to rapid acid hydrolysis.[42]


11

Phosphoric acid forms salts with hydrazine. With phosphoryl or thiophosphoryl halides (**12**), the corresponding hydrazides (**13**) are obtained (eq. 15),

$$R_nPX_{(3-n)} \xrightarrow{N_2H_4} R_nP(NHNH_2)_{3-n} \quad \text{(eq. 15)}$$
(Y = O or S)
12 **13**

X = halide
n = 0,1,2
Y = O,S

where R can be any of a large number of organic groups. Such compounds (Y=S) and their hydrazone derivatives have undergone study in the treatment of carcinomas.[43] Phosphoryl trihydrazide (**14**) is obtained from phosphoryl trichloride and anhydrous hydrazine at -12°C in ether (eq. 16).[44] This is a white, crystalline solid, fairly

$$POCl_3 + 6N_2H_4 \longrightarrow \quad \text{(eq. 16)}$$
$$O=P(N_2H_3)_3 + 3N_2H_5Cl$$
14

stable in aqueous base; in acid solutions, it hydrolyzes to phosphoric acid and the hydrazinium ion, $N_2H_5^+$. Thiophosphoryl trihydrazide (**13**, n = 0, Y = S) has been prepared from anhydrous hydrazine and SPF_3.[45]

Hydrazine-borane compounds are made by reaction of sodium borohydride and a hydrazine salt (chloride, bromide or sulfate) in THF.[46,47] The mono-and diadducts are obtained, depending on reaction conditions (eq. 17 and 18). These compounds

$$NaBH_4 + N_2H_4 \cdot HCl \longrightarrow \quad \text{(eq. 17)}$$
$$N_2H_4 \cdot BH_3 + NaCl + H_2$$

$$2NaBH_4 + N_2H_4 \cdot H_2SO_4 \longrightarrow \quad \text{(eq. 18)}$$
$$N_2H_4 \cdot 2BH_3 + Na_2SO_4 + 2H_2$$

have been suggested as rocket fuels,[48] stabilizers for polyacrylonitrile[49] and for chemical deposition of nickel-boron alloys on nonmetallic surfaces.[50] Polymeric salts of the form $(N_2H_4BH_2X)_n$ have also been reported.[51]

In reactions with transition metals, hydrazine frequently does not act as a reducing agent but rather as a ligand to form complexes. This rather broad area of hydrazine chemistry was reviewed earlier by Audrieth[4] and recently by Bottomley[52] and Dilworth.[53]

IV. ORGANIC REACTIONS

Hydrazine reacts with many organic functional groups to form derivatives valuable in areas of application already mentioned. Some of these reactions and the classes of compounds to which they lead are covered briefly in the following. In most cases, aqueous hydrazine (generally 54 or 64%) may be used.

Alkyl and Aryl Hydrazines

Alkyl hydrazines can be made by a variation of the Raschig process, using an amine rather than ammonia in the reaction with chloramine as the aminating agent (eq. 1b). Hydroxylamine-*O*-sulfonic acid, NH_2OSO_2OH, is a convenient aminating agent for lab-scale preparations.* Alkyl hydrazines can also usually be prepared from alkyl halides or sulfates (eq. 19). In

$$RX + N_2H_4 \longrightarrow \quad \text{(eq. 19)}$$
$$RNHNH_2 + HX$$

this reaction, the tendency is to polyalkylation on the same nitrogen leading to **1** and **2**. Monoalkylation is favored by sterically bulky alkyl groups (such as benzyl) or by the use of a large excess of hydrazine. For example, isopropylhydrazine can be prepared from isopropyl bromide in acceptable yields by using a 5-fold molar equivalent excess of hydrazine.[54]

unsym-Dimethylhydrazine (UDMH), currently produced in commercial quantities, can be made by the Raschig process, using dimethylamine instead of ammonia (eq. 1b). It can also be made by catalytic reduction of dimethylnitrosamine (eq. 20)

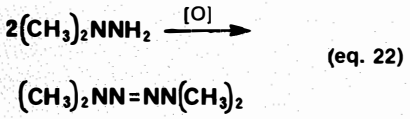
$$(CH_3)_2NNO \xrightarrow[Pd(C)]{H_2} (CH_3)_2NNH_2 \quad \text{(eq. 20)}$$

or by reductive alkylation of a hydrazide with formaldehyde and hydrogen (eq. 21).[55]

$$RCONHNH_2 + CH_2O/H_2 \longrightarrow$$
$$RCONHN(CH_3)_2 \xrightarrow{H_2O} \quad \text{(eq. 21)}$$
$$RCOO^- + UDMH$$

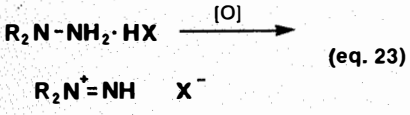
*For a review, see R.G. Wallace, *Aldrichimica Acta*, 13, 3 (1980).

These and other procedures for the preparation of mono-, di-, tri- and tetraalkylhydrazines and their properties have been reviewed.[56-58] N,N'-Dialkylhydrazines oxidize to azoalkanes, RN=NR.[59] The behavior of unsymmetrical dialkylhydrazines is quite different, the result depending on reaction conditions. McBride[60,61] has shown that in alkaline solution, the oxidation of UDMH by any number of oxidants (HgO, halogens, halates) gives the tetrazene (eq. 22). Tetrazenes are inherent-



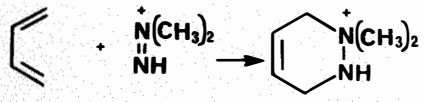
(eq. 22)

ly unstable and split out N_2 under thermal or photolytic conditions to give, in the above case, 1,1,2,2-tetramethylhydrazine.[62] Under acidic conditions in the cold, diazenium salts are formed (eq. 23).[63] The



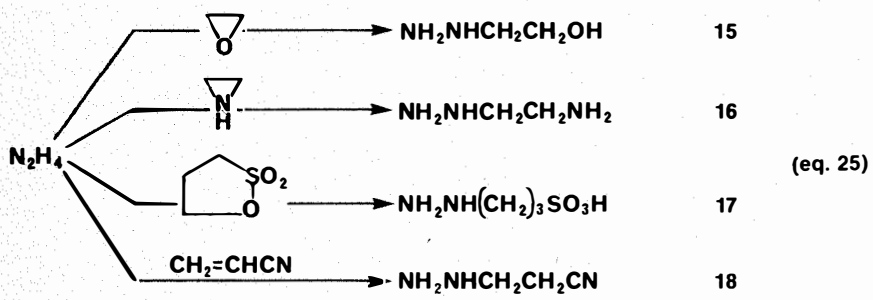
(eq. 23)

dialkyl diazenium cations readily react as dienophiles with conjugated dienes in the Diels-Alder reaction (eq. 24).[64]



(eq. 24)

Substituted alkylhydrazines are prepared from suitable alkylating agents. Epoxides yield hydroxyalkyl derivatives;[65] aziridines, the β-aminoalkyl derivatives;[66,67] sultones, ω-sulfoalkylhydrazines;[68-70] and acrylonitrile gives the β-cyanoethylhydrazine[71] (eq. 25). These compounds are all

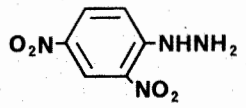


(eq. 25)

potentially useful in further syntheses. They contain an active substituent on the alkyl group and, since the hydrazine moiety is intact, they undergo many of the reactions of hydrazine itself.

Hydroxyethylhydrazine (**15**) is a plant-growth regulator.[72] Use of **15** and cyanoethylhydrazine (**18**) has been suggested for color prevention in acrylonitrile polymerization.[73] Nitriles react with β-aminoethylhydrazine (**16**) to give substituted triazines with possible pharmacological value.[74] The ω-sulfoalkylhydrazines (**17**) have also been recommended as pharmaceutical as well as photographic intermediates.[69] The degree of polysubstitution in the above reactions (eq. 25) depends on the reactant ratios, although it is difficult to avoid at least some disubstitution even with a 1:1 molar reactant ratio. Hydrazinopolyols can be made from hydrazine and excess ethylene or propylene oxides and might have application in polyurethane technology.[75]

Arylhydrazines, $ArNHNH_2$, are not generally prepared from haloaromatics unless the halogen is sufficiently activated by adjacent negative groups. The classic example of the latter is the conversion of 2,4-dinitrochlorobenzene to 2,4-dinitrophenylhydrazine (**19**), a reagent long used for identification of ketones and aldehydes.



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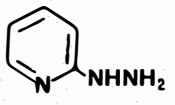

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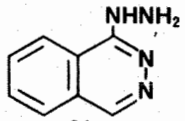


21

Likewise, 2-hydrazinopyridine (**20**) and 1-hydrazinophthalazine (**21**) may be prepared from the corresponding chloro derivatives. As a rule, arylhydrazines are made by diazotization of aromatic amines and reduction of the resulting diazonium salts. Brown[58] and Enders[76] have reviewed the preparation and properties of arylhydrazines.

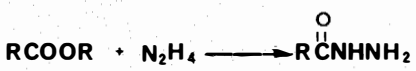
Hydrazides

In a formal sense, hydrazides are compounds of hydrazine and an acid in which the -OH(-SH) of the acid is replaced by the hydrazino group, $-NHNH_2$. Some "inorganic" members of this class were mentioned in Section III. Among the organic representatives, the carboxylic acid (**22**) and sulfonic acid (**23**) hydrazides have achieved considerable commercial importance. A number of other compounds of

22 **23**

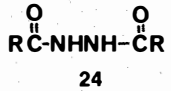
commercial significance belong structurally in this class but are not necessarily prepared from the corresponding acid or its derivatives. The major classes of hydrazides and their relationship to the corresponding acids are shown in Table I.

Carboxylic acid hydrazides are best made from the ester (eq. 26), but the acid,



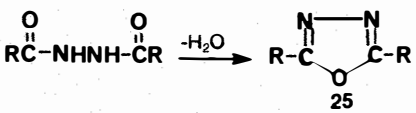
(eq. 26)

anhydride, amide or acyl halide may also be used. These componds are weakly basic solids soluble in dilute mineral acids. Diacylhydrazines (**24**) are acidic, however,



24

and will form mono- and disubstituted salts with alkali metal hydroxides or alkoxides; heavy-metal salts are known also. Under dehydrative conditions (P_2O_5 or $ZnCl_2$), diacylhydrazines undergo ring closure to give 1,3,4 -oxadiazoles (**25**).



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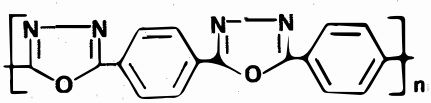
Similarly, polyhydrazides, formed from hydrazine and dibasic acids, give polyoxadiazoles. Such compounds of terephthalic acid and hydrazine (**26**) decompose only at



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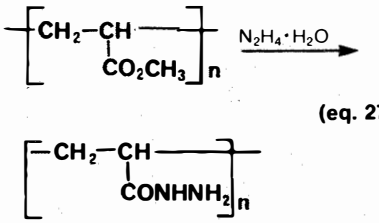
very high temperatures (>350° C) and give fibers and membranes resistant to hot acids and bases. With hydrazine hydrate, polymers of methyl acrylate form polyacrylic hydrazide (eq. 27).[79]



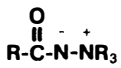
(eq. 27)

Table 1

HYDRAZIDES

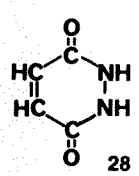
Acid	Hydrazide	Structure	Ref
Carboxylic, RCOOH	Carboxylic hydrazide (Acyl hydrazine)	$RC(=O)NHNH_2$	77,78
Sulfonic, RSO_2OH	Sulfonyl hydrazide	RSO_2NHNH_2	85
Dithioic, RCSSH	Thiohydrazide	$RC(=S)NHNH_2$	88,89
Carbamic, NH_2COOH	Semicarbazide	$H_2NC(=O)NHNH_2$	94
	Hydrazodicarbonamide	$H_2NC(=O)NHNHC(=O)NH_2$	95
Dithiocarbamic, NH_2CSSH	Thiosemicarbazide	$H_2NC(=S)NHNH_2$	98
Carbazic, $NH_2NHCOOH$	Carbohydrazide	$NH_2NHC(=O)NHNH_2$	100
Dithiocarbazic, $NH_2NHCSSH$	Thiocarbohydrazide	$NH_2NHC(=S)NHNH_2$	100

Exhaustive alkylation of hydrazides yields aminimide ylides (**27**) which have



27

been suggested as adhesives, surfactants, photographic chemicals and pharmaceuticals.[80] These compounds suffer thermal -N-N- cleavage to give the unstable nitrene, R-(C=O)-$\bar{N}$ which undergoes the Curtius rearrangement to an isocyanate, RNCO.[81,82] Maleic anhydride and aqueous hydrazine give the cyclic hydrazide (**28**), pyridazine-3,6[1*H*,2*H*]-dione[83,84] used as a plant-growth regulator. Phthalic anhydride yields the cyclic phthalic hydrazide (**29**), a phthalazine derivative. Similar cyclic hydrazides (pyridazinediones) are obtained from 1,2-dicarboxylic esters in the furan, thiophene, pyridine, pyrrole, pyrazole, pyrazine and pyrimidine series.



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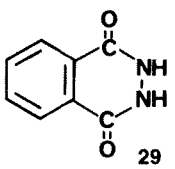

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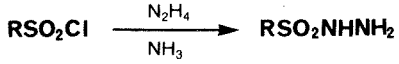
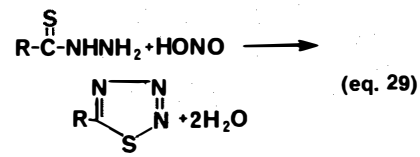
Sulfonyl hydrazides are prepared most easily from the corresponding sulfonyl halides in the presence of an HCl acceptor (eq. 28). A number of these compounds are



(eq. 28)

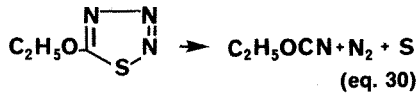
manufactured in commercial quantities as foaming agents for polymers.[86,87]

Thiohydrazides are best prepared from aqueous hydrazine and the appropriate dithio acid or carboxymethyl dithioate, $RCSSCH_2COONa$, as thioacylating agent. These hydrazides are amphoteric compounds. Reaction with nitrous acid provides a general procedure for making 1,2,3,4-thiatriazoles (eq. 29).[90] Xanthates,



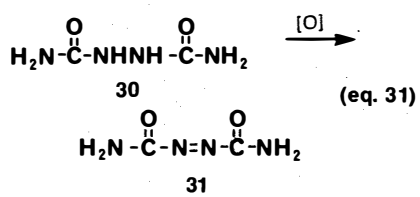
(eq. 29)

RO-(C=S)-SNa, yield thiohydrazides (eq. 29, R = alkoxy)[91] which also react with nitrous acid to give 5-alkoxy-1,2,3,4-thiatriazoles.[92] These are very unstable; 5-ethoxy-1,2,3,4-thiatriazole in ether solution at room temperature gives nearly quantitative yields of ethyl cyanate (eq. 30).[93]



(eq. 30)

Semicarbazide is prepared from urea and hydrazine hydrate. With excess urea, hydrazodicarbonamide (**30**) forms as an insoluble precipitate. Commercially, this is oxidized with chlorine to form azodicarbonamide (**31**), the largest-volume chemical blowing agent for the foaming of polymers (eq. 31).

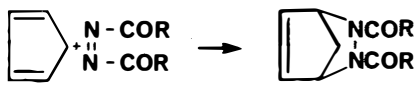


30

(eq. 31)

31

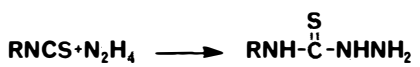
Azodicarbonamide,[96] as well as azodicarboxylic acid diesters, ROOC-N=N-COOR,[97] function as dienophiles in the Diels-Alder reaction (eq. 32).



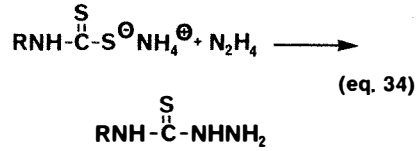
R = $-NH_2$, -OEt

(eq. 32)

Thiosemicarbazide can be made from inorganic thiocyanates, *e.g.*, KSCN. Such compounds substituted in the 4-position are made from organic isothiocyanates (eq. 33), or from alkyl dithiocarbamates (eq. 34).[99] These may be used in the synthesis of

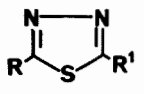


(eq. 33)



(eq. 34)

1,3,4-thiadiazoles (**32**), compounds which have found applications as agricultural pesticides and corrosion inhibitors.



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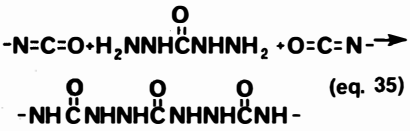
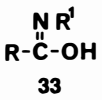
Carbohydrazide and thiocarbohydrazide are also used as intermediates. These compounds undergo many of the reactions of hydrazine itself; for example, chain extension of polymers with terminal isocyanate groups (eq. 35). Carbohydrazide will also react with formaldehyde (eq. 36) and thus function as a scavenger for free formaldehyde.



(eq. 35)

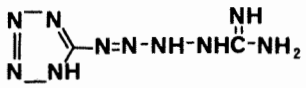
(eq. 36)

Several classes of compounds structurally related to hydrazides may be thought of as derivatives of the hypothetical imidic acids (**33**). These are summarized in Table 2 (IUPAC nomenclature first).



33

Amidrazones and hydrazidines (Table 2) are stronger bases than carboxylic hydrazides, although few measurements have been made.[103] All of these compounds undergo facile ring closure to give nitrogen heterocycles (pyrazoles, triazoles, tetrazoles, triazines, tetrazines, etc.). Formazanes constitute a class of commercially useful dyes. The aminoguanidines yield explosives such as tetracene (**34**)[107] and the herbicide aminotriazole (**35**).[108]



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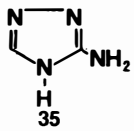

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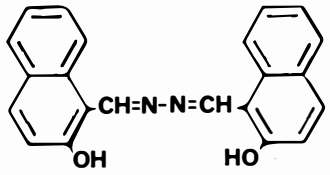
Hydrazones and Azines

Aldehydes and ketones react with hydrazine to give hydrazones (**36**) or azines (**37**). The lower members of this series, such as acetone azine (**37**, R=CH_3), are colorless

liquids. When the -C=N-N=C- azine group is part of a conjugated system, colored compounds result (**42**, *vide infra*). Yellow fluorescent (**38**) and red-violet dyes (**39**) are based on azines. A general synthesis of pyrazoles involves the reaction of hydrazine and 1,3-diketones. For example,



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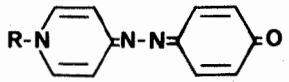

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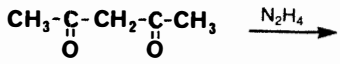
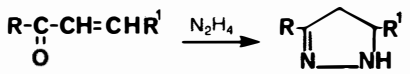
acetylacetone and hydrazine give 3,5-dimethylpyrazole. The first step of this reaction is probably formation of a cyclic azine, followed by a proton shift and bond rearrangement (eq. 37).



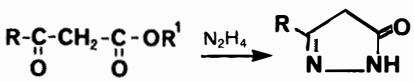
(eq. 37)

Pyrazolines (**40**) are formed from hydrazine and β-keto olefins (eq. 38); pyrazolones (**41**) result from the reaction of β-keto esters with hydrazine (eq. 39).



40

(eq. 38)



41

(eq. 39)

Diketones that cannot cyclize with hydrazine generally form polymeric azines. The chemistry of hydrazones[58] and azines[109] has been reviewed.

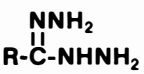
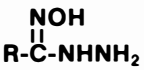
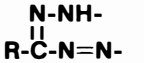
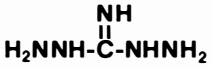
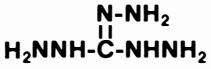
Hydrogenation with Hydrazine

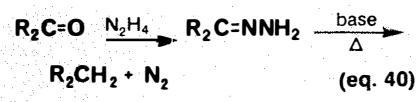
As a reducing agent, hydrazine is able to hydrogenate many organic functional groups such as C=O, C=C, C≡C, C≡N, N=N, NO, NO_2 and COOH; in addition, alkyl and aryl halides may be dehalogenated. These procedures have been reviewed by Furst[110] and House.[111]

Ketones and aldehydes are reduced to alcohols or, more typically, to hydrocarbons by the well known Wolff-Kishner reaction (eq. 40).[112-115] Ketones may be converted to olefins in a sequence known as

Table 2

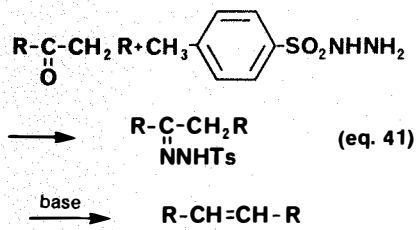
"HYDRAZIDE TYPE" STRUCTURES

Class	Structure	Ref
Amidrazone		101, 102
Hydrazidine (Dihydroformazane)		101, 102
Hydroximoylhydrazine (Hydroximic acid hydrazide)		104
Formazane		105
Aminoguanidine		106
Diaminoguanidine		106
Triaminoguanidine		106



$$R_2C{=}O \xrightarrow{N_2H_4} R_2C{=}NNH_2 \xrightarrow[\Delta]{base} R_2CH_2 + N_2 \qquad \text{(eq. 40)}$$

the Bamford-Stevens reaction (eq. 41).[116] This involves the initial formation of the tosyl hydrazone of the carbonyl compound



$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2R + CH_3\text{-}C_6H_4\text{-}SO_2NHNH_2 \longrightarrow R\text{-}\overset{NNHTs}{\overset{\|}{C}}\text{-}CH_2R \qquad \text{(eq. 41)}$$

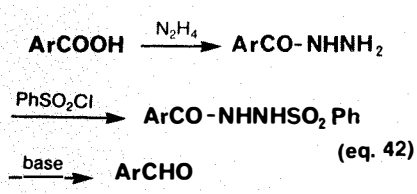
$$\xrightarrow{base} R\text{-}CH{=}CH\text{-}R$$

followed by deprotonation with a strong base to eliminate N_2 and the tosyl group.

Aromatic nitro compounds are reduced to the corresponding amines (or partial reduction products such as azo, azoxy, hydrazo and hydroxylamino intermediates); nitriles are converted to hydrazones.[117] These reactions generally, but not always, require catalysts such as Raney nickel or noble-metal hydrogenation catalysts. They are also frequently highly selective when several reducible groups are present.

Aromatic aldehydes may be synthesized from the corresponding acids by the McFadyen-Stevens reaction (eq. 42). This procedure works, but less well, with aliphatic acids.[118]

Olefins, acetylenes and azo compounds are reduced by hydrazine in the presence of

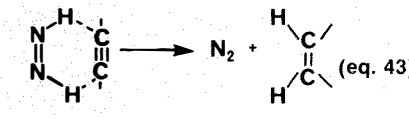


$$ArCOOH \xrightarrow{N_2H_4} ArCO\text{-}NHNH_2 \xrightarrow{PhSO_2Cl} ArCO\text{-}NHNHSO_2Ph \qquad \text{(eq. 42)}$$

$$\xrightarrow{base} ArCHO$$

an oxidizing agent such as oxygen or hydrogen peroxide. The mechanism of this reaction probably involves the intermediate formation of diazene, HN=NH, the actual hydrogenation agent (eq. 43). The conversion of acetylenes exclusively into *cis*-olefins speaks for this mechanism.

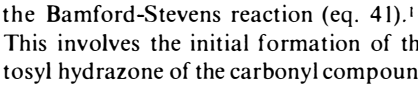
None of the hydrogenation procedures mentioned here require pressure.



$$\text{(HN=CH-NH-CH=N)}_2 \longrightarrow N_2 + \text{(HC=CH)}_2 \qquad \text{(eq. 43)}$$

V. HYDRAZINE ANALYSIS

Hydrazine may be analyzed by titration as a weak base with standardized hydrochloric acid, using methyl purple as indicator. A more universally applicable procedure is an iodometric titration with standard I_2 at a pH of 7.0-7.2 (bicarbonate buffer, eq. 44).[119]

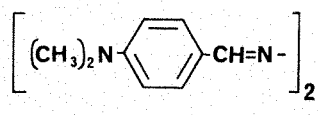


$$N_2H_4 + 2I_2 \longrightarrow N_2 + 4HI \qquad \text{(eq. 44)}$$

Potassium iodate also quantitatively oxidizes hydrazine in strong acid (eq. 45).[120]

$$N_2H_4 + KIO_3 + 2HCl \longrightarrow KCl + ICl + N_2 + 3H_2O \qquad \text{(eq. 45)}$$

Trace amounts of hydrazine in the ppm and ppb range may be determined spectrophotometrically (458nm) as the highly colored azine of *p*-dimethylaminobenzaldehyde (**42**), a standard ASTM method, D-1385-78. A continuous air monitor based on this method has been described.[121] An electrochemical apparatus has also been developed[122] and an air-monitoring device based on the reduction of a phosphomolybdate-impregnated paper



$$\left[(CH_3)_2N\text{-}C_6H_4\text{-}CH{=}N\text{-}\right]_2$$

42

tape (blue color, photoelectric detector) is available.[123] Other procedures involve thin-layer chromatography,[124] higb-pressure liquid chromatography,[125] polarography[126] and gas chromatography.[127]

CAUTION: Hydrazine is toxic. Avoid ingestion, inhalation and skin contact. Read labels carefully and determine appropriate handling procedures and storage conditions before using.

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About the Author

Dr. Schiessl received a B.Ch.E. degree from Cornell University in 1950. After a stint in industry, he resumed his studies at the Universities of Bonn and Heidelberg in Germany under Dr. R. Appel and obtained a Ph.D. in 1964. As Research Associate with Olin Corp., his present work includes the development and application of new hydrazine derivatives. He is author of the hydrazine chapter in the new edition of Kirk-Othmer's Encylopedia of Chemical Technology (in press).

Dr. Schiessl is also Adjunct Professor of Chemistry at the University of New Haven.

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About Our Cover:

Our chemist-collector loves puzzles of iconography and authorship of paintings.

There is no iconographic problem, of course, with this moving depiction of *The Good Samaritan*, but who painted this fine, large (oil on canvas, 41″ x 58″) work? Our chemist believes it is Dutch, *circa* 1630-1640, by an artist strongly influenced both by Italian art and pre-Rembrandtists. In time, the right name will be known, as happens to most works of such competence.

The story of the Good Samaritan (St. Luke *10*, 25-37) has excited artists' imaginations throughout the ages, for it raises that most important question about the greatest of all the Biblical commandments, in Leviticus *19*, "Love thy neighbor as thyself." For who is your neighbor? Almost always, when we say — as did the priest and the Levite — "It's none of my business," we are mistaken. If only we understood the lesson truly, that our neighbor is all mankind, we would try harder to give the best possible service, to all who need help.

Are you interested in our Acta covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by Professor Wolfgang Stechow is available to all chemist art-lovers.

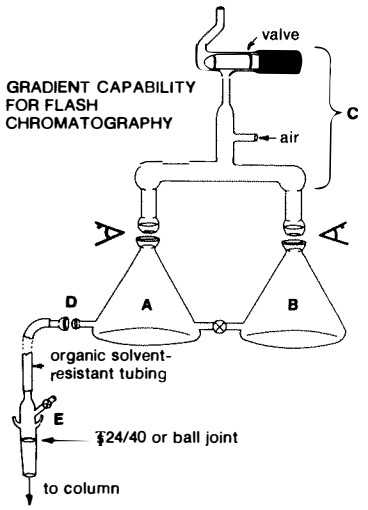
Also, many paintings reproduced on our Acta covers were shown at the Milwaukee Art Center in an exhibition, "The Bible Through Dutch Eyes," arranged by Dr. Bader in 1976. The fully illustrated catalog with 66 black-and-white and 4 full-color reproductions contains many art historical and Biblical comments.

Eight paintings that have been depicted on Acta covers and four that have been on catalog covers were among 18 Old Master paintings in an exhibition in honor of Professor Herbert C. Brown at Purdue University in October. If you would like the fully illustrated catalog of the exhibition entitled "Old Students and Old Masters: The School of Rembrandt," please send your check for $4.00 to the Department of Creative Arts, Purdue University, West Lafayette, IN 47907, and you will receive the catalog postpaid.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

Lab Notes

Flash chromatography reported by Still *et al.*, [*J. Org. Chem.*, **43**, 2923 (1978)] is rapidly replacing gravity flow chromatography because of the quickness and the better resolution it affords. As originally introduced, the system is isocratic. We have designed an apparatus which allows one to perform this and other types of chromatography in the gradient mode. The modification basically consists of two 1-L

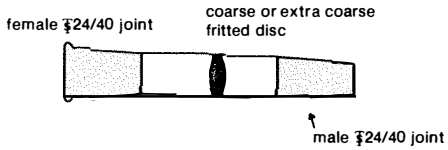


flasks with ball joints, connected by a stopcock and an upper segment C for introduction of air pressure. Solvent of low polarity is contained in flask A while that of higher polarity is in flask B. After the flasks are filled to the same level, the stopcock is opened and the solutions are stirred (magnetic stirring bars). The solvent is introduced into the column through outlet D. Air is forced through the system using part C as shown in the diagram. To obtain an air-free system, unit E which fits on top of the column is necessary. If outlet D is sealed and the upper portion C removed, this apparatus also can be used for medium- and high-pressure gradient LC work.

Bruce B. Jarvis
Professor of Chemistry
and
Jacob O. Midiwo
Research Assistant
Department of Chemistry
University of Maryland
College Park, Maryland 20742

A common problem encountered when adsorbing a sample on a chromatography support, especially when the adsorption solvent is much too polar for elution of the column, is the fast and complete removal of the adsorption solvent before the sample-support mixture is placed on the chromatography column.

We have found that a glass adapter made by having our glass blower place one male 24/40 ground glass joint on a cylindrical sealing tube with a sealed-in fritted disc (extra-coarse- or coarse-porosity disc) to be convenient for this purpose. The insertion of this adapter between the round-bottom



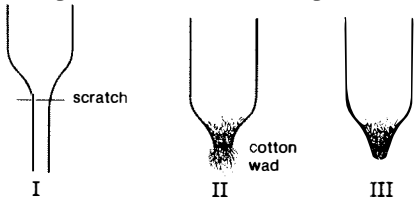
flask containing the solvent-adsorbent-sample mixture and the vapor duct of any rotary evaporator allows the *in vacuo* removal of solvent without the sample-adsorbent mixture being sucked into the condenser of the rotary evaporator.

Similarly, this adapter prevents any solid from being sucked into the condenser when it is necessary to remove all solvent from a solid-solvent mixture.

Aldean J. Kolar, Ph.D.
Research Associate
Department of Medicinal Chemistry
School of Pharmacy
The University of Kansas
Lawrence, Kansas 66045

Editor's Note: For our customers' convenience, we now offer the adapter described above.

An applicator for preparative TLC can be made conveniently from a Pasteur pipet. The narrow end of the pipet is scratched and broken off leaving a small constriction (I). A small wad of absorbent cotton is pushed from the wider end of the pipet and tapped into the constriction (II) (another Pasteur pipet may be used to put the wad into place). The end of the cotton is pulled until the wad is securely in place. Scissors are then used to trim the end of the wad to the desired shape (III). The sample, dissolved in a suitable solvent, is sucked up through the cotton wad using a rubber



bulb. The sample can be added in a controlled fashion to the TLC plate by applying slight pressure to the rubber bulb.

Gerald W. Kutney
Erindale College
University of Toronto
Mississauga, Ontario, Canada

Many laboratories keep solvents handy by storing them in polyethylene squeeze bottles. Unfortunately, the labels often wash off these bottles very readily. I have found that by marking the bottle with a felt tip pen and then carefully heating the bottle with a heat gun, the label will become permanently affixed. This makes the wash bottle easier to find and much safer to use.

Scott Stoltzmann
Laboratory Technician
Aldrich-Boranes, Inc.

Any interesting shortcut or laboratory hint you'd like to share with Acta readers? Send it to Aldrich (attn:Lab Notes) and if we publish it, you will receive a handsome red-and-white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** *(see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.*

"Please Bother Us."

by Ayra Bader.

When I visited the Converse Labs at Harvard the other day, Dr. Leo Letendre indicated that our deuterochloroform has too much TMS (1%) to be useful for Fourier Transform NMR; 0.02 mole % would be much more useful. When working with very small samples, the intensity of the TMS peak might mask small peaks, yet some TMS is necessary.

We now offer chloroform-*d*, 99.8 atom % D, containing 0.03% (v/v) TMS.

It was no bother at all, just a pleasure to be able to help.

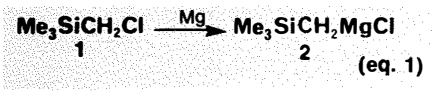
Organosilicon Reagents for Carbon-Carbon Bond-Forming Reactions

Philip Magnus
Department of Chemistry
The Ohio State University
140 West 18th Avenue
Columbus, Ohio 43210

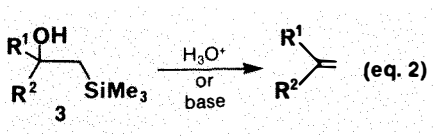
The development of new synthetic methods for use in organic synthesis is one of the areas of organic chemistry that has experienced a major renaissance during the past fifteen years or so. More recently there has been an extremely large number of publications describing the use of organosilicon chemistry in synthesis. Nearly every journal that synthetic organic chemists read contains papers devoted to the use of silicon-based chemistry for the construction of organic molecules. Since the carbon-carbon bond is a focal point of organic synthesis it is important to have many and varied ways to construct this bond in a predictable fashion. The intention of this article is to describe how certain organosilicon-based reagents, some of which are commercially available, can be used to make carbon-carbon bonds in a controlled and predictable way that is useful to the practicing synthetic organic chemist.

α-SILYL CARBANIONS

The first reported α-metallosilane was prepared by Whitmore and Sommer in 1946.[1] Treatment of α-chloromethyltrimethylsilane (**1**) with magnesium in ether gave the stable Grignard reagent **2** (eq. 1). Surprisingly, the reagent did not

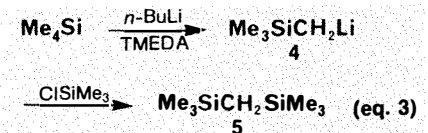


reappear until 1968 when Peterson developed an alkene synthesis based on this Grignard reagent.[2] Treatment of aldehydes or ketones with **2** gave, after mild hydrolysis, the β-hydroxysilanes **3** (eq. 2). Frequently, when R^1 and R^2 are alkyl

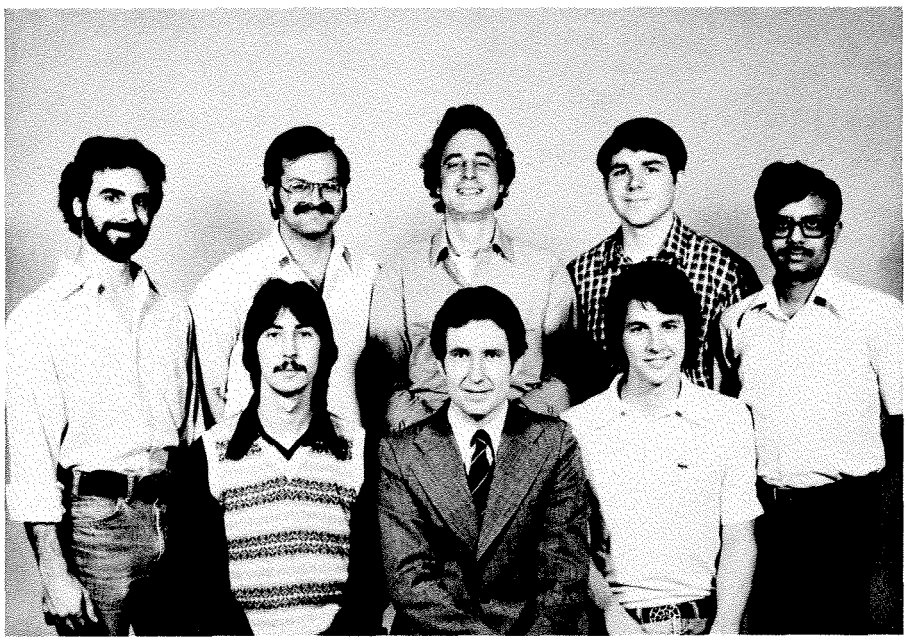


groups or part of a carbocyclic ring the adducts **3** are not stable, and eliminate trimethylsilanol to give an alkene. When the adducts **3** are isolable they may be converted into an alkene under either acidic or basic conditions. When the elimination of trimethylsilanol is conducted with sodium or potassium hydride in tetrahydrofuran the process is a *syn*-elimination. Treatment of the adducts **3** with acid (5% H_2SO_4 or HCO_2H) results in an *anti*-elimination, leading to an alkene of opposite geometrical configuration.[3]

Tetramethylsilane can be deprotonated using *n*-butyllithium in tetrahydrofuran containing tetramethylethylenediamine (eq. 3) to give the α-lithiomethyltrimethyl-



silane (**4**), as evidenced by treatment with chlorotrimethylsilane to give bis(trimethylsilyl)methane (**5**).[4] This type of hydrogen-metal exchange is by far the

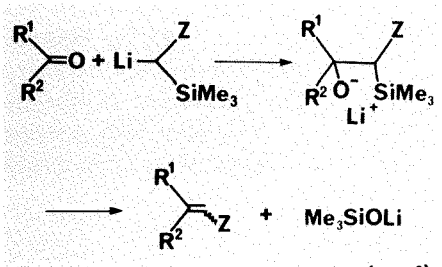


Back row — left to right: D. Quagliato, J. Venit, G. Roy, J. Schwindeman, T. Sarkar
Front row: S. Djuric, P. Magnus, D. Gange

most convenient way of preparing α-metallosilanes, since α-halosilanes are not so readily available. Table 1 lists a number of α-metallosilanes that have usually been prepared by hydrogen-metal exchange.

Other anions that are made by halogen-metal exchange or *trans*-metallation include $(Me_3SiCCl{=}CHCH_2)Li$,[32] Me_3SiCCl_2Li, $(Me_3Si)_2CClLi$, Me_3SiCBr_2Li and $Me_3SiCHBrLi$.[33]

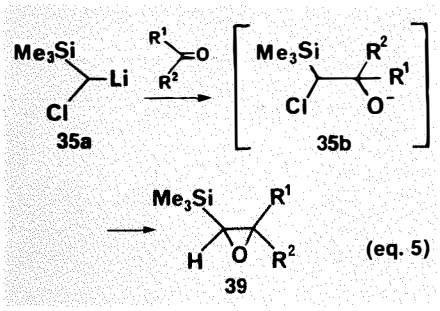
The reagents **6-38** are largely used for the so-called Peterson olefination reaction, which may be classified, in its most general sense, as follows (eq. 4):



(eq. 4)

The wide variations in the nature of Z give this synthetic method its useful versatility. It should be noted that apart from the cases described below, the elements of trimethylsilanoxide are lost in a *syn*-elimination even when Z is an excellent leaving group, to give an olefin. As such, the main advantage of the Peterson reactions over the conventional Wittig reaction is their greater flexibility for the synthesis of heterosubstituted alkenes, and perhaps more importantly, the carbanions listed (particularly **29**, **35**, and **37**) are more nucleophilic than their phosphonate counterparts.

α-Chloromethyltrimethylsilane (**35**) is deprotonated by treatment with *s*-butyllithium in tetrahydrofuran at -78° C to give **35a**. It is essential to use *s*-butyllithium to obtain good yields of **35a**; *n*-BuLi, *t*-BuLi, alkoxides and amides give unsatisfactory results. Treatment of **35a** with aldehydes or ketones leads to α,β-epoxysilanes **39** *via* the intermediacy of the chlorohydrin (eq. 5). This is a surprising result since the intermediate chlorohydrin (**35b**), by analogy with the examples described above (Z=Cl), would have been expected to eliminate the



(eq. 5)

Table I

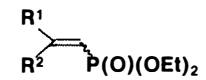
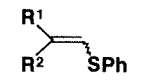
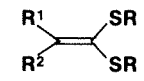
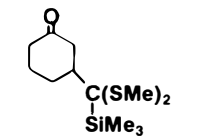
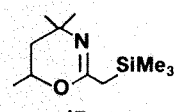
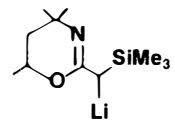
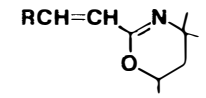
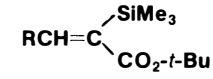
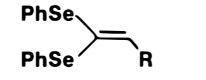
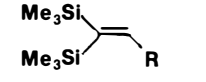
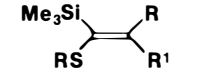
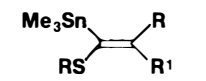
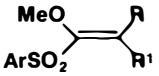
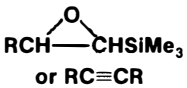
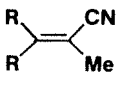
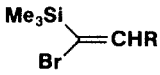
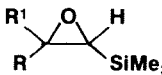
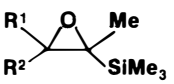
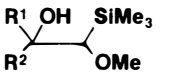
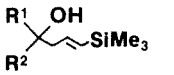
Substrate	Reagent	α-Lithiospecies	Electrophile	Product	Ref.
Me_3SiCH_2Ph **6**	*n*-BuLi/-HMPA	$Me_3SiCHPh$ | Li	PhCHO	PhCH=CHPh	5
$Me_3SiCH_2SiMe_3$ **7**	*t*-BuLi/-HMPA	$Me_3SiCHSiMe_3$ | Li	PhCHO	PhCH=CHSiMe$_3$	6
$Me_3SiCH(SiMe_3)_2$ **8**	*n*-BuLi	$Me_3SiC(SiMe_3)_2$ | Li	CH_2O	$CH_2=C(SiMe_3)_2$	6
$Me_3SiCH_2PPh_2$ **9**	*n*-BuLi	$Me_3SiCHPPh_2$ | Li	Ph_2CO	$Ph_2C=CHPPh_2$	7
$Me_3SiCH_2P(S)Ph_2$ **10**	*n*-BuLi	$Me_3SiCHP(S)Ph_2$ | Li	Ph_2CO	$Ph_2C=CHP(S)Ph_2$	7
Me_3SiCH_2SMe **11**	*n*-BuLi	$Me_3SiCHSMe$ | Li	Ph_2CO	$Ph_2C=CHSMe$	7
$Me_3SiCH_2P(O)(OEt)_2$ **12**	*n*-BuLi	$Me_3SiCHP(O)(OEt)_2$ | Li			8
Me_3SiCH_2SPh **13**	*n*-BuLi	$Me_3SiCHSPh$ | Li			8,9
Me_3SiCH_2SOPh **14**	*n*-BuLi	$Me_3SiCHSOPh$ | Li			10
$Me_3SiCH(SR)_2$ **15**	*n*-BuLi	$Me_3SiC(SR)_2$ | Li			11
$Me_3SiCH(SMe)_2$ **16**	*n*-BuLi	$Me_3SiC(SMe)_2$ | Li			12
 **17**	*n*-BuLi		RCHO		13
$(Me_3Si)_2CHCO_2$-*t*-Bu **18**	LDA	$(Me_3Si)_2CCO_2$-*t*-Bu | Li	RCHO		14
$PhSeCHSiMe_3$ | Ph **19**	$LiNEt_2$	Li | $PhSe-C-SiMe_3$ | Ph	MeI	Me | $PhSe-C-SiMe_3$ | Ph	15
$PhSeCH_2SiMe_3$ **20**	LDA	$PhSeCHSiMe_3$ | Li	RCH_2I	$PhSeCHSiMe_3$ | CH_2R	16
$(PhSe)_2CHSiMe_3$ **21**	LDA	$(PhSe)_2CSiMe_3$ | Li	RCHO		17
$(Me_3Si)_3CH$ **22**	MeLi	$(Me_3Si)_3CLi$	RCHO		17
$(Me_3Si)_2CHSR$ **23**	*n*-BuLi	$(Me_3Si)_2CSR$ | Li	$RCOR^1$		17
Me_3SiCH | $SnMe_3$ | SR **24**	LDA	Me_3SiC | $SnMe_3$ | SR -Li	$RCOR^1$		17

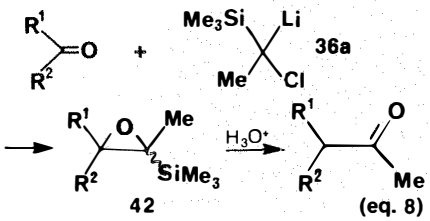
Table I (cont'd.)

Substrate	Reagent	α-Lithiospecies	Electrophile	Product	Ref.
$ArSO_2CH(OMe)SiMe_3$ **25**	*n*-BuLi	$ArSO_2C(OMe)(Li)SiMe_3$	$RCOR^1$		18
$Me_3SiCH_2CH{=}NR$ **26**	LDA	$Me_3SiCH(Li)\text{-}CH{=}NR$	R^1CHO	$R^1CH{=}CH\text{-}CH{=}NR$	19
Me_3SiCH_2CN **27**	LDA	$Me_3SiC(Li)HCN$	RCHO	$RCH{=}CHCN$	20
$Me_3SiCH_2CO_2H$ **28**	LDA	$Me_3SiC(Li)HCO_2Li$	RCHO	$RCH{=}CHCO_2H$	21
$Me_3SiCH_2CO_2Et$ **29**	LDA	$Me_3SiC(Li)HCO_2Et$	RCHO	$RCH{=}CHCO_2Et$	22
Me_3SiCHN_2 **30**	*n*-BuLi	$Me_3SiC(Li)N_2$	RCHO	 or $RC{\equiv}CR$	23
$PhMe_2SiCH(Me)CN$ **31**	LDA	$PhMe_2SiC(Me)(Li)CN$			24
$(Me_3Si)_2CHBr$ **32**	*n*-BuLi	$(Me_3Si)_2C(Li)Br$	RCHO		25
$Me_3SiCH_2N(NO)\text{-}t\text{-}Bu$ **33**	LDA	$Me_3SiCH(Li)N(NO)\text{-}t\text{-}Bu$	RCHO	$t\text{-}BuN{=}CHCR(NOH)$	26
$Me_3Si\text{-}Cl$ **34**	*t*-BuLi	Me_2SiCH_2Li (Cl)	Me_3SiCl	$Me_3SiCH_2SiMe_2Cl$	27
Me_3SiCH_2Cl **35**	*s*-BuLi	$Me_3SiC(Li)HCl$ **35a**	$RCOR^1$		28
$Me_3SiCH(Cl)\text{-}Me$ **36**	*s*-BuLi	$Me_3SiC(Cl)(Li)\text{-}Me$ **36a**			29
Me_3SiCH_2OMe **37**	*s*-BuLi	$Me_3SiC(Li)HOMe$ **37a**			30
$Me_3SiCH_2CH{=}CH_2$ **38**	*s*-BuLi	$(Me_3SiCH{=}CHCH_2)Li$ **38a**			31

elements of trimethylsilanoxide to give a vinyl chloride rather than an α,β-epoxysilane. This useful result can be exploited in synthesis (eq. 6) since α,β-epoxysilanes are precursors to carbonyl compounds.[34]

The addition of CTC (abbreviation for **35a**) to estrone *O*-methyl ether (eq. 7) is particularly noteworthy since 17-keto-steroids are hindered, readily enolizable carbonyl compounds. Merely dissolving the α,β-epoxysilane **41** in 90% formic acid gave the 20-aldehyde in excellent yield. The overall transformation of a carbonyl group to the homologous aldehyde, where the original electrophilic carbonyl group has been reduced, is termed REDUCTIVE NUCLEOPHILIC ACYLATION.[35]

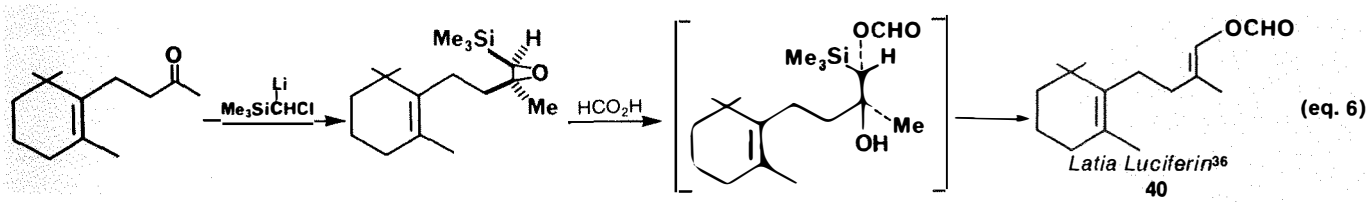
The methyl analog of CTC, namely MCTC (**36a**), is made from **36** by deprotonation with *s*-butyllithium in tetrahydrofuran at -78°C. Treatment of **36a** with ketones or aldehydes (eq. 8) gives



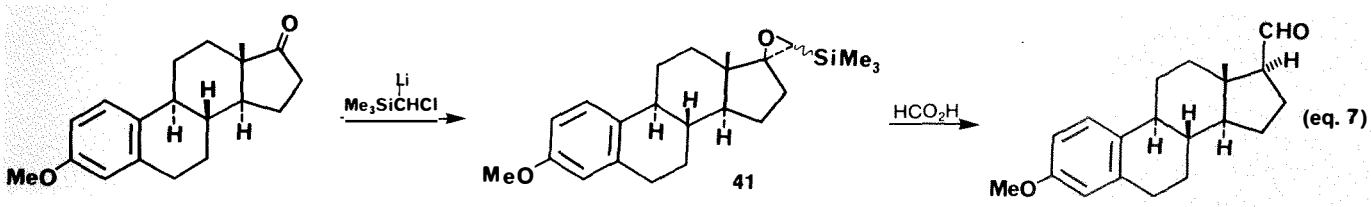
42 (eq. 8)

α,β-epoxysilanes **42**. This new methodology has been used in a short synthesis of (*R*)-(+)-frontalin **43**,[35,36] the aggregation pheromone of the Southern Pine beetle, *Dendroctonus frontalis* (Scheme 1).

Another silicon-based reagent that can be used for reductive nucleophilic acylation reactions is methoxymethyltrimethylsilane (**37**). It can be deprotonated selectively using *s*-butyllithium in tetrahydrofuran (Scheme 2) to give the lithio species **37a**. The use of *s*-butyllithium is vital to the success of this reaction. *n*-Butyllithium reacts with **37** to give products that appear to result from nucleophilic attack at silicon and subsequent cleavage of the $-CH_2OMe$ group; *t*-butyllithium gave the lithio species **44**.[30]



Latia Luciferin[36] **40** (eq. 6)



41 (eq. 7)

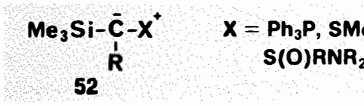
The lithio species **37a** reacts with carbonyl compounds to give adducts such as **56**. Treatment of these adducts with potassium hydride results in the elimination of potassium trimethylsilanoxide to give enol ethers. When the adduct **45** is treated with cesium fluoride in dimethyl sulfoxide, disilylation takes place to give the compound **46** (Scheme 3).[30] Surprisingly no elimination takes place, giving enol ethers.

Synthetic equivalents of the β-acyl anion equivalent (homoenolate) have been widely investigated. A solution to this problem utilizing allyltrimethylsilane is forthcoming.

The allyltrimethylsilyl anion (**38a**) is readily prepared from allyltrimethylsilane (**38**) by treatment with *s*-butyllithium in tetrahydrofuran. As an illustration of the use of **38a** in synthesis, and its high nucleophilicity, the synthesis of the 17-spirolactone steroid is described (Scheme **4**).[37] 3-Methoxyandrosta-3,5-dien-17-one (**47**) reacts with allyltrimethylsilylzinc chloride (**38a** plus $ZnCl_2$) to give the adduct **48** after acidic workup. The vinylsilane side chain present in **48** was epoxidized with $VO(acac)_2$/ *t*-BuOOH to give **49**. Methanolysis of **49** gave **50** which, on Jones oxidation, yielded the lactone **51**. The yield of **48** exceeded 90%, demonstrating that even in the case of hindered and readily enolizable 17-ketosteroids, the allyltrimethylsilyl anion is sufficiently nucleophilic to give excellent yields of addition products, namely **48**.

SILICON-STABILIZED YLIDES FOR CARBON-CARBON BOND FORMATION

We can represent a silicon-stabilized ylide by the general formula **52**. Such com-



52

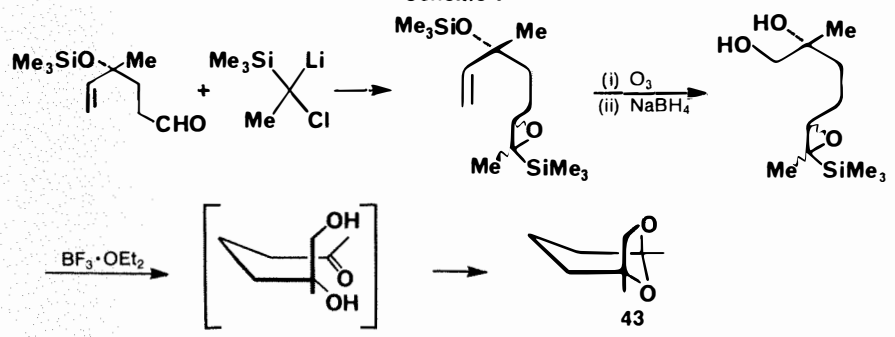
pounds have been known for a considerable time; notably, the works of Gilman,[38] Schmidbaur[39] and Miller[40] described how to make these ylides, but these reagents have not been used in synthesis.

We were concerned with developing a reagent that would convert α,β-unsaturated carbonyl systems into silylcyclopropyl ketones **53**. Methylthio-

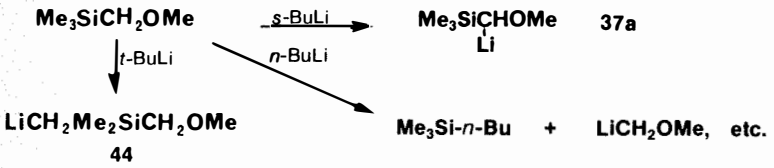
53

methyltrimethylsilane was converted into the methiodide **54** (Scheme 5), and deprotonated[41] using *s*-butyllithium in tetrahydrofuran to give the ylide **55**.[41]

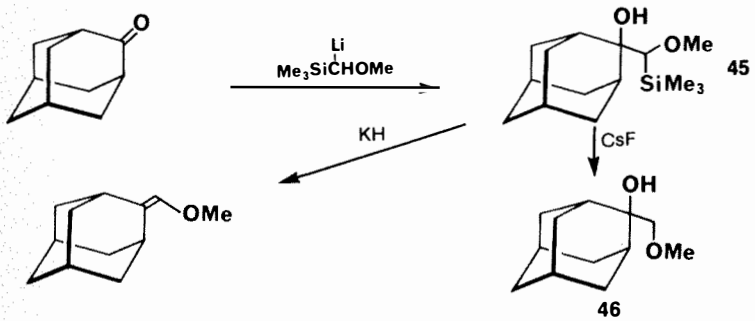
Scheme 1



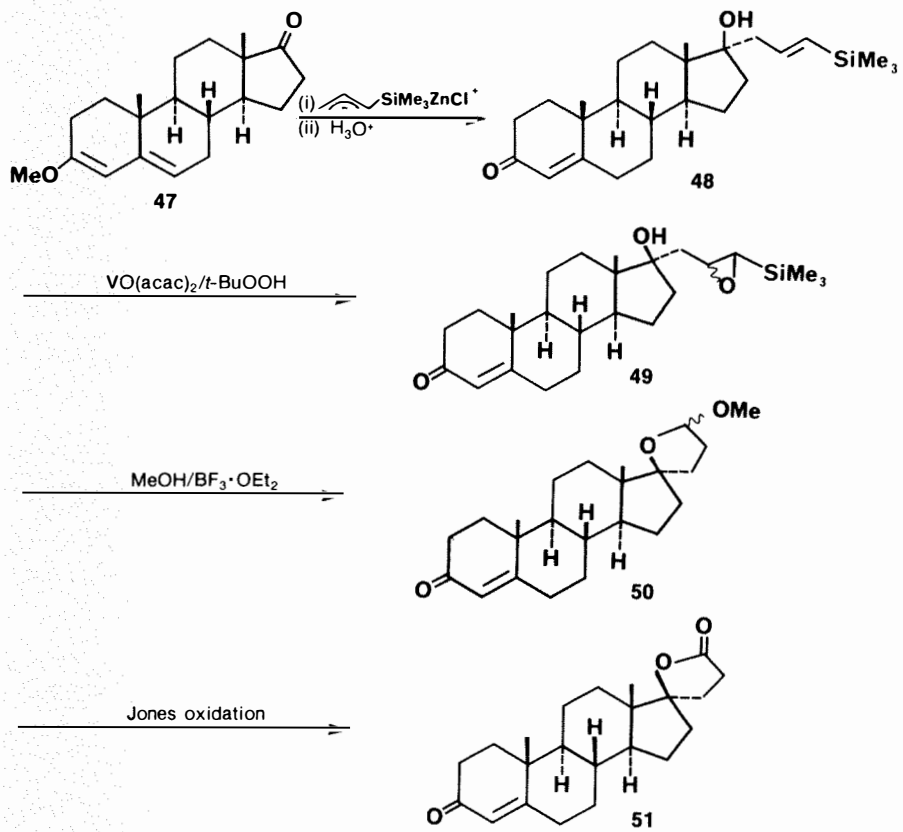
Scheme 2



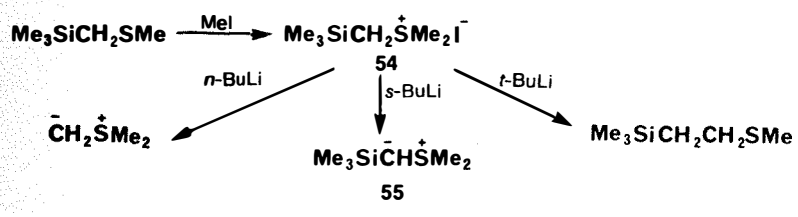
Scheme 3



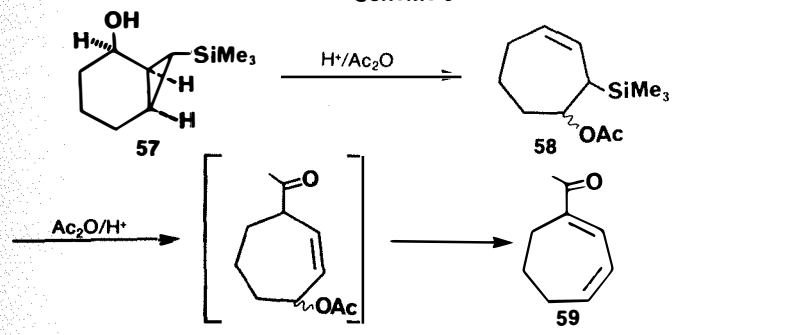
Scheme 4



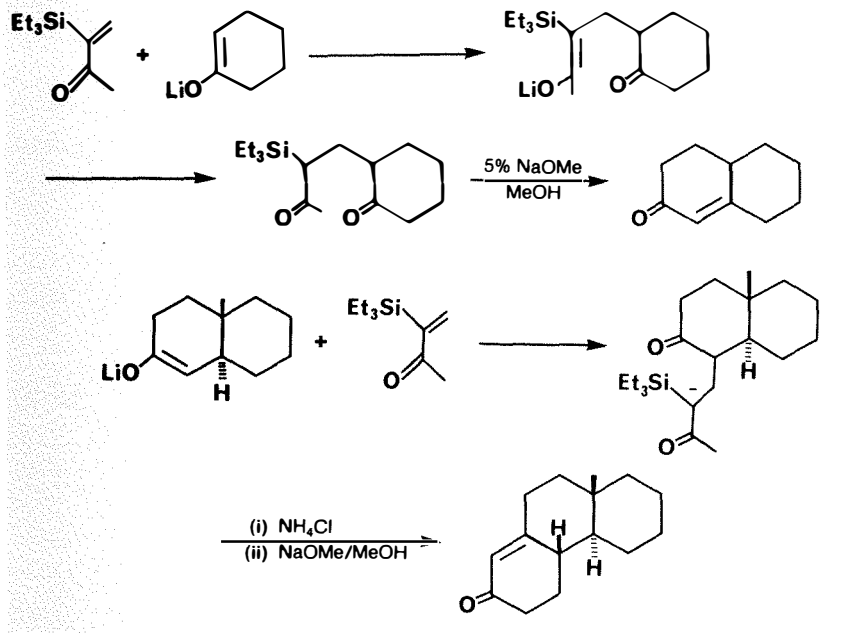
Scheme 5

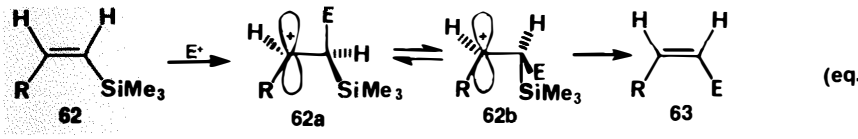


Scheme 6

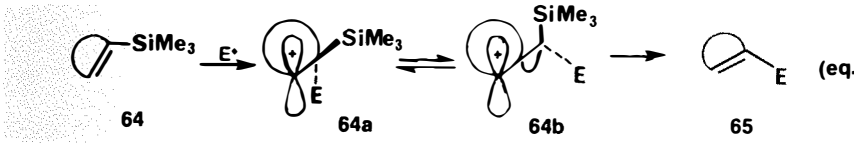


Scheme 7



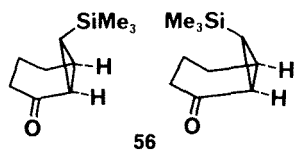


(eq. 9)



(eq. 10)

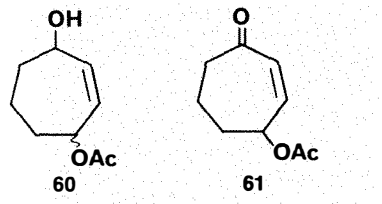
This new class of compounds offers the opportunity to conduct some useful synthetic transformations by exploiting the ability of the silicon atom to stabilize a β-carbonium ion. Treatment of **56** with sodium borohydride gave the alcohol **57**. When this alcohol was treated with acetic anhydride in the presence of a catalytic amount of perchloric acid (Scheme 6) the



56

exo:endo 7:1

compound **58** was formed. Further exposure of **58** to the above conditions gave the dienone **59**. The allylsilane has been acylated under these mild conditions. Another variation on this sequence is to treat **57** with AcOH/AcOOH/H^+ to oxidize the intermediate allylsilane **58** to the allylic alcohol **60**. Oxidation with pyridinium chlorochromate gave the ring-expanded γ-acetoxyenone **61**.[42]



VINYLSILANES FOR CARBON-CARBON BOND FORMATION

While this section will concentrate on the addition of carbon electrophiles to vinylsilanes mention is made of an important advance in annulation reactions. The conjugate addition of enolate anions to activated vinylsilanes (Scheme 7) has solved a long-standing problem in organic synthesis, namely the trapping of regiospecifically generated enolates in aprotic solvents with a methyl vinyl ketone equivalent, and subsequent reactions to produce an annulated product.[43]

The addition of an electrophile to a vinylsilane (**62**) results in the build-up of electrophilic character β to the carbon-silicon bond (eq. 9).[44] Such a species (**62a**) is said to be stabilized either by bridging,[45] or by so-called vertical stabilization (hyperconjugation).[46] The addition has the geometrical requirement that the electrophilic character of the β-position can only enjoy stabilization if the developing positive charge is contained in a $2p_z$ orbital that is in the same plane as the C-Si α-bond. This geometrical condition imposes a severe limitation upon the use of the β-effect for stabilizing electrophilic additions to vinylsilanes. In acyclic systems there is usually no problem; as the incoming electrophile approaches the vinylsilane π-system, rotation about the central carbon-carbon bond can take place to bring the β-carbonium ion into the same plane as the carbon-silicon bond,[47] **62**→**62a**⇌**62b**→**63**.

For cyclic vinylsilanes, particularly in conformationally rigid systems, it may be difficult, and in certain cases impossible, (eq. 10) for the carbon-silicon bond to move into the same plane as the $2p_z$ orbital carrying the positive charge, **64**→**64a**⇌**64b**→**65**.

As can be seen from the above mechanistic consideration, electrophilic substitution of vinylsilanes takes place with retention of geometrical configuration, and with the incoming electrophile replacing the trimethylsilyl group.

Treatment of the cyclic vinylsilane **66**

with acetyl chloride-aluminum trichloride at 0° (eq. 11) gave the enone **67** uncontaminated by other regioisomers.[48] It should be noted that the same electrophilic substitution when carried out on 4,4-dimethylcyclohexene gave a mixture of **67** and **68**. Several other examples of the electrophilic substitution of vinylsilanes with carbon-carbon bond formation are shown below (eq. 12-16).

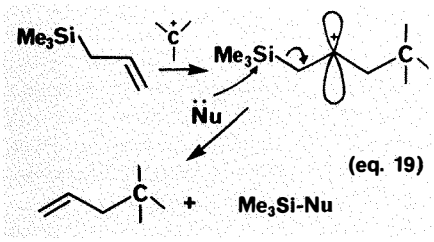
Vinyltrimethylsilane can act as an ethylene equivalent in Friedel-Crafts reactions to synthesize fused cyclopentenones. For example, treatment of the α,β-unsaturated acid chloride **69** with vinyltrimethylsilane (eq. 17) in the presence of stannic tetrachloride gave bicyclo[3.3.0]-Δ^7-octen-1-one **70** (52%).[54]

The roles of reagent and substrate in this annulation reaction may be reversed; treatment of the vinylsilane **71** with 3,3-dimethylacryloyl chloride in the presence of aluminum trichloride (eq. 18) gave **72**, which was cyclized with stannic tetrachloride to a mixture of isomers **73**. Treatment of this mixture with rhodium trichloride in ethanol at reflux converted unwanted isomers into **74**.[55]

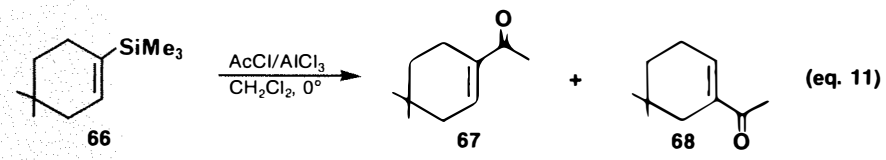
Another annulation reaction that utilizes a new vinylsilane reagent has been developed in our laboratories (Scheme 8). Treatment of vinyltrimethylsilane with phenylsulfenyl chloride in dichloromethane at -70° gave the adduct **75** in excellent yield. Dehydrohalogenation of the adduct **75** with DBU or DBN provided the substituted vinylsilane **76**.[56] When **76** was treated with α,β-unsaturated acid chlorides in nitromethane followed by silver tetrafluoroborate, the 3-thiophenylcyclopentenones **77** were produced.[57]

ALLYLSILANES FOR CARBON-CARBON BOND FORMATION

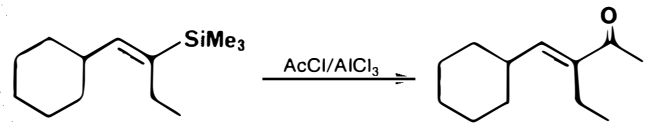
Without doubt allylsilanes have found the premier place in organosilicon chemistry, as applied to synthesis. This is primarily because allylsilanes are stable compared with other allylmetal species. As a result they usually give regiospecific reactions with electrophilic species. The general representation, in mechanistic terms, of the reaction of allylsilanes with carbon electrophiles is illustrated in eq. 19.



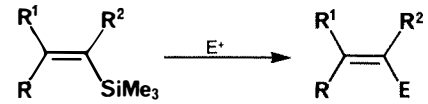
(eq. 19)



(eq. 11)

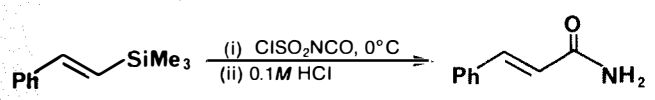


(eq.12)[49]

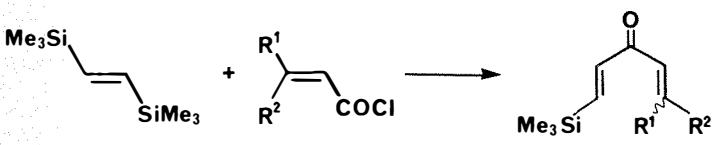


(eq. 13)

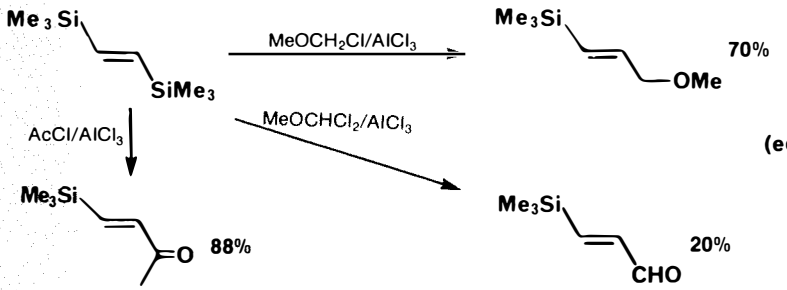
E = CH_2OMe,[50] E = $CH(OH)CCl_3$,[51] E = CHO[52]



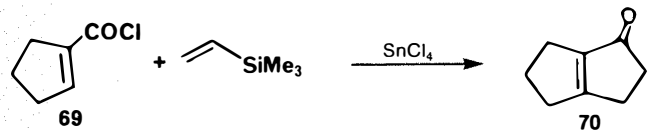
(eq.14)[53]



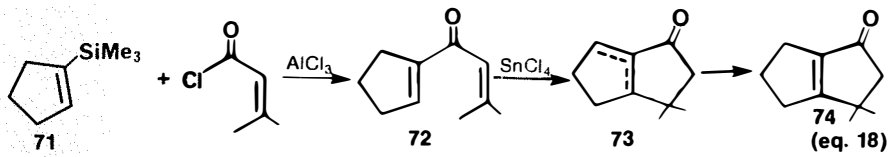
(eq.15)[51]



(eq. 16)



(eq. 17)



(eq. 18)

Scheme 8

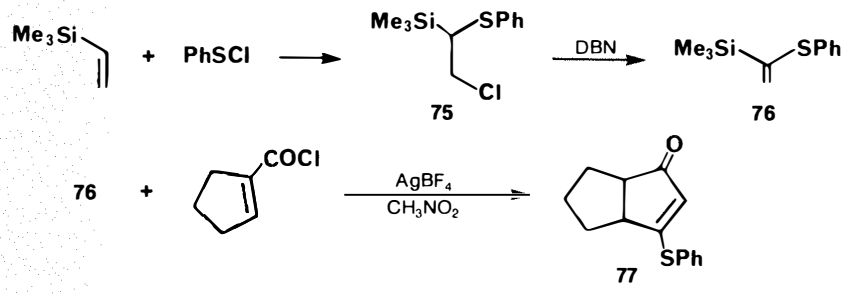
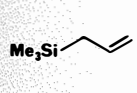
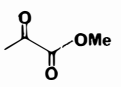
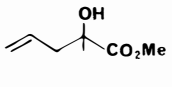
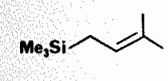
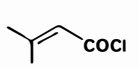
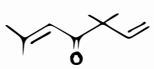
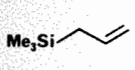
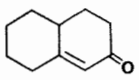
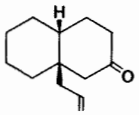
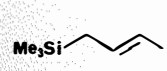
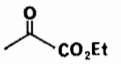
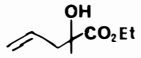
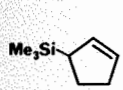
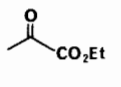
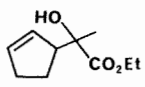
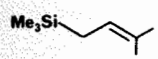
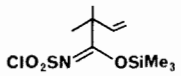
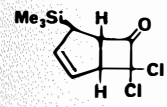
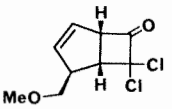
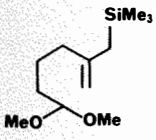
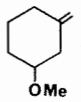
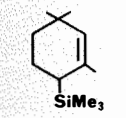
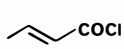
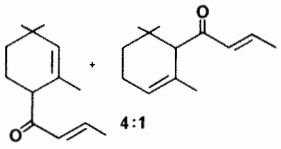
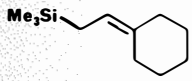
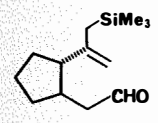
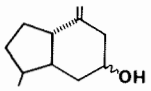
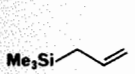
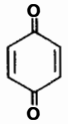
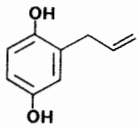
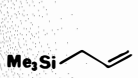
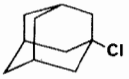
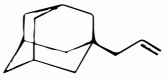
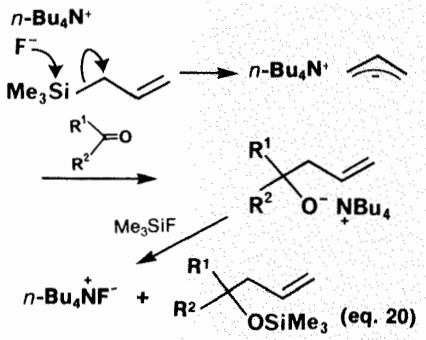


Table II

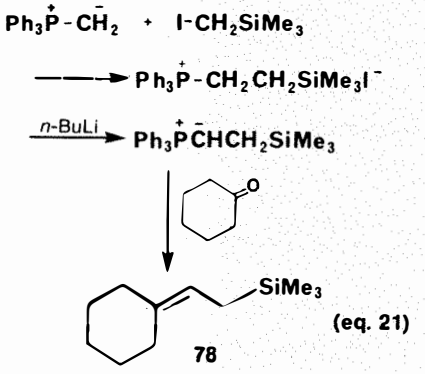
Substrate	Electrophile	Catalyst	Product	Ref.
				58
		$AlCl_3$/-60°		59
		$TiCl_4$/-30°		60
		$TiCl_4$/RT		61
		$TiCl_4$/-15°		62
	$ClSO_2NCO$	no catalyst, 0°		63
	$MeOCH_2Cl$	$SnCl_4$		64
	—	$SnCl_4$		65
		$SnCl_4$/0°	 4:1	66
	*t*-BuCl	$TiCl_4$		67
	—	$BF_3 \cdot OEt_2$		68
		$TiCl_4$		69
				70

The cleavage of the C-Si bond may be concerted with the build-up of electrophilic character β to the Si atom. The most important feature of this reaction is that the electrophile enters on the terminus of the allyl system, and the π-system is relocated adjacent to its original position. Because of this predictability, and the high nucleophilicity of allylsilanes, they have found many imaginative uses in synthesis. Table II provides a number of specific examples of this chemistry for carbon-carbon bond formation.

The silicon-fluorine bond is remarkably strong, *ca.* 140 kcal/mole. This can be applied in allylsilane chemistry by treating allyltrimethylsilane with tetra-*n*-butylammonium fluoride in the presence of an electrophile to generate the allyl anion.[71] The reaction is catalytic in fluoride ion, and explained by the mechanistic rationale in eq. 20.



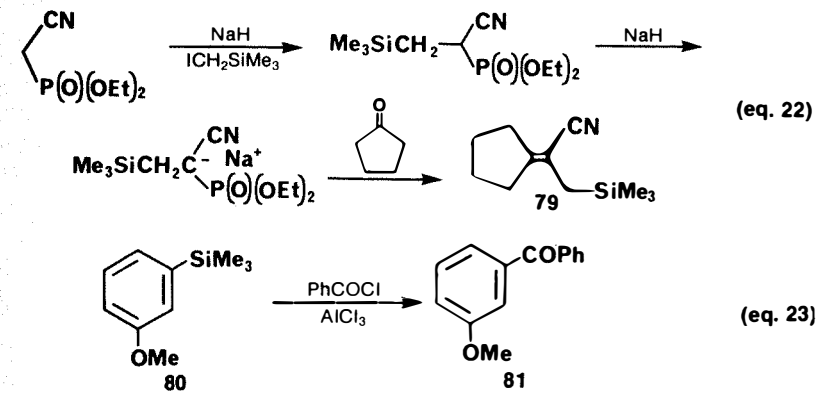
One of the major limitations of allylsilane chemistry is that there are no really versatile methods for preparing allylsilanes. It is not intended to discuss preparative methods for allylsilanes here[72] but to indicate the current trend. If allylsilane chemistry is to find a really useful place in organic synthesis then one must have ways of introducing this functional group into a relatively complex molecule in a predictable fashion. The Wittig reaction can be used to prepare allylsilanes by the sequence shown in eq. 21.[73]



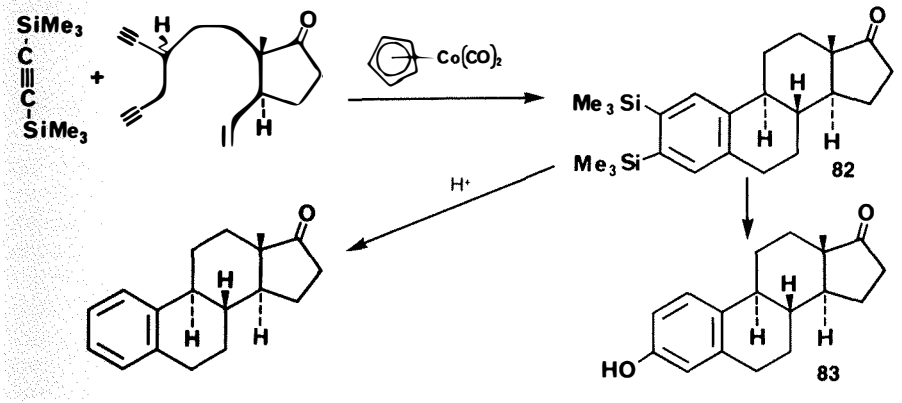
This sequence is adequate for aldehydes and reactive ketones, but unfortunately with cyclopentanone and acyclic ketones the yields of allylsilanes are extremely low.[74] A modification of the Wadsworth-Emmons-Wittig reaction allows the synthesis of functionalized allylsilanes.[75] The yield of **79** is 75% (eq. 22) and the reaction works with a wide range of ketones. As might be expected, since **79a** is an electron-deficient allylsilane it is relatively unreactive towards electrophiles.

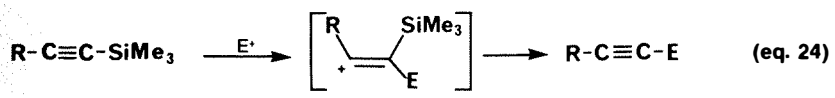
ARYLSILANES FOR CARBON-CARBON BOND FORMATION

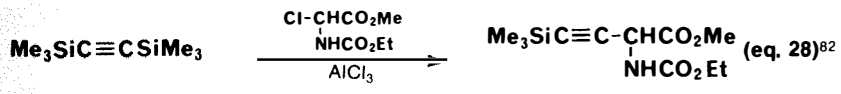
The use of arylsilanes for carbon-carbon bond-forming reactions is limited by the availability of the arylsilane, but it does

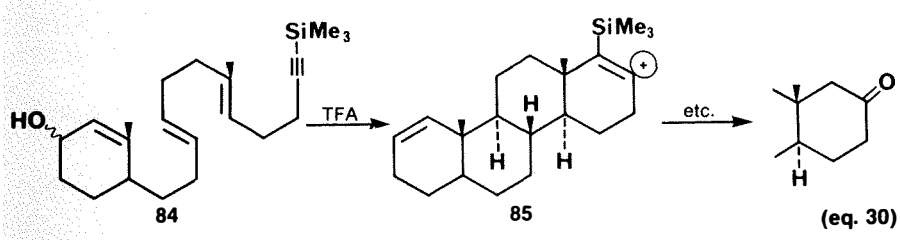


Scheme 9









have interesting and useful orientation value. It was shown by Eaborn that arylsilanes such as **80** (eq. 23) on treatment with benzoyl chloride in the presence of aluminum trichloride underwent electrophilic aromatic substitution (*ipso facto*) to give the *meta*-substituted anisole **81**.[76] The most dramatic example of the use of arylsilanes[77] in steroid synthesis is the total synthesis of estra(10)-trien-17-one by Vollhardt (Scheme 9).[78]

This sequence can be modified by the appropriate use of different electrophiles to convert **82** into estrone **83** itself.[78]

ALKYNYLSILANES FOR CARBON-CARBON BOND FORMATION

Alkynylsilanes react with electrophiles in much the same way as vinylsilanes; the electrophile attaches itself to the carbon atom bearing silicon, with the corresponding build-up of electrophilic character β to silicon (eq. 24).

Equations 25-29 are examples of this electrophilic substitution.

An excellent illustration of a polyene cyclization directed by a trimethylsilyl group is the conversion of the trienyne **84** into the D-homosteroid **85** (eq. 30). If the $-SiMe_3$ group is replaced by a methyl group then cyclization leads to the normal five-membered D-ring.[84]

CONCLUSION

The large number of examples of carbon-carbon bond-forming reactions shown in this review is by no means exhaustive, but illustrates the leading features that have brought organosilicon chemistry to its prominent position during the last several years.

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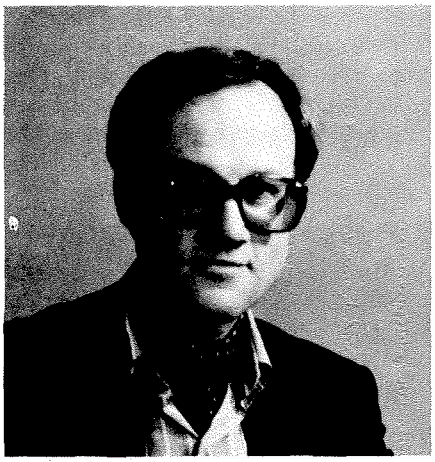
About the Author

Dr. Philip Magnus was born in England in 1943. From 1962 to 1968, he attended Imperial College in London, obtaining the Bachelor and Ph.D. degrees. He was on the faculty staff of Imperial College from 1966 to 1975 and has been at Ohio State University since 1975.

Dr. Magnus was awarded the Corday-Morgan medal and prize for organic chemistry by the British Chemical Society in 1978. He is also the recipient of the Akron ACS Award in 1980.

PTC in PracTiCe

Kjell Sjöberg
Department of Chemical Technology
Royal Institute of Technology
S-10044 Stockholm, Sweden



During the last few years articles and books on phase-transfer catalysis — PTC — have appeared in a steadily increasing stream.[1] The stream is likely to continue increasing and will change conventional chemical syntheses and processes greatly as many areas have been touched upon only briefly.

The transfer of hydrophilic ions into a lipophilic organic medium seems strange at first, but in practice the technique is remarkably simple.

For this article I have abstracted PTC information that has been valuable in our own process development work. Some ideas are taken directly from the literature while others have been developed further through our daily use. Areas focused upon are:

- replacement of sodium or sodium hydride by 50% NaOH in alkylation reactions
- extended uses of inorganic salts in organic reactions
- C- *vs.* O-alkylations
- transfer of "nonionic" species like H_2O_2 and HCl
- extractive separations.

I will also discuss catalyst cost and advantages of catalyst recovery. A simple quantitative analytical method for quaternary ammonium ions, the most common PTC catalysts, is described.

The reader who has had only brief contact with PTC techniques will find background information in the literature given in reference 1.

Use of 50% NaOH instead of sodium in alkylations

PTC sometimes allows strong bases like sodium hydride or sodium amide to be replaced by 50% aqueous sodium hydroxide[2] or, better still, a mixture of solid sodium hydroxide and sodium carbonate.[3] Zwierzak has shown that benzamides and formamides can be N-alkylated in good yields in such a solid base-organic liquid two-phase system.[4a] He uses about 10 mole % of $TBAHSO_4$, but this figure can probably be lowered under optimized industrial conditions. However, at a conventional PTC catalyst level of 1 mole % the yield is halved. One of Brändström's coworkers, Ulf Junggren, in his thesis of 1972, showed that benzamide could not be alkylated using 50% sodium hydroxide in the "Extractive Alkylation Procedure."[4b] Junggren states that "the limit for the practical application of this procedure is for compounds with a p*Ka* of about 15." For the alkylations of weaker acids he gives sodium hydride as the alternative. Using Zwierzak's modification, however, this limit moves to a p*Ka* of 22-25.

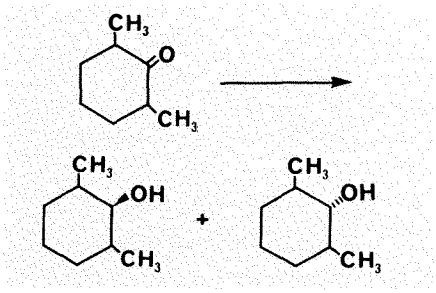
Alkylation of *N*-alkylformamides, general procedure

The mixture of the *N*-alkylformamide (0.1 mol), finely powdered sodium hydroxide (14.0g), potassium carbonate (8.0g), tetra-*n*-butylammonium hydrogen sulfate (3.4g, 0.01 mol), and benzene (60ml) is stirred vigorously at 35-40°C for 30 min. The resultant slurry of the sodium salt of the amide is heated to 60° and a solution of the alkylating agent (0.2 mol of dimethyl sulfate or 0.1 mol of alkyl halide) in benzene (40ml) is then added at this temperature over a period of 1 h. Stirring is continued at 60-70° for 4h. The mixture is then cooled to room temperature, diluted with benzene (50ml) and filtered. The precipitate is washed with benzene (2 x 30ml) and the washings are combined with the filtrate. The benzene solution is washed with water (2 x 20ml), dried with anhydrous magnesium sulfate and evaporated. The oily residue is kept at 30-40°/0.2 torr for 1 h to remove volatile impurities. Crude products are analytically pure.

Uses of "new" inorganic anions

TBA salts of a number of common inorganic ions which have not been found to have extensive organic chemical use earlier are now being reported. The high solubility of inorganic anions as their TBA salts in nonpolar organic solvents never ceases to surprise traditional chemists. Try 40% TBAOH in water with an equal amount of petroleum ether!

Quaternary ammonium dithionite has already been used in reductions of ketones to alcohols.[5] It may become a cheap alternative to established reducing agents.



To our knowledge the anion of sodium carbonate peroxyhydrate ("solid H_2O_2") has not yet been tried with the PTC technique. This salt has been put on the market recently by Interox America and might find use as an oxidizing or epoxidizing agent using the PTC technique.[6]

$TBABF_4$ is reported as a useful electrolyte in electrochemical synthesis.[7]

$TBAClO_4$ has interesting solubility properties. It is almost insoluble in water.

$TBAMnO_4$ is frequently used in oxidations.[8] However, it is unstable and thus dangerous to use as an isolated salt.[9]

Although borohydrides are well established in organic synthesis, an extra advantage of using $TBABH_4$ deserves attention. In an earlier survey on "Applications of Phase-Transfer Catalysis in Organic Synthesis," reduction with $TBABH_4$ was reported.[1a] $TBABH_4$ is readily obtained from $TBAHSO_4$. Applications of this lipophilic BH_4^- salt are presently arousing interest.

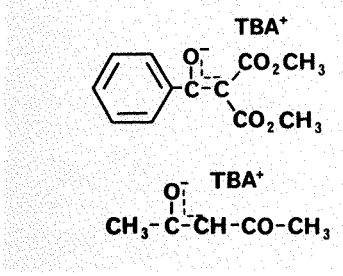
Not only can solid $TBABH_4$ be isolated, its solution in a non-ethereal solvent can be obtained.[10] The replacement of ether or THF by dichloromethane is a contribution to laboratory and industrial safety. Diborane is easily obtained from a dry solution of $TBABH_4$ in dichloromethane by treatment with an alkyl halide such as methyl iodide or 1,2-dichloroethane. The diborane solution thus obtained can be used for all the common reductions and hydroboration reactions.

C- *vs.* O-alkylation

Solvents have a well-known effect on C- *vs.* O-alkylation. Similarly, application of the PTC technique can change the C/O ratio.

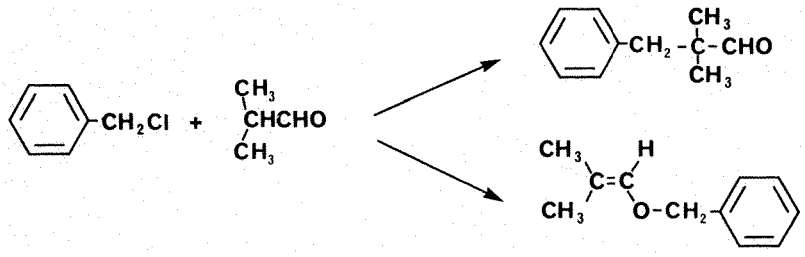
Brändström and Junggren have studied factors influencing C- *vs.* O-alkylation of ambident anions such as those of methyl acetoacetate and dimethyl benzoylmalonate. The expected importance of the alkylating agent is verified.[11,12,13]

These three papers introduce the concept of "extractive alkylation." The authors have isolated the crystalline TBA salts of dimethyl benzoylmalonate and acetylacetone.



C- *vs.* O-alkylation of aldehydes

We have studied the alkylation of isobutyraldehyde in our laboratories.[14] In the manufacture of 1-butanol by the OXO-process between 10 and 25% of isobutyraldehyde is formed as a by-product. This compound is available worldwide in quantities of 500 million lbs/year and premium outlets are sought. After treating isobutyraldehyde with benzyl chloride, we have isolated, not only the C-alkylated product, but also the O-alkylated one which has not been previously reported.



The highest C/O ratio (10.9) is obtained using tetrapropylammonium iodide. The bigger tetrabutylammonium ion gives a smaller C/O ratio. TBA counterions less lipophilic than iodide, *viz.*, bromide, chloride and sulfate all give smaller C/O ratios (see Table 1).

Most surprising is the higher yield obtained when iodide is the counterion. The known poisoning effect of iodide in PTC reactions seems not to apply to this reaction. A yield of 80% is obtained although only 1 mole % of catalyst is used. Furthermore, the reaction is faster when iodide is the counterion.

Transfer of neutral molecules

Transfer of hydrogen peroxide anions from an alkaline aqueous phase is not practically possible.[15] Hydrogen peroxide anions remain mainly in the aqueous phase. However, in neutral or acidic media hydrogen peroxide molecules are indeed transferred, probably solvated, by TBA bromide. Dehmlow has demonstrated that the more lipophilic the ion pair, the better it transfers H_2O_2.[15] $TBAHSO_4$ transfers only 10% of the equivalent amount of H_2O_2, whereas TBABr transfers 68%. The still more lipophilic tetrahexylammonium bromide transfers H_2O_2 equivalently. Similarly, hydrogen chloride can be transferred into benzene.

Recovery of TBA ions

Catalysts are expensive and are normally used over and over again. In industrial processes, recovery and regeneration of ineffective catalysts are standard procedures.[3] The cost of these operations plus make-up catalyst is included as catalyst cost in the process cost calculation. The price/lb of the catalyst itself is seldom representative of catalyst cost in a process.

Table 1

Alkylation of isobutyraldehyde with benzyl chloride in 50% sodium hydroxide/toluene at 70°C for 4 hours

No.	Catalyst (1.25 mole %)	C/O ratio	Benzyl chloride reacted (%)
1	TBA iodide	7.6	82.7
2	TBA hydrogen sulfate	4.3	71.0
3	TBA bromide	3.7	74.0
4	Tetrapropylammonium iodide	10.9	79.3
5	Methyltrioctylammonium chloride	5.8	68.5
6	TBA chloride	4.3	69.2

Let us examine the figure used as catalyst cost in the PTC field. A PTC catalyst is recovered by an extractive procedure. Regeneration (*i.e.*, requaternization of a tertiary amine) is probably not of interest.

We have made a catalyst-cost calculation on the propylation of phenylacetonitrile by 1-chloropropane.[16] We use $TBAHSO_4$ as a catalyst at $8/lb and 50% NaOH as a base. At the laboratory scale it was possible to recover 87% of the catalyst as TBACl after the reaction. This puts the figure for catalyst cost, including recovery cost, at about $2 per pound of $TBAHSO_4$ charged in an industrial scale.

Recovery at such a high percentage is only possible for quaternary ammonium ions with a balanced hydrophilicity/lipophilicity. The TBA ion outstandingly combines the lipophilicity necessary for an efficient PTC catalyst with the hydrophilicity necessary for efficient recovery.

How is this recovery achieved?

There are three different ways to recover a quaternary ammonium ion.

1) Salt it out from an aqueous phase with sodium hydroxide.[17]
2) Transfer it selectively into the desired phase using a suitable counterion.[18]
3) Transfer it selectively into the aqueous phase by cooling.[19]

Recovery according to method 1 is accomplished as follows. The solubility of tetrabutylammonium bromide in sodium hydroxide solutions varies markedly with the concentration. A solution of 1% NaOH can dissolve 27% TBABr, whereas a 15% NaOH solution only dissolves 0.07% of TBABr. This spectacular difference in solubility can be utilized in synthetic work as well as in process design. The factor to keep in mind is that hydroxide ions often are consumed during the course of the reaction. If NaOH is not in excess during the latter part of the reaction, the availability of the PTC catalyst will drop, thus changing the reaction conditions.

An example of method 2 is the addition of a lipophilic sulfonate, such as sodium naphthalenesulfonate, or a lipophilic carbonic acid to an aqueous solution containing a quaternary ammonium compound.[18] By this procedure TBA^+ is transferred into an organic phase. If TBA^+ is to be moved into an aqueous phase, the system should be acidified with sulfuric acid. The naphthalenesulfonic acid will remain in the organic layer and TBA^+ as the hydrogen sulfate will move into the water. Unfortunately, this simple procedure does not work for all quaternary ions. The more lipophilic they are, the less easy it is to transfer them into water.

Walters has demonstrated the third method of recovery by showing that the distribution of TBA salts between an aqueous and an organic phase is strongly temperature-dependent.[19] In the hydrodimerization of acrylonitrile to adiponitrile TBA salts are used as electrolytes. When the adiponitrile is purified there is the problem of removing TBA salts dissolved in the product. This has been done effectively by cooling the product emulsion from 25°C to 0°C.

$$K = \frac{\text{wt \% of TBA in the organic phase}}{\text{wt \% of TBA in the aqueous phase}}$$

$K_{25°C} = 1.4$; $K_{0°C} = 0.01$

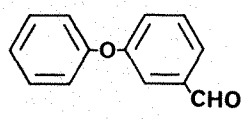
The distribution of the organic products is not affected by the change in temperature.

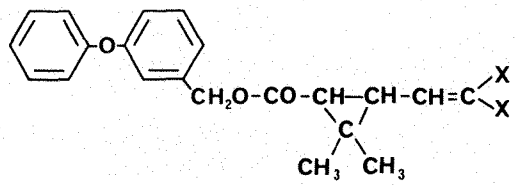
In the recovery of quaternary ammonium ions the best results are obtained with TBA ions. Generally, methyltrioctyl ions are too lipophilic to reenter an aqueous phase to a practical degree.

Extractive separations

Quaternary ammonium salts may also be used in purifications. Harmful ions like cyanides or phenolates can be transferred from an aqueous waste stream into an organic phase. Valuable compounds like penicillins can be separated as TBA salts and thus recovered.

Aldehydes are purified as bisulfite complexes. $TBAHSO_3$ is easily transferred into the organic phase and the formation of bisulfite complexes of lipophilic aldehydes is rapid. Mizutani and co-workers report the purification of 3-phenoxybenzaldehyde in this manner. The impure aldehyde itself serves as the organic phase and the crystalline bisulfite adduct is easily separated from the impurities. Again TBA salts give the best results and purities of more than 99% are obtained. The purity of the aldehyde is important in the manufacture of chrysanthemic esters, well-known insecticides.[20]





In the subsequent esterification of chrysanthemic acid with 3-phenoxybenzyl chloride, PTC is also favorably used.

Environmental aspects

In earlier days the LD_{50} value of a compound gave sufficient information about its toxicity. Today additional information, such as fish toxicity (LC_{50}), plays an important environmental role. A comparison of the LD_{50} and LC_{50} values of the two TBA salts seems to show a practical PTC example. The LD_{50} values on $TBAHSO_4$ and TBABr are both between 500 and 600mg per kilo of body weight. In the case where the salt is administered into the test animal, the impact of the counterion is low.

A look at the LC_{50} values gives a very different picture of the two salts. A zebrafish, generally accepted as a representative test fish, tolerates a 2.5 times higher concentration of $TBAHSO_4$. This can be attributed to the more lipophilic nature of TBABr. The values are:

$TBAHSO_4$	3370mg/l, 96 hours
TBABr	1380mg/l, 96 hours

Titration of TBA ions

An important method of titration of lipophilic cations like TBA ions is well-hidden in Brändström's "Preparative Ion-Pair Extraction".[18] The method is important because it is a simple quantitative analytical technique for quaternary ammonium ions. Other methods used to determine quaternary ammonium ions, *e.g.*, ion-exchange to the quaternary ammonium iodide, then transfer of the iodide to an organic phase followed by treatment with mercuric acetate and titration of acetate ions with perchloric acid, gives the amount of the counterion from which the figure for TBA ions can be calculated indirectly only.

Brändström titrates in a two-phase system, water and methylene chloride. Thus, the titration itself is a practical application of PTC (what else!). The titrant is a sulfonate, potassium 3,5-di-*tert*-butyl-2-hydroxybenzenesulfonate, that is very lipophilic. At the beginning of the titration the amount of TBA ions in the sample is distributed between the aqueous and the organic phase. During the titration all TBA ions present in the aqueous phase move as ion pairs with the sulfonate into the organic phase. The TBA ions already present in the organic phase at the beginning of the titration, owing to the distribution, pull an equivalent amount of sulfonate ions into the organic phase. When all TBA ions are present in the organic phase, an indication that the titration end point is reached is necessary. The sulfonate with an *o*-hydroxy function also acts as a chelating agent for ferric ions. The chelate is greenish blue. The addition of ferric chloride to the aqueous phase gives the indication.

Experimental part

1) Titration of crystalline TBA salts

Dissolve an accurately weighed sample of about 320mg TBABr or 340mg $TBAHSO_4$ in 20ml of dichloromethane. Add 20ml of indicator solution B (see below).

Titrate under stirring with solution A (see below) until the lower dichloromethane layer gets a faint blue color. The upper aqueous layer, at this stage, will have changed from yellow to blue-green.

Calculations:

$$\text{TBABr \%} = \frac{A(322.4)(M)}{100(\text{mg TBABr})}$$

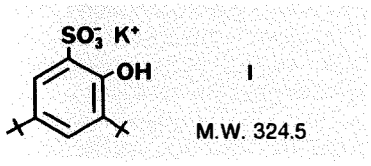
$$\text{TBAHSO}_4\text{ \%} = \frac{A(339.5)(M)}{100(\text{mg TBAHSO}_4)}$$

A = ml of solution A
M = molarity of solution A

2. Titration of TBA salts in solution

A solution containing about 0.3g of TBABr or $TBAHSO_4$ is made alkaline and extracted twice with ether if contaminated with organic compounds other than the TBA ion (such as amines) and then acidified. To the sample is then added 20ml of dichloromethane and 10ml of solution B. The mixture is then titrated as in procedure 1.

Solution A: A 0.1 *M* solution of potassium 3,5-di-*tert*-butyl-2-hydroxybenzenesulfonate (**I**) is prepared by dissolving 32.4g of **I** in water containing 10% acetone to a total volume of 1 liter.



I

M.W. 324.5

Solution B (indicator): A 0.1 *M* solution of $FeCl_3 \cdot 6H_2O$ in 0.1 *M* HCl is prepared by dissolving 27g of $FeCl_3 \cdot 6H_2O$ (M.W. = 270.3) in 1 liter of 0.1 *M* HCl.

Procedures:

Solution A is standardized prior to use with a reference sample of TBABr or $TBAHSO_4$. See titration procedure 1.

Calculations:

$$\text{Molarity Solution A} = \frac{\text{mg TBABr}}{(322.4)(\text{A})} = \frac{\text{mg TBAHSO}_4}{339.5\ (\text{A})}$$

Accuracy of the method:

Titration of 20ml of a 0.01 *M* solution of a TBA salt will give a breakpoint within 0.03ml of the sulfonate solution.

At lower concentrations of TBA (0.001 *M*) there is no color in the organic phase, but the aqueous phase will change from light green to light blue. The change interval is now larger.

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About the Author

Dr. Kjell Sjöberg studied organic chemistry at the University of Stockholm, Sweden and obtained his doctorate in 1971 for a thesis on synthetic penicillins. In the course of the work he spent a year at the University of Munich and concluded at the Royal Institute of Technology in Stockholm. He had also spent a year at Harvard University (1967) working on organometallic chemistry.

In 1968 he joined the Swedish chemical company KemaNobel, and in 1975 returned to the Royal Institute of Technology as a Professor of Chemical Technology. At present he is on a half-time appointment at Bofors Nobel Kemi AB, which recently took over a company he had founded, Synecon Chemicals AB.

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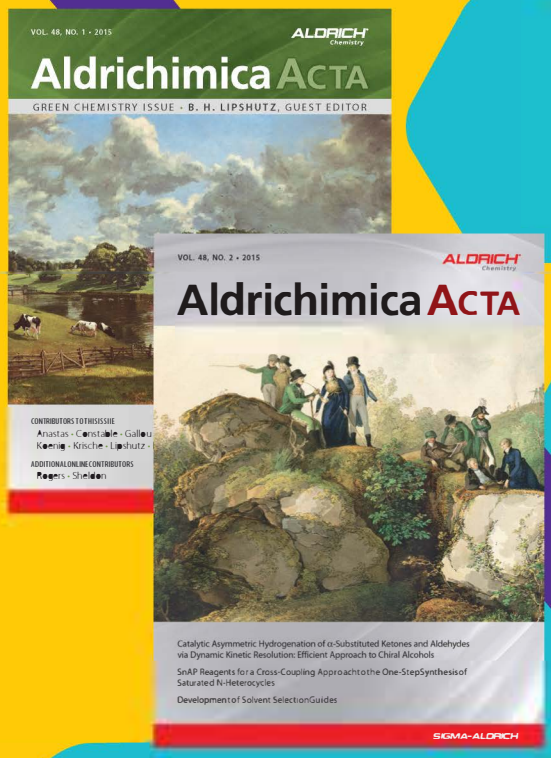

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