Aldrichimica Acta

Applications of Sulfoximines in Synthesis

The Use of Carbon-13-Labeled Compounds in Organic Chemistry, Biochemistry and Medicine

Aldrichimica Acta

About Our Cover:

Our chemist-collector prefers Biblical paintings of the School of Rembrandt to all others, and believes that this moving landscape (oil on canvas, 33 × 50 inches) qualifies. Philips Koninck, probably a Rembrandt student in the early 1640's, became one of the greatest landscape artists ever. This painting is done with such assurance, that it must be a mature work of the artist, done around 1675. The whole world is before us in this sunset scene, and how insignificant is man. Perhaps Koninck was inspired by one of the Psalms: "The Heavens declare the glory of God, and the firmament showeth His handiwork."

The painting was sold recently at Christie's in London, and brought only a small fraction of the value of a fine Koninck landscape. The sky had been completely overpainted and most connoisseurs feared that it had been overcleaned and then overpainted. Fortunately, a subsequent cleaning proved this fear groundless: the original, beautiful sky is intact, and had just been glazed over by an inexperienced restorer.

It is our collector's finest landscape.

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

Reprints of Aldrich Catalog Covers

Six beautiful 14 × 11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta*, we now offer a collection of articles selected from volumes 1-15. We chose those articles which we believe are still of interest to our readers — 354 pages of great review articles, in one beautiful hardbound volume.

Lab Notes

I have devised some simple solutions to prevent refluxing solvents or splashing reaction mixtures from entering an all-glass stirrer shaft and bearing assembly.

For non-refluxing or non-heated systems, a straight glass joint *ca.* 6″ long, with male and female ends will serve as a "spacer" between the bearing and the system (see Fig. 1). (This spacer could take the form of, *e.g.*, the straight portion of a Claisen adapter if an extra neck is needed.)
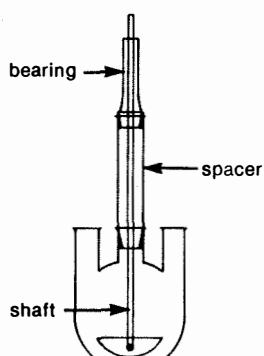

Figure 1

For refluxing systems, a short spacer-condenser, *ca.* 6″ long, with a wide internal diameter will keep the hot vapors refluxing below the bearing (see Fig. 2). (Existing water-cooled bearings do not prevent solvents from forming a plug between the rotating shaft and bearing walls.)
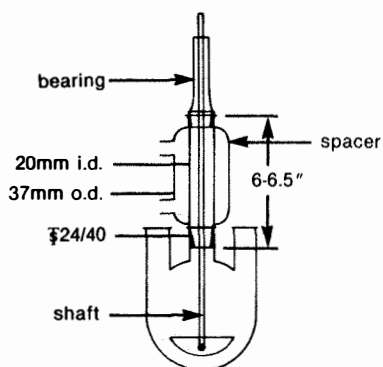

Figure 2

Use of these spacers prevents accumulation or escape of liquids or freeze-ups caused by either trapped solid particles or dissolving bearing lubricants.

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I have found that flash chromatography tends to give broad elution bands and, therefore, decreased resolution. This is caused in part by the need to load the sample in a large volume of the solvent mixture to obtain the required R_f value for the desired product, or to load with a more polar solvent, decreasing separatory resolution by an increase in the R_f value.

These problems can be overcome and increased resolution achieved by preadsorbing the sample onto anhydrous sodium sulfate, fine powder, in a ratio by weight of *ca.* 1:5 to 1:10, respectively.

The mixture is easily eluted from the sodium sulfate and adsorbed onto the top of the silica packing in a tight band. The sodium sulfate then acts as a protective layer for the column packing when adding more solvent. Adsorbing the mixture onto the sodium sulfate is no problem if the trap shown below is used in conjunction with rotary evaporation, and a gentle take-off of solvent (CH_2Cl_2 is a good choice).

coarse glass sinter
or cotton wool
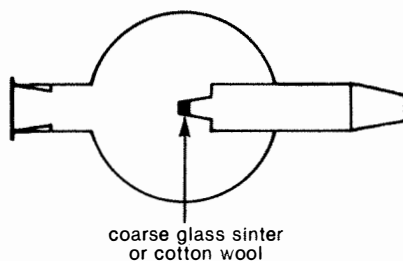
When all the solvent is removed, a "flowable" powder is obtained, easily removed from the round-bottom flask and poured directly onto the top of the silica packing, pre-eluted with the desired solvent system (it is best if the top of silica packing is slightly dry).

A small amount of solvent, *ca.* 4″ deep, is placed over the sodium sulfate layer and sucked through it. Chromatography then proceeds normally. This preadsorption technique is as quick as wet loading, and I now use it routinely.

Dr. Ian Dawson
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Editor's note: We have employed this technique successfully here at Aldrich, using neutral alumina instead of sodium sulfate.
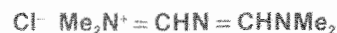
Aldrich offers an adapter with extra-coarse fritted disc, for use with rotary evaporator.

Recently Prof. John T. Gupton at the University of Central Florida suggested that we offer Gold's Reagent[1] which reacts in many ways like the DMF acetals, with some distinct advantages.[2-6]

$$Cl^- \ Me_2N^+ = CHN = CHNMe_2$$

It is an efficient β-dimethylaminomethylenating agent for ketones.[2,3] It also reacts easily with esters and lactones to yield the corresponding enamino derivatives.[4] Perhaps its greatest utility will be in the conversion of Grignard reagents to the corresponding aldehydes.[5]

Naturally we made Gold's Reagent.

1) Gold, H. *Angew. Chem.* **1960**, *72*, 956.
2) Gupton, J.T. *et al. J. Org. Chem.* **1980**, *45*, 4522.
3) Gupton, J.T.; Andrew, S.S.; Colon, C. *Synth. Commun.* **1982**, *12*, 35.
4) Gupton, J.T.; Lizzi, M.J.; Polk, D.E. *ibid.* **1982**, *12*, 939.
5) Gupton, J.T.; Polk, D.E. *ibid.* **1981**, *11*, 571.
6) Gupton, J.T.; Correia, K.F.; Hertel, G.R. *ibid.* **1984**, *14*, 1013.

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

Applications of Sulfoximines in Synthesis

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I. INTRODUCTION

In 1946, Sir Edward Mellanby established that dogs fed a diet rich in "commercially improved" (nitrogen-trichloride-treated) flour were subject to "hysteria" or "running fits"; he concluded that nitrogen trichloride gave rise to the responsible toxic factor.[1] Since a significant portion of commercial flour was treated with nitrogen trichloride, this became a matter of c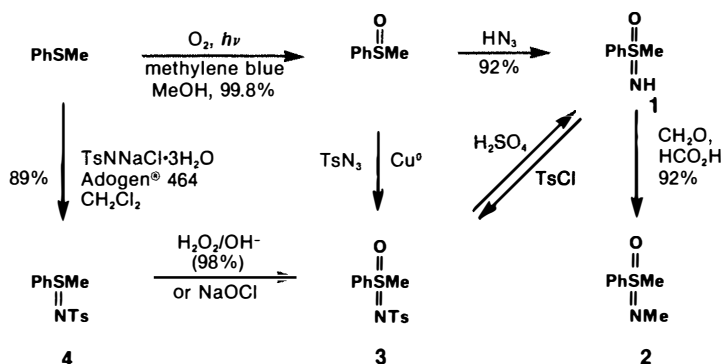oncern and a number of research groups initiated efforts to isolate and determine the structure of the toxic factor.[2] In 1949 Bentley, McDermott, Pace, Whitehead, and Moran[2b] reported the isolation of the crystalline toxic factor which was soon shown to be a "sulfoximine" of methionine by a synthesis involving treatment of "methionine sulfoxide" with hydrazoic acid.[2d,e,h] The sulfoximine functionality had been previously unknown. Following this initial activity, interest in this area quieted. In 1968 our laboratories began a long-range program to explore the synthetic applications of S-methyl-S-phenylsulfoximine (1) which appeared to us to be remarkably versatile.[3] The compound is chiral at sulfur. It has acidic hydrogens on carbon and nitrogen. The nitrogen is sufficiently basic to form salts with mineral acids and can serve as a point for additional substitution. The nature of the substituent on nitrogen

dramatically influences the acid/base properties of the compound (Table 1).[4] The general topic of sulfoximines has been featured in a number of recent reviews.[5,6] This review will focus on the synthesis of reagents derived from S-methyl-S-phenylsulfoximine (and a few related substances) and their applications in synthetic organic chemistry.

II. PREPARATION OF S-METHYL-S-PHENYLSULFOXIMINE

The method routinely used in our laboratory for the preparation of S-methyl-S-phenylsulfoximine is that of Whitehead and Bentley[2f] in which methyl phenyl sulfoxide is treated with hydrazoic acid generated by addition of sulfuric acid to a slurry of sodium azide in chloroform (Scheme 1).[7] Any reaction involving hydrazoic acid has a high hazard liability; we carefully maintain the temperature of the reaction mixture at ca. 45 °C. We have run the reaction several hundred times without incident. In general, this method works very well for the production of sulfoximines from sulfoxides when both carbon substituents are either primary or aryl; otherwise heterolysis of carbon-sulfur bonds occurs in the highly acidic and polar

Table 1
pKa's of S-Methyl-S-phenylsulfoximine and Related Compounds

In DMSO

PhSCH$_3$	PhS(=O)CH$_3$	PhS(=O)$_2$CH$_3$	PhS(=O)(=NMe)CH$_3$	PhS(=O)(=NTs)CH$_3$	PhS(=O)(=NTs)CH$_3$
~49	~32.5	29.0	~32	27.7	24.5

PhS(=O)(=NH)CH$_3$	PhS(=O)(=NMe$_2$)CH$_3$ BF$_4^-$	*In Water*	PhS(=O)(=NH$_2$)CH$_3$ Cl$^-$
24.3	14.4		2.7

Scheme 1

reaction medium.

Numerous methods can be used for the high-yield oxidation of thioanisole to methyl phenyl sulfoxide. We have found that a singlet oxygen procedure is superior.[8] We use methanol as the solvent, a high-pressure sodium "street" lamp as the light source, methylene blue or rose bengal as the sensitizer, and technical-grade oxygen as the oxidant. The reaction can be readily run on a large scale; we often oxidize as much as 6 moles in a run, with yields better than 99%.
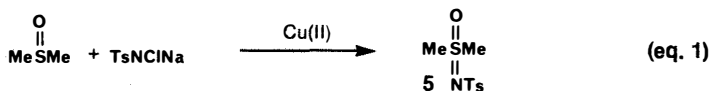
Neither the simple N-H sulfoximine nor its N-sodio (or N-lithio) salt is highly nucleophilic and attempts to alkylate these substances with typical alkylating reagents gave unsatisfactory results. The Clarke-Eschweiler procedure using formaldehyde and formic acid, however, provides a very effective method for the transformation of **1** to *N,S*-dimethyl-*S*-phenylsulfoximine (**2**).[9,10] Since the NH of **1** is more acidic than the CH's, the presence of a blocking group on nitrogen is necessary to direct mono-deprotonation to the alpha carbon. The N,C-dilithio derivative of **1** is readily generated but its chemistry has not been explored much.[11]

N-Tosylsulfoximines (*e.g.*, **3**) can be prepared by the tosylation of N-H sulfoximines with *p*-toluenesulfonyl chloride in the presence of base (Scheme 1).[12] Two other general methods for the preparation of N-tosylsulfoximines are (1) the oxidation of N-tosylsulfilimines (*e.g.*, **4**) with basic hydrogen peroxide[13] or sodium hypochlorite in the presence of a phase-transfer catalyst[14] and (2) the copper-powder-promoted reaction of sulfoxides with *p*-toluenesulfonyl azide (Scheme 1).[12,15]

S,S-Dimethyl-*N*-tosylsulfoximine (**5**) can be readily prepared from dimethyl sulfoxide and Chloramine-T in the presence of copper (Cu[0], Cu[I], or Cu[II]) (eq. 1);[12,16] this reaction fails with most other sulfoxides. These N-tosylsulfoximines can serve as a source of N-H sulfoximines by hydrolytic removal of the tosyl group with concentrated sulfuric acid; once again, carbon-sulfur bond heterolysis can be a serious problem with secondary or tertiary alkyl groups on sulfur.

Compound **1** can be readily resolved using 10-camphorsulfonic acid.[9,17] From the *d*-acid the salt of (+)-(*S*)-**1** is obtained pure by recrystallization. Optically pure (+)-(*S*)-**1** has $[\alpha]^{25} + 36.5°$ (c = 1.2, acetone); optically pure (+)-(*S*)-**2** has $[\alpha]^{25} + 184°$ (c = 1.7, acetone).

A number of other specialized methods are available for the synthesis of sulfox-imines; the interested reader should consult recent reviews.[5,6]

Compound **2** is rapidly deprotonated with butyllithium in tetrahydrofuran to provide *N*-methylphenylsulfonimidoyl-methyllithium (**6**). The deprotonation can be monitored conveniently by use of a trace of triphenylmethane as an indicator; butyllithium is added at 0 °C until a slight pink coloration persists. Lithio reagent **6** is an excellent nucleophile, particularly with respect to addition to carbonyl compounds.[18,19] The addition reaction occurs in high yield with a wide range of carbonyl compounds in the temperature range of -78 to 25 °C. The reaction may be reversible at the higher temperatures, particularly in the cases of hindered carbonyl compounds. The major side reaction is enolization. Both the enolization and reversibility problems generally can be circumvented by conducting the addition at low temperatures followed by quenching the reaction mixture at low temperatures. Quench is usually achieved by pouring the cold reaction mixture into a mixture of diethyl ether and saturated ammonium chloride.

Addition of optically pure **2** (as the lithio reagent **6**) to a simple acyclic prochiral ketone or aldehyde results in the production of two optically active diastereomeric adducts **7** (Scheme 2). The ketone adducts are usually separable by chromatography on silica gel. Treatment of the purified adducts with Raney nickel in wet diethyl ether at room temperature results in the production of optically pure tertiary methyl carbinols **8**.[20] The aldehyde adducts are less readily separable by chromatography and are treated directly with Raney nickel to yield 2-alkanols in optical purities of 30 to 46% dependent on the extent of asymmetric induction in adduct formation.

β-Ketosulfoximines **9** have been prepared by the condensation of optically pure **6** with nitriles[21] (Scheme 2) or esters.[22] Treatment of the β-ketosulfoximines with a variety of reducing agents afforded β-hydroxysulfoximines in varying diastereomeric ratios. Cinquini and co-workers observed asymmetric induction in the range of 0 to 50% upon treatment of β-ketosulfoximines with sodium borohydride.[22] In our hands, highest asymmetric inductions (18-69%) were observed upon introduction of gaseous diborane into a solution of the β-ketosulfoximine in benzene.[21] A sulfoximine-borane complex was suggested as an intermediate. In related work, optically pure β-hydroxysulfoximines **7** were treated in toluene solution at -78 °C with gaseous diborane, and the resulting complexes used to reduce prochiral ketones; alcohols

(eq. 1)
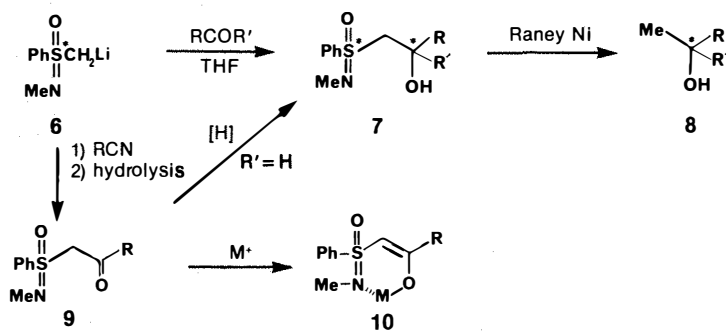
Scheme 2

Scheme 3
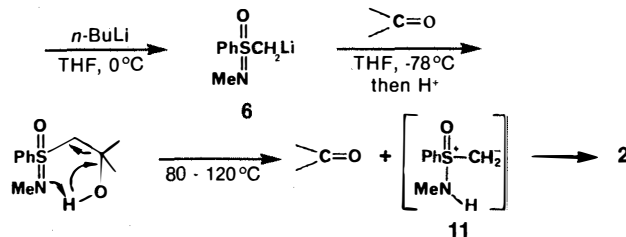
with optical purities ranging from 3 to 82% were obtained.[23] β-Ketosulfoximines are excellent bidentate ligands and form complexes (e.g., 10) with a number of metal ions.[24]

We have found that β-hydroxysulfoximines are thermally unstable and revert to the starting carbonyl compound and sulfoximine in the temperature range of 80 to 120 °C.[19,25] The reversion is probably facilitated by the transfer of the OH proton to the sulfoximine nitrogen such that carbon-carbon bond cleavage occurs with the ylide 11 as the leaving group.[9] The ylide self-quenches by tautomerization to the starting sulfoximine (Scheme 3). One might envision the overall procedure of adduct formation and thermal release of the starting materials as a carbonyl protection/deprotection procedure. The deprotection step is especially intriguing in that it occurs without the intervention of acid or base. The non-stereoselective addition of optically pure 2 (as the lithio reagent 6) to a chiral dl-ketone will result in four optically active diastereomeric adducts. Thermolysis of each optically pure adduct should lead to optically pure ketone and the regenerated and recyclable sulfoximine reagent. Generally, the separation of four adducts would not be considered practical for a ketone resolution. Ideally, complete diastereoselectivity in the addition reaction should prevail as it would result in only two diastereomers and considerably simplify the separation problem, e.g., Scheme 4. The two classes of ketones that are most likely to exhibit good diastereoface selectivity are substituted cycloalkanones and open-chain ketones bearing chelating substituents in the vicinity of the C=O. Indeed, the above chemistry has been found to be an interesting and novel method for the resolution of a variety of ketones, a sampling of which is shown in Table 2.[19,25] In all cases of substituted cyclohexanones which we have examined, two major adducts and a trace of a third diastereomer were produced in the addition reaction. A significant advantage inherent in the method is the rapidity with which the ultimate success of a ketone resolution can be predicted. Chromatographic examination (thin-layer chromatography or HPLC on silica gel) of a small-scale reaction mixture resulting from the addition of racemic 2 to racemic ketone, optically pure 2 to racemic ketone (assuming that complete mutual kinetic resolution is not obtained), or racemic 2 to an optically pure ketone will reveal the number and separability of the various diastereomers. The method has reciprocity and a number of ketones, particularly

l-menthone, have been found useful to resolve dl-2. This method complements the camphorsulfonic acid resolution method noted above. We have often used the menthone method to raise the optical purity of the material (after methylation) recovered from the mother liquors of the sulfonic acid resolution.[26]

β-Hydroxysulfoximines, obtained by the addition of 6 to aldehydes or ketones, undergo reductive elimination to yield alkenes upon treatment with aluminum amalgam in a mixture of THF, water, and

acetic acid (eq. 2)[18,27] In the case of conjugated enones and dienones, the addition of 6 occurs at the carbonyl; when the resulting adducts are reduced, dienes and trienes, respectively, are produced, e.g., eq. 3. The method often works in cases where olefination with a less reactive phosphorus ylide, such as triphenylphosphonium methylide, fails.[28] A recent example is found in the work of Ansell, Mason, and Caton.[29] These workers were unable to achieve the transformation of 13 to 14 using either triphenylphosphonium methylide or diiodomethane/Mg(Hg). However, a 66%

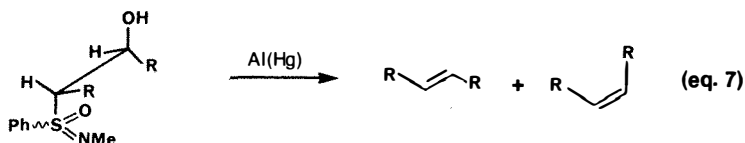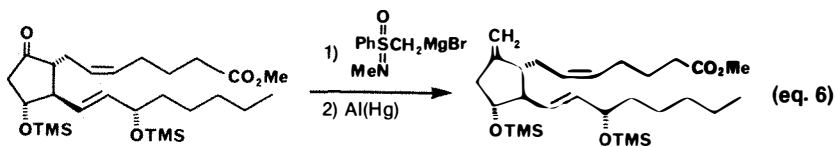Scheme 4

Table 2

(eq. 2)

(eq. 3)

(66%)

(eq. 4)
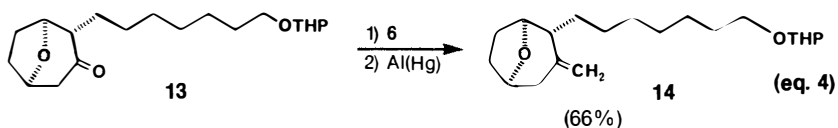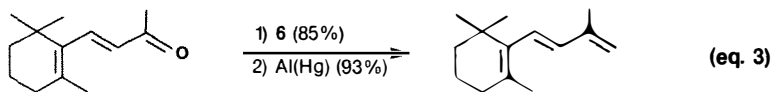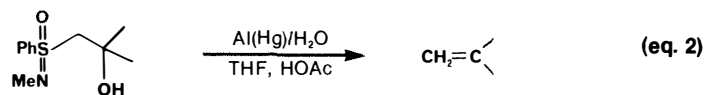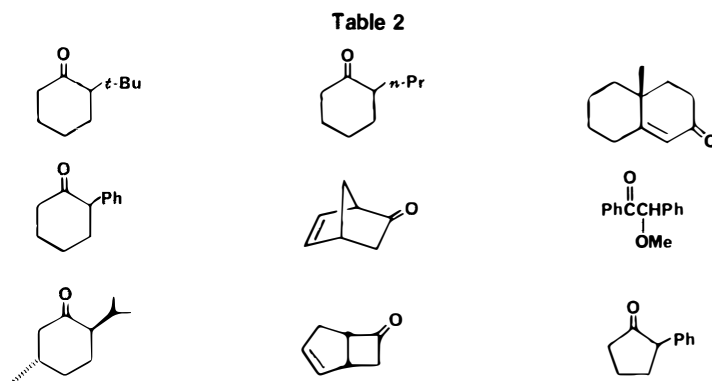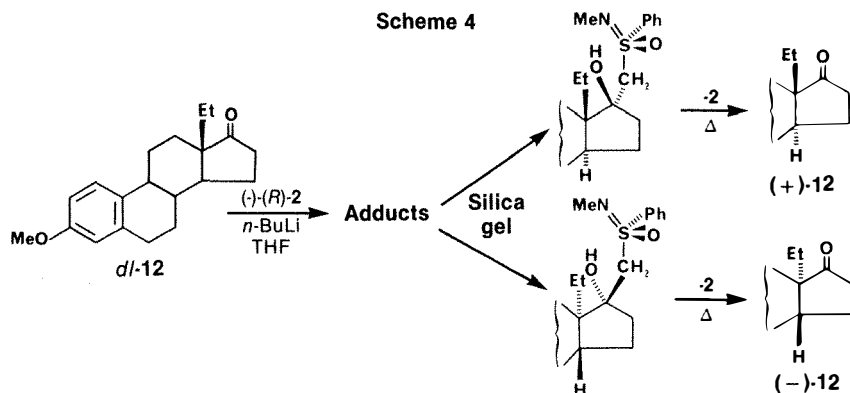
yield of **14** was obtained *via* the addition of **6** to **13** followed by reductive elimination under the usual conditions (eq. 4). Equations 5[30] and 6[31] also illustrate the utilization of this methodology in cases where the Wittig reagent failed, presumably due to base sensitivity of the substrates.

The use of higher homologs of **2** in this olefination procedure results in *cis/trans* mixtures of alkenes with the *trans* as the major product. In order to shed light on the origin of the *cis/trans* mixtures formed in these reactions, independent syntheses of individual diastereomers of 5-(*N*-methylphenylsulfonimidoyl)-4-octanol were carried out. All four *dl*-diastereomers gave rise to a *cis/trans* mixture of 4-octene with the *trans* product major (60 to 84%) in each case, *e.g.*, eq. 7. Control experiments revealed that, under the reaction conditions, starting hydroxysulfoximines as well as alkenes were not significantly equilibrated. It was concluded that a carbenoid intermediate was responsible for the loss of stereochemical integrity.[18] An example of the application of a homolog of **2** in the elaboration of a base-sensitive prostanoid precursor is illustrated in Scheme 5.[32]

The combination of the chromatographic separation of optically active β-hydroxysulfoximine diastereomers and the reductive elimination has resulted in methodology which leads to ketone methylenation with optical resolution. The technique was the keystone in the total synthesis of the ginseng sesquiterpene (-)-β-panasinsene (**18**) and its enantiomer.[33] Several points concerning this synthesis are noteworthy. Previously the ketone **15** had been found by McMurry and Choy to be "inert to methylenetriphenylphosphorane in DMSO".[34] In a reaction exhibiting remarkable diastereoselectivity, the addition of *dl*-**6** to *dl*-ketone **15** gave a 30:1 mixture of **16** and its diastereomer **17** (opposite relative configuration at S). The (S)-reagent **6** kinetically selects a single carbonyl face of the (-)-enantiomer of **15** and the (*R*)-**6** selects the same carbonyl face of (+)-**15** to give *dl*-**16** as the major product (Scheme 6). Addition of (*S*)-**6** to *dl*-ketone **15** resulted in about 1:1 mixture of optically active **16** and **17** which were readily separated by flash chromatography. Treatment of (+)-**16** with Al/Hg resulted in **18** with [α]^{25} -27.7°; (-)-**17** gave the unnatural (+)-β-panasinsene with [α]^{25} +29.7°.
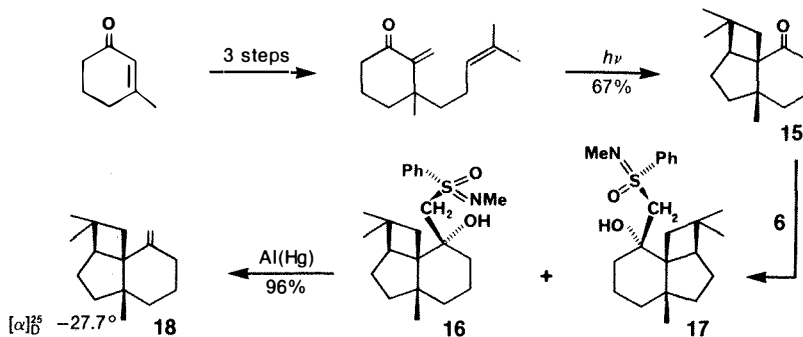
The addition of optically pure **2** as the lithio reagent **6** to prochiral enones, or the diastereoface-selective addition to racemic chiral enones, results in the formation of two optically active diastereomeric adducts,
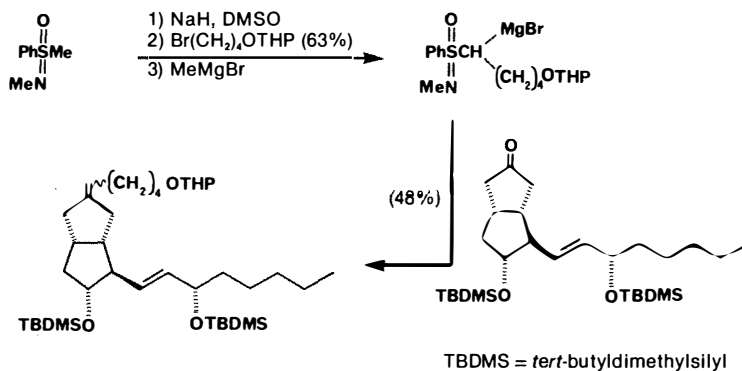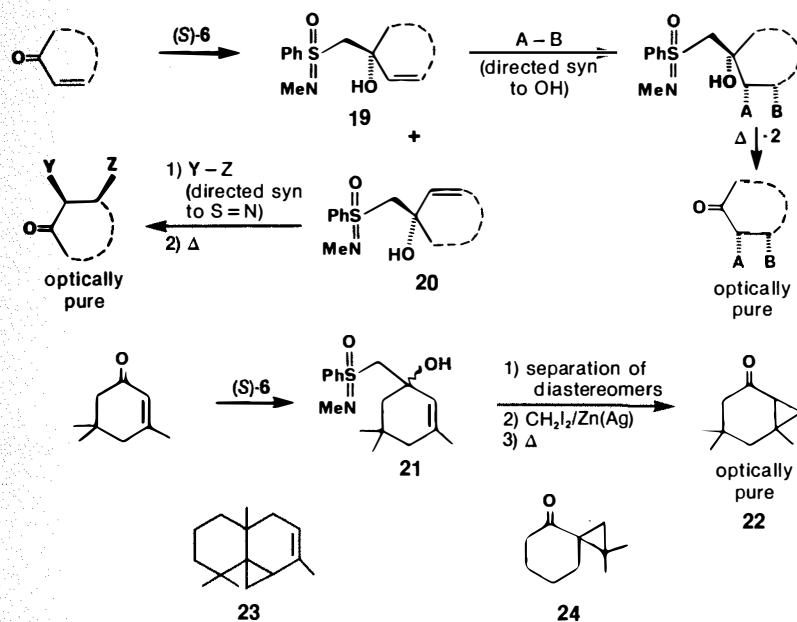
e.g., **19** and **20**, Scheme 7. In such adducts we envisioned that the hydroxyl group and/or the sulfoximine nitrogen might serve to control diastereoface selectivity in addition reactions to the remaining carbon-carbon double bond. Combining this diastereoface selectivity of the addition with a subsequent thermal reversion of the sulfoximine addition would result, in effect, in enantioface-controlled additions to the carbon-carbon double bond of the original enone (Scheme 7). For our first test

of this concept, the Simmons-Smith cyclopropanation reaction was chosen as it has been well documented to be directed by oxygen coordination.[35] Treatment of the individual diastereomeric isophorone/sulfoximine adducts **21** with diiodomethane/Zn(Ag) in refluxing diethyl ether followed by thermolysis resulted in the enantiomeric cyclopropyl ketones **22** with [α]^{25} +160.6° and -164°. This methodology has been applied to the synthesis of (-)- and (+)-thujopsene (**23**) and

(eq. 5)

(eq. 6)

(eq. 7)

Scheme 5

TBDMS = *tert*-butyldimethylsilyl

Scheme 6

Scheme 7

(S)-6

19

+

20

optically
pure

1) Y – Z
(directed syn
to S = N)
2) Δ

A – B
(directed syn
to OH)

Δ↓·2
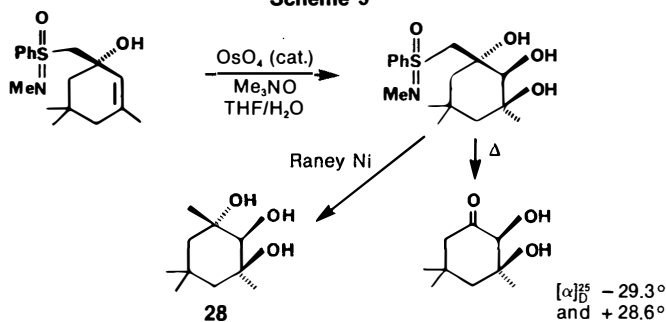
optically
pure

(S)-6

21

1) separation of
diastereomers
2) CH₂I₂/Zn(Ag)
3) Δ

optically
pure
22

23

24

Scheme 8

(R)-6

25

CH₂I₂/Zn(Ag)

Al(Hg)

27

26

Scheme 9

OsO₄ (cat.)
Me₃NO
THF/H₂O

Raney Ni

Δ

28

$[\alpha]_D^{25}$ −29.3°
and +28.6°

provide a synergistic enhancement of the diastereoface selectivity.[39–41] The overall result would be a novel optical activation method involving directed osmylation and thermal reversal of the sulfoximine addition to afford optically pure dihydroxy cycloalkanones and the recyclable resolving agent **2**. Again, the optically pure adducts of isophorone and **2** were chosen for initial study (Scheme 9).[40] Treatment of the individual diastereomers in water/THF solutions containing trimethylamine N-oxide dihydrate (1.5 equiv.) with solutions of osmium tetroxide (5 mol. %)[42] in THF afforded, in each case, a single triol. Desulfurization of each triol provided a material which exhibited ten resonances in the decoupled ^{13}C-NMR spectrum and four methyl singlets in the ^{1}H-NMR spectrum, consistent with the unsymmetrical structure **28**. The optically active cis-hydroxylated sulfoximine adducts undergo clean thermal elimination of the sulfoximine in refluxing solvent (2-butanol, toluene, or xylene) to provide optically pure dihydroxycycloalkanones. A selection of compounds prepared by this technique is shown in Table 3. Of particular note are the successes obtained with a 3-cyclohexenone substrate

Table 3

Product	$[\alpha]_D^{25}$
	+0.7° −0.8°
	+21.6° −21.2°
	+24.0° −24.2°
	+51.2° −52.3°
	+35.2° −34.7°

(homoallylic oxidation) and the cyclopentenone substrate. In the latter case, preparation of the diols shown represents formal total syntheses of both optical isomers of the antibiotics pentenomycin I and II since Smith and co-workers[43] have successfully converted racemic material to these substances. To date, attempts to extend this oxidation methodology to the preparation of enantiomerically pure acyclic diol ketones have not been successful.

a variety of other optically pure cyclopropyl ketones, e.g., **24**.[36] Scheme 8 outlines the total synthesis of the non-head-to-tail monoterpene, (-)-rothrockene **(27)**.[37] In this sequence it is interesting to note the multifaceted role of sulfoximine chemistry. Incorporation of the β-hydroxysulfoximine moiety allowed for the resolution of the precursor **(25)**, regio- and diastereoface selectivity in the cyclopropanation which selectively formed **26**, crystallographic determination of the absolute configuration of **26** (and hence **27**) by relating carbon

stereochemistry to the known absolute stereochemistry at sulfur, and introduction of the final carbon-carbon double bond in **27**.

Osmium tetroxide is known to form adducts reversibly with basic ligands such as pyridine and quinuclidine.[38] We anticipated that the methylimino group of adducts **19** and **20** would provide, by "chelation control", diastereoface selection in the osmylation of the adjacent carbon-carbon double bond. Furthermore, the "anti-periplanar" effect of the allylic hydroxyl group should

The generation of N-*p*-tolylsulfonyl-sulfonimidoyl-stabilized carbanions can be accomplished by treatment of N-tosylsulfoximines in DMSO with sodium hydride or butyllithium, or in THF by treatment with butyllithium.[12] Generally, the sodium hydride/DMSO method is preferable. These anions, which are quite stable at room or slightly elevated temperatures, form a class of nucleophilic alkylidene transfer reagents. The mechanism of these transfer reactions is similar to that of sulfonium ylide reactions but the leaving groups are water-soluble anions rather than neutral molecules (Scheme 10).
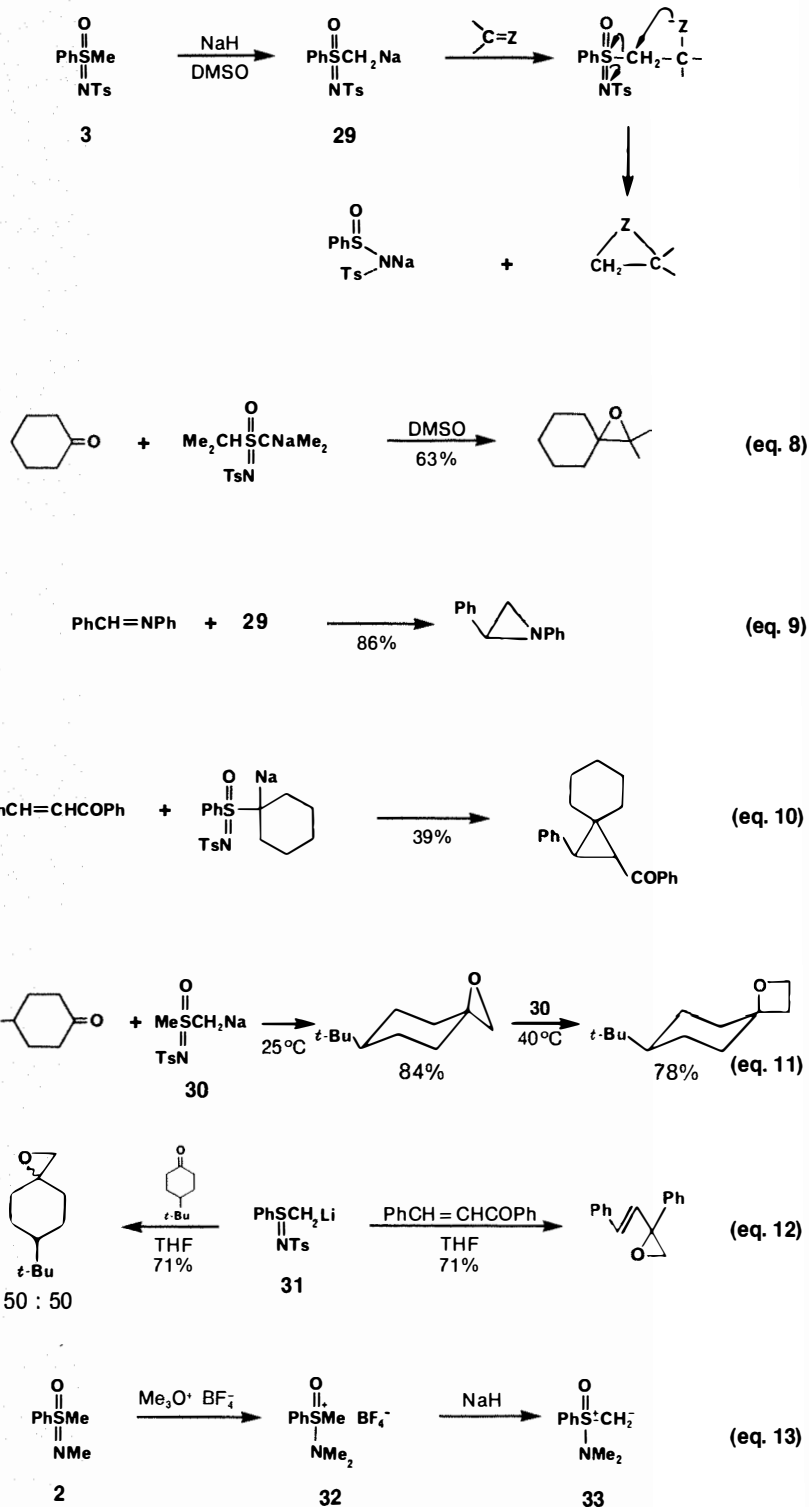
These reagents have been used to prepare oxiranes from aldehydes and ketones (eq. 8),[12] aziridines from imines (eq. 9),[12] cyclopropanes from enones (eq. 10),[12] and oxetanes from epoxides or ketones (eq. 11).[44] Alkylidene groups which have been transferred using reagents in this series include methylene, ethylidene, isopropylidene, benzylidene, cyclopentylidene, and cyclohexylidene. Our experience in working with these and many related reagents has led us to the conclusion that, for simplicity of preparation (see Part II, above) and manipulation, these reagents are competitive with or superior to others for the preparation of substituted oxiranes from ketones.

Similar reagents, *e.g.*, **31**, can be prepared from N-tosylsulfilimines.[45,46] These reagents are complementary to the N-tosylsulfoximine reagents in that products from them reflect kinetic control rather than thermodynamic control (eq. 12).

(Dimethylamino)methylphenyloxo-sulfonium tetrafluoroborate (**32**), prepared by the exhaustive methylation of either **1** or **2** with trimethyloxonium tetrafluoroborate (eq. 13), was the first member of a new class of oxosulfonium salts.[7,47,48] Treatment of **32** with sodium hydride in DMSO or THF results in the rapid and quantitative evolution of hydrogen and the formation of ylide **33** (eq. 13). Interest in this and related ylides was fostered by the work of Corey and Chaykovsky on dimethyl-oxosulfonium methylide.[49] The latter is probably the most widely used sulfonium ylide in synthetic chemistry.[50] The precursor to this ylide, trimethyloxosulfonium iodide, is readily available by the S-
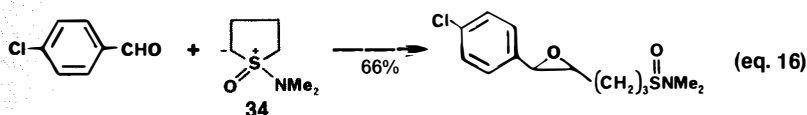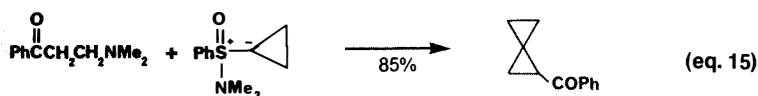
methylation of DMSO. This S-alkylation of sulfoxides is not a general reaction[51] and oxosulfonium ylides derived from alkylated sulfoxides are not available with wide structural variations. On the other hand, the N-alkylation of sulfoximines is quite general.

The chemistry of these (dialkylamino)-oxosulfonium ylides parallels that of dimethyloxosulfonium methylide. Additions to carbonyl groups are reversible and the final products of alkylidene transfer are generally thermodynamically controlled products, *e.g.*, epoxides formed from equatorial addition of the ylides to cyclohexanones (eq. 14) and cyclopropanes from enones or masked enones (eq. 15).

Scheme 10

(eq. 8)

(eq. 9)

(eq. 10)

(eq. 11)

(eq. 12)

(eq. 13)

(eq. 14)

(eq. 15)

(eq. 16)

Scheme 11

(eq. 17)

(eq. 18)

(eq. 19)

(eq. 20)

(eq. 21)

(eq. 22)
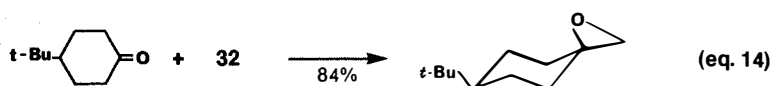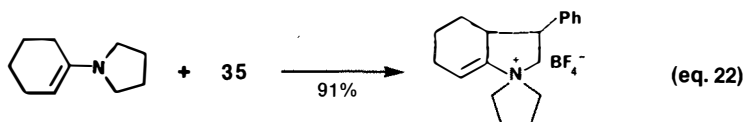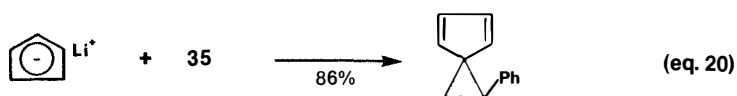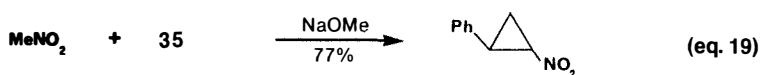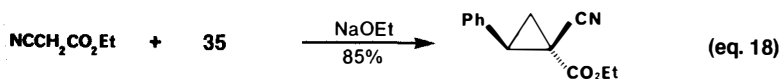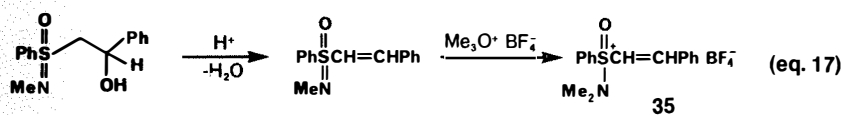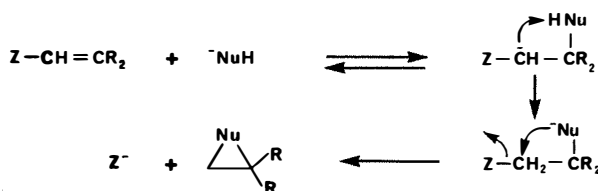
Reactions of optically pure ylide **33** provided optically active products with modest optical purities.[48,52] Related ylides, *e.g.*, **34**, can be elaborated from cyclic sulfides; reactions of these novel ylides provide functionalized sulfinamides (eq. 16).[53]

Michael acceptors in which the electronegative activating group is also an excellent leaving group are capable of ethylene transfer to dibasic nucleophiles (Scheme 11). The preparation of a model reagent of this type is shown in eq. 17.[54] Dibasic nucleophiles to which ethylene transfer from salt **35** has been achieved include active methylene compounds (eqs. 18-20), primary amines (eq. 21), and enamines (eq. 22). Note that in some instances five-membered rings are formed in preference to three-membered rings. Optically pure (-)-(*S*)-**35**, when treated with methyl cyanoacetate/sodium methoxide, provided methyl (+)-(1*S*, 2*R*)-1-cyano-2-phenylcyclopropanecarboxylate in 82% yield with an optical purity of 25%. Similar transformations can be achieved with N-tosyl-S-vinylsulfoximines and in some cases with N-methyl-S-vinylsulfoximines. None are as reactive as the salts exemplified by **35**. S-Vinylsulfoximines can act as dienophiles in Diels-Alder reactions and have been suggested for use as acetylene equivalents in this connection.[55]

VI. SUMMARY

Sulfur bound in organic molecules can exist in a number of stable oxidation states which provide for a variety of regional and stereochemical substitution patterns. The structural versatility allows for the "tailoring" of sulfur molecules to perform specific functions. In the case of sulfoximines, the nitrogen substituent markedly influences the chemistry of the compound making possible a variety of sulfoximine-mediated synthetic transformations. Sulfoximines and their derivatives have been found to be useful in the synthesis of oxiranes, aziridines, cyclopropanes, oxetanes, dihydrofurans, alcohols, and alkenes. Examples from all of these classes have been prepared in optically active, and in many cases, optically pure, forms using optically active sulfoximines. (+)- and (-)-*N,S*-dimethyl-S-phenylsulfoximine have been shown to be novel resolving reagents for ketones.

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The Use of Carbon-13-Labeled Compounds in Organic Chemistry, Biochemistry and Medicine

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Carbon-13 was first detected in nature over 50 years ago.[1] However it is only in the last dozen years that this stable isotope of carbon has been used extensively in a wide variety of chemical and biological studies.[2] Most of the early work carried out to elucidate biosynthetic and metabolic reactions was achieved with the radioactive isotope carbon-14, simply because it was much easier to detect and assay. Carbon-14 was less expensive and many compounds containing this isotope were commercially available.

Many investigations have been carried out using compounds enriched with carbon-13, yielding results which could not have been accomplished with the radioactive isotope. The natural abundance of ^{13}C is 1.11%, but compounds are now commercially available which are enriched at specific positions with 99 atom % [13]C. In this brief review examples will be given of problems which have been solved using carbon-13-enriched compounds. Since ^{13}C is magnetic, with a nuclear spin of 1/2, it is readily detectable by nuclear magnetic resonance spectroscopy. The magnetogyric ratio of ^{13}C nuclei is about 1/4 that of ^{1}H nuclei. This physical constant is a function of the magnetic moment and spin quantum number of a nucleus. Since the sensitivity of a nucleus in a magnetic resonance experi-

ment is proportional to the cube of the magnetogyric ratio, ^{13}C nuclei give rise to 1/64 the signal detected for ^{1}H nuclei on excitation at similar isotopic concentrations.[3] The other extensively used method of assaying ^{13}C-enriched compounds is mass spectrometry.

Chemical Syntheses with Carbon-13 Labeled Compounds

Since the location of ^{13}C in an organic molecule can be readily established by ^{13}C NMR spectroscopy, many reactions which involve carbon shifts and rearrangements have been investigated by labeling specific positions in the starting material with excess [13]C. The synthesis of the desired ^{13}C-labeled compound from commercially

available ^{13}C compounds can often be found in the vast literature on the synthesis of ^{14}C compounds.[4-9] However, it is often desirable to carry out the synthesis on a larger scale than was previously used for the corresponding ^{14}C compound. *The Journal of Labelled Compounds and Radiopharmaceuticals* is an excellent source of information on syntheses from simple ^{13}C compounds. If radioactivity in the final product is acceptable, it is often helpful for quantitation to have ^{14}C present at the same position as the enriched ^{13}C label. The yields at the various steps in the synthesis are then readily monitored by radioactive assay. It should be pointed out that when one is introducing more than one ^{13}C label into a molecule there will be a statistical
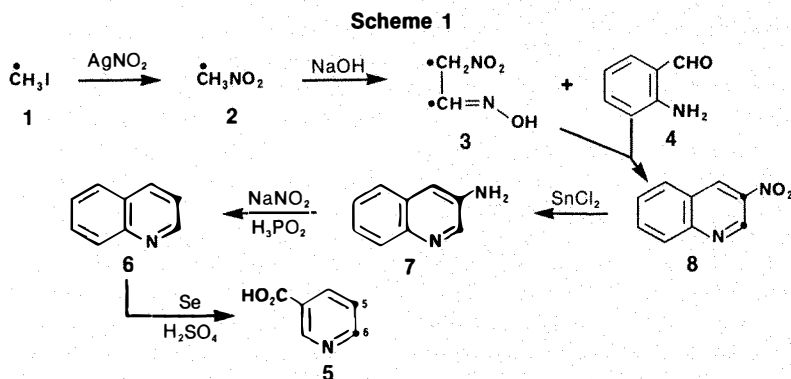
Scheme 1

distribution of labeled species depending on the degree of enrichment of the starting materials. For example, the nicotinic-5,6-$^{13}C_2$ acid (5) prepared from iodomethane-^{13}C (1) (90% ^{13}C) according to Scheme 1,[10] will statistically consist of 81% [5,6-$^{13}C_2$], 9% [5-^{13}C], 9% [6-^{13}C], and 1% unlabeled nicotinic acid. Starting materials of ^{13}C enrichment >99 atom % yield insignificant amounts of these singly labeled contaminants.

Organic Chemistry

An obscure synthesis of quinoline (10)[11] involves heating N-methylacetanilide (9) with zinc chloride at 290°C. When the reaction was carried out with N-methylacetanilide-*carbonyl*-^{13}C, the resultant quinoline was shown by ^{13}C NMR spectroscopy to have excess ^{13}C at its C-4 position.[12] This result disproved a previous mechanism in which 2-methylindole had been proposed as an intermediate.[13] The mechanism illustrated in Scheme 2 is consistent with the labeling observed.

A solvolysis of *trans*-1,2-diphenyl-2-(phenylthio)vinyl-*1*-^{13}C tosylate (11) in acetic acid led to the formation of the corresponding vinyl acetates (13a, 13b) in which the ^{13}C was distributed equally between the two vinyl carbons (detected by NMR spectroscopy).[14] The result is rationalized by postulating the intermediacy of the thiirenium ion 12, as illustrated in Scheme 3.

The dimerization of 2,5-dihydropyridine (16) to afford the tobacco alkaloid anatabine (20) was shown to be completely regiospecific by labeling the dihydropyridine with ^{13}C at the C-6 position.[15] The dihydropyridine was produced by the oxidative decarboxylation of baikiain (17), which was prepared from diethyl acetamidomalonate-*2*-^{13}C (15)[15,16] and *cis*-1,4-dichloro-2-butene (14) as indicated in Scheme 4. It is thought that the anatabine is formed by the condensation of 1,2-dihydropyridine [(18) formed by the isomerization of 2,5-dihydropyridine] with a second molecule of the 2,5-dihydropyridine to yield the dihydroanatabine (19), which is then oxidized to anatabine. By ^{13}C NMR spectroscopy it was established that the anatabine was labeled only at the C-2 and C-2' positions.

The mechanism of the conversion of 1,5,9-cyclododecatriyne (21) to hexaradialene (23) has been studied by Vollhardt.[17] (Scheme 5). The triyne-1,10-$^{13}C_2$ was converted by pyrolysis to the labeled hexaradialene which was then converted to hexamethylbenzene (25). Ozonolysis afforded 2,3-butanedione (27). If the reaction proceeds *via* tricyclobutabenzene (22), Route
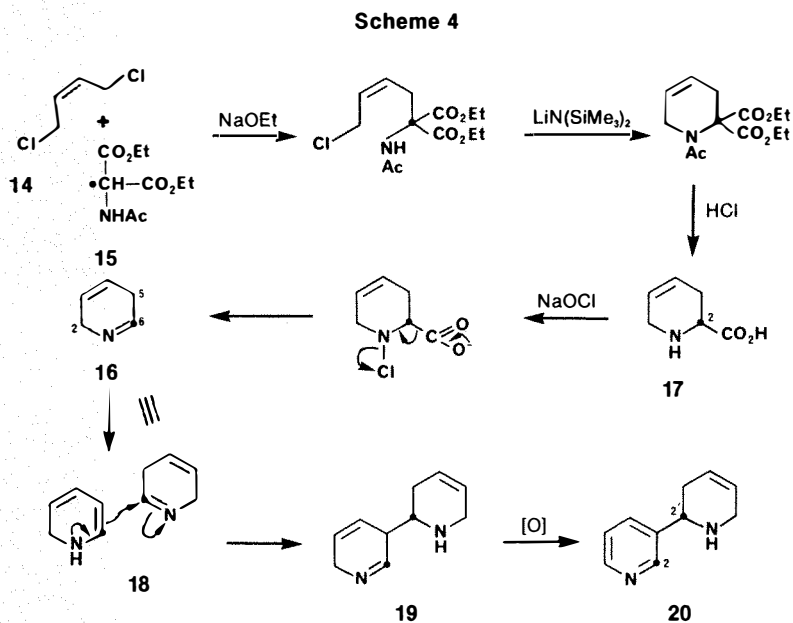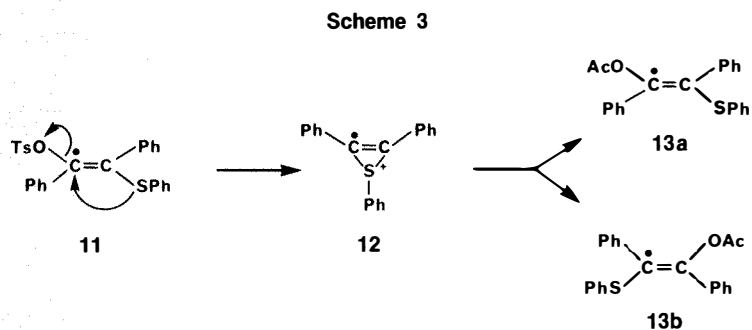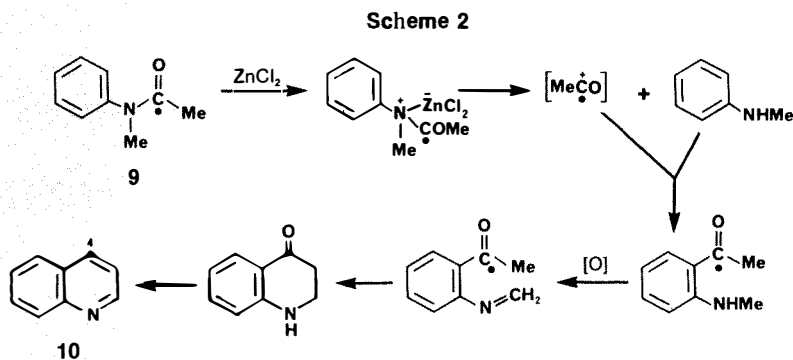
A in Scheme 5, the hexaradialene will be labeled as indicated, and the ratio of unlabeled to monolabeled to dilabeled butanedione will be 3:2:1. The abundance of the 86, 87, and 88 molecular ion peaks in the mass spectrum of the butanedione did not correspond to this ratio, but was consistent with a 1,4-labeling pattern in the hexaradialene! A convoluted mechanism *via* 24 and 26 (Route B) was proposed to explain this remarkable result. The numbering of the hexaradialene produced by this mechanism indicates the origin of the carbons in the

original cyclododecatriyne.

The mechanism for the formation of 1,3,5,7-cyclooctatetraene (30) from acetylene, a reaction first discovered by Reppe, has also been investigated by Vollhardt.[18] Acetylene-*1*-^{13}C (29) was prepared from acetic-*1*-^{13}C acid (28) by the route illustrated in Scheme 6. The pattern of labeling expected in the cyclooctatetraene, if the polymerization proceeds *via* simple coordination of the acetylene molecules around the nickel catalyst, is as indicated. This pattern of labeling was in fact established by chem-

Scheme 2

Scheme 3

Scheme 4

Scheme 5

21 A 22 23

B 25

24 O₃

26 27

Scheme 6

MeĊO₂H → (COCl / COCl) MeĊOCl →[LiAlH₄] MeĊH₂OH
28

P₂O₅

HC≡ĊH ←[LiN(SiMe₃)₂] BrCH₂ĊH₂Br ←[Br₂] CH₂=ĊH₂
29

Ni(acac)₂
Et₂AlOEt
THF, N₂, 85°C, 24h

30

Relative amounts   4   2   1   1
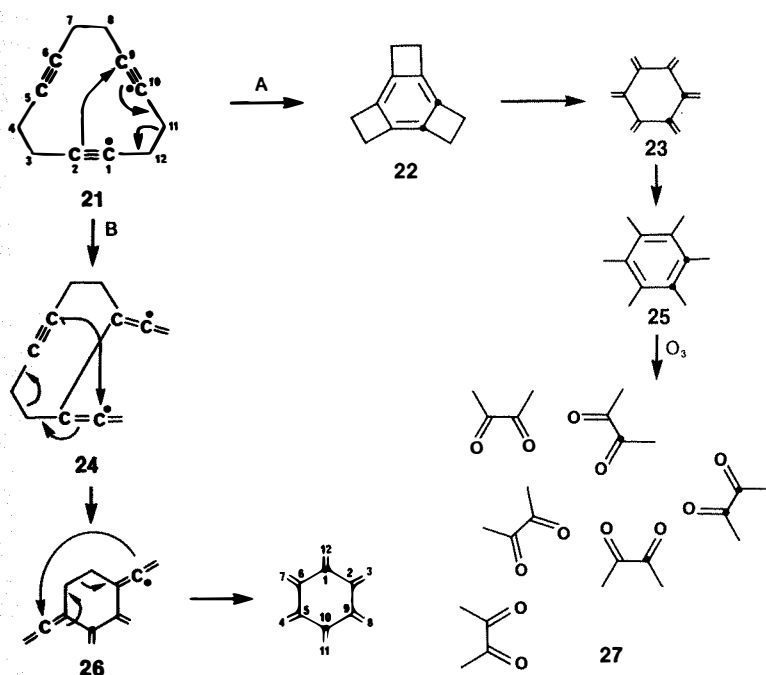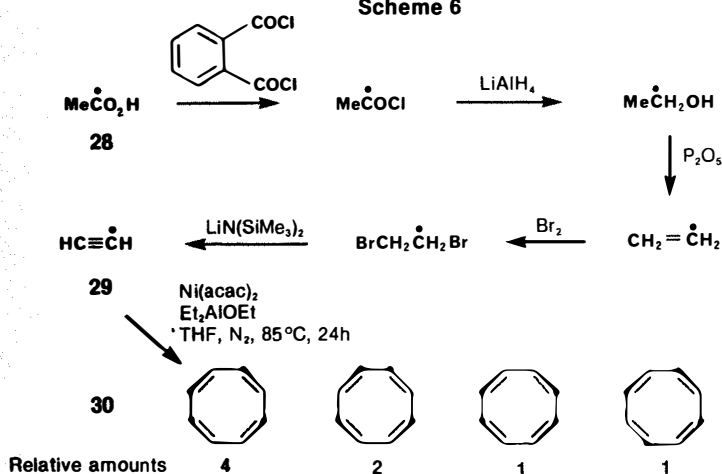
Scheme 7

ically degrading the cyclooctatetraene to a four-carbon unit and then carrying out an analysis by mass spectrometry.

The mechanism of the thermal automerization of aromatic compounds has been studied with ¹³C labels.[19,20] Some of these remarkable reactions, which are still not clearly understood, are illustrated in Scheme 7.

It is possible to measure internuclear distances (1% accuracy) in amorphous solids from homonuclear dipole splitting (e.g., between two contiguous ¹³C atoms) using nutation NMR.[21,22] The observed dipole-dipole splitting of two bonded nuclei (for ¹³C) varies inversely as the third power of the internuclear distance. This NMR technique has been used to study the mechanism of the Ziegler-Natta polymerization of acetylene.[23] A mixture of 4% acetylene-¹³C_2 and 96% acetylene-¹²C_2 (¹³C depleted, 99.9% ¹²C) was polymerized with titanium tetra-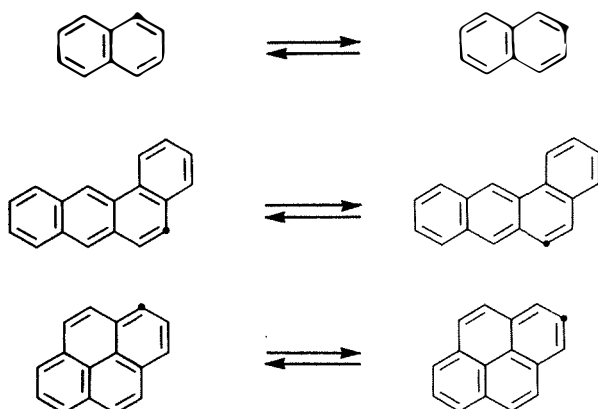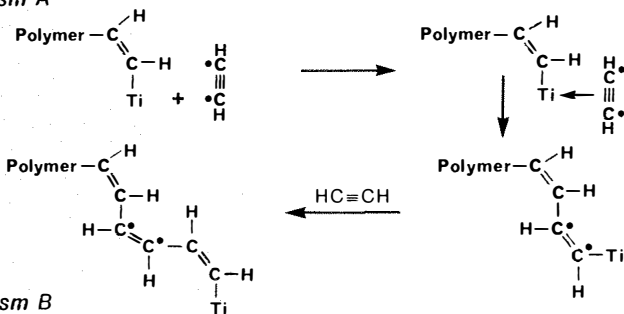n-butoxide and triethylaluminum at 196 °K. The resultant polymer was found to have its contiguous ¹³C atoms 1.37Å apart (i.e., a typical double-bond length). This result favors mechanism A in Scheme 8, where there is a direct insertion of the acetylene molecule into the titanium-polymer bond. Mechanism B,[24] which involves the intermediacy of a metallocycle, would have resulted in a single bond between the contiguous ¹³C atoms.

The remarkable conversion of 2,2-dimethyl-3-hydroxy-3-phenylpropanoic acid (31) to 3-methyl-2-phenyl-2-butenoic acid (32) with superacid (FSO₃H) at 0 °C (Scheme 9) was shown to involve an intramolecular 1,2-migration of the carboxyl group.[25] Compound 31 was labeled with ¹³C at C-1 and C-3. The ¹³C NMR spectrum of the product 32 indicated the presence of enriched carbons at 180.2 ppm (COOH) and 122.1 ppm (C-2). Furthermore, these signals were split into doublets by the direct ¹³C-¹³C coupling of the contiguous atoms (¹J = 68.7 Hz). When the rearrangement was carried out with a 1:1 mixture of the doubly labeled 31 and unlabeled material, there was no increase in the mono-labeled product 32 (detectable as a peak between the doublet due to the contiguous ¹³C atoms). This result indicates that the rearrangement was intramolecular. The mass spectrum of the isolated 32 from this experiment was also consistent with an intramolecular reaction, with no crossover between the labeled and unlabeled starting materials.
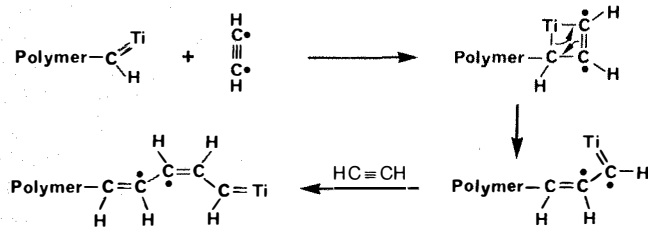
The use of stable isotopes, especially ¹³C, for determining biosynthetic pathways in plants, animals, and microorganisms, has

Scheme 8

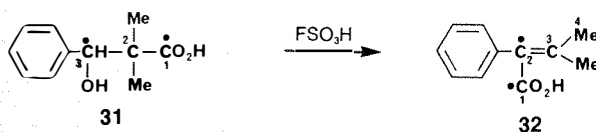**Mechanism A**

Polymer—C ... Ti + ... HC≡CH ...

Polymer—C ... Ti

Mechanism B

Polymer—C ... Ti + ... HC≡CH ...

Polymer—C ... Ti

Scheme 9

31 → FSO₃H → 32

been reviewed by Tanabe.[26-28] The normal procedure is to label a potential precursor of a natural product with ^{13}C at one or more positions. This material is then administered to the living organism. If the labeled compound is incorporated into the ultimate natural product, the ^{13}C NMR spectrum of the enriched material will exhibit signals which are enhanced due to incorporation of the ^{13}C label. Occasionally the incorporation of ^{13}C-labeled compounds has been demonstrated by infrared spectroscopy. Replacement of ^{12}C for ^{13}C results in predictable shifts for some resonances of infrared absorption. Thus the cyanide group of kinamycin D (33) (Scheme 10) is derived from the carboxyl group of acetic-1-^{13}C acid.[29] The $^{13}C≡N$ absorbs at 2139 cm^{-1}, while the $^{12}C≡N$ in the unenriched material is at 2155 cm^{-1}.

Scheme 10

33
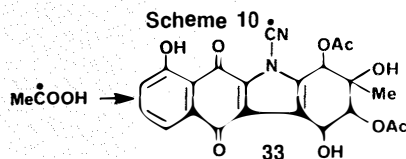
Some examples of the incorporation of precursors labeled with a single ^{13}C atom into alkaloids are illustrated in Scheme 11. Autumnaline-1-^{13}C (34) was incorporated into colchicine (35).[30] Isovincoside-5-^{13}C lactam (36) was a precursor of camptothecin (37).[31] Anatabine-2-^{13}C (38) was con-

verted into α,β'-dipyridyl (39) in drying tobacco leaves.[32] Figure 1 depicts the ^{13}C NMR spectrum of natural abundance shihunine (40), and Figure 2 shows that derived from o-succinyl-1-^{13}C-benzoic acid (41), a product of a biosynthetic transformation which occurs in the orchid *Dendrobium pierardii.*[33] This method of establishing biosynthetic pathways is only useful when a good, specific incorporation of the ^{13}C-labeled precursor into the ultimate natural product is obtained.

Specific incorporation is defined as follows:

$$\text{Specific incorporation} = \frac{\% \text{ excess } ^{13}C \text{ in the natural product}}{\% \text{ excess } ^{13}C \text{ in the administered precursor}}$$

$$= \frac{a-b}{b}$$

where a = integrated NMR signal of the enriched carbon in the natural product

b = integrated NMR signal of the same carbon in the unenriched natural product, where acquisition parameters are identical.
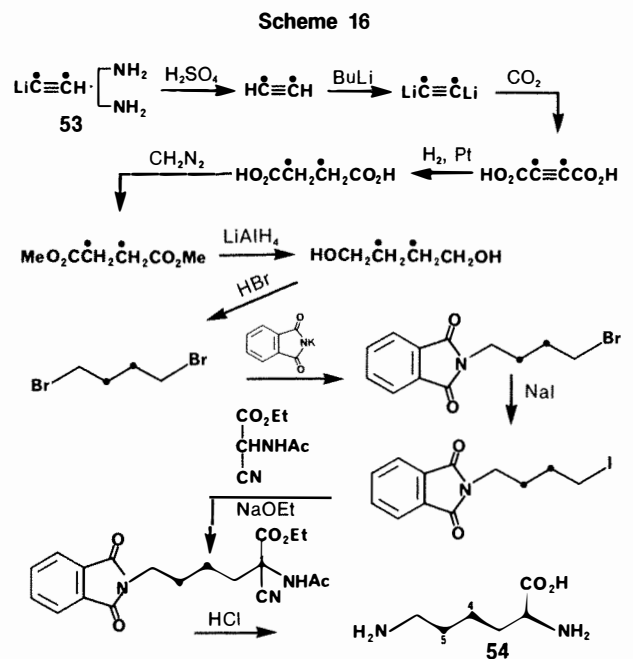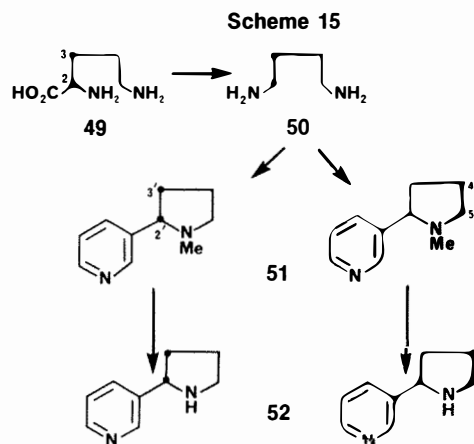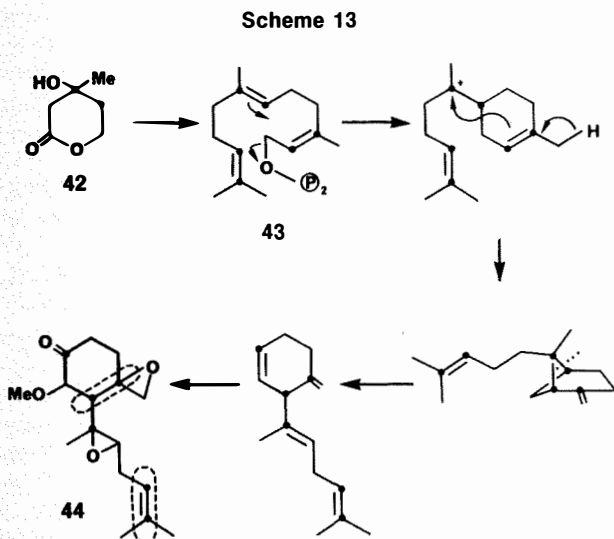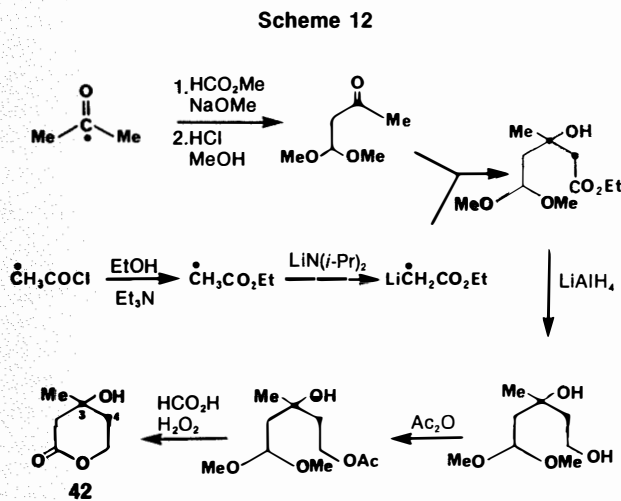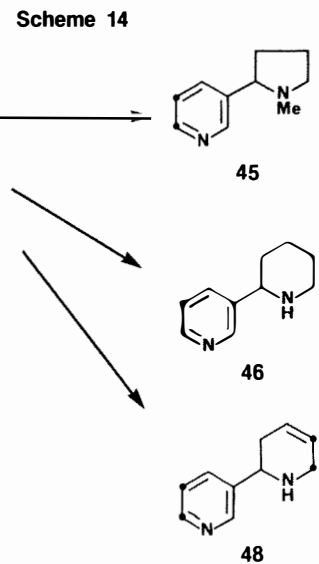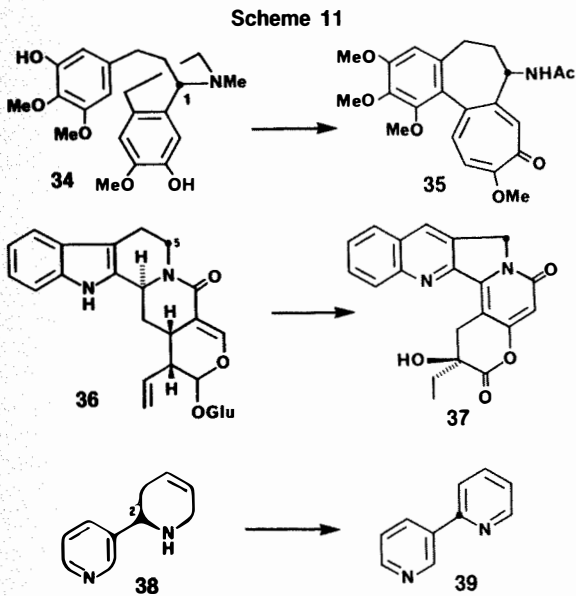
Because of the variability in the intensity of the NMR peaks, one usually cannot be sure of an enrichment of a particular carbon unless the specific incorporation is greater than 0.5%. A much greater dilution of the administered precursor can be tolerated if one labels with two contiguous ^{13}C atoms. The natural abundance of such contiguous carbons is 1.11 x 1.11% = 0.0123%. Furthermore, these adjacent ^{13}C atoms engage in spin-spin coupling giving

rise to satellites in the ^{13}C NMR spectrum, as previously mentioned. A large number of biosynthetic studies have been carried out with acetic-$^{13}C_2$ acid (usually fed as its sodium salt) as a tool for determining whether a natural product is a polyketide. This approach was first reported in the literature by Seto and coworkers[34,35] in studies on the biosynthesis of microbial products. Vining[36,37] and his coworkers independently published similar procedures for the investigation of natural product biosynthesis.

Cane[38] prepared mevalonolactone-$3,4$-$^{13}C_2$ (42) by the route illustrated in Scheme 12 and used it in a study of the biosynthesis of ovalicin (44), a sesquiterpene produced by the fungus *Pseudorotium ovalis*. The pattern of labeling in the ovalicin was rationalized on the basis of the biosynthetic sequence illustrated in Scheme 13. One of the three pairs of contiguous ^{13}C atoms in the intermediate farnesol pyrophosphate (43) is separated in this sequence. Thus only two pairs of contiguous ^{13}C atoms (indicated with dotted lines) were detected in the ^{13}C NMR spectrum of the ultimate ovalicin.

Nicotinic-$5,6$-$^{13}C_2$ acid (5), the synthesis of which has been outlined previously (Scheme 1), was incorporated into the tobacco alkaloids nicotine (45), anabasine (46), and anatabine (48).[16] It was also shown to be a precursor of part of the isoquinuclidine ring system found in the alkaloid dioscorine (47),[39] produced by the tropical yam *Dioscorea hispida*. The pattern of labeling in these alkaloids, as illustrated in Scheme 14, was readily determined by observation of the satellites produced by the contiguous ^{13}C atoms in their ^{13}C NMR spectra.

Ornithine-$2,3$-$^{13}C_2$ was incorporated into the pyrrolidine rings of nicotine (51) and nornicotine (52) *via* a symmetrical intermediate, putrescine (50). The alkaloids were thus labeled with contiguous ^{13}C atoms at the C-2' — C-3' and C-4' — C-5' positions as indicated in Scheme 15.[40] Lysine-$4,5$-$^{13}C_2$ (54) was prepared from the ethylenediamine complex of the lithium salt of acetylene-$^{13}C_2$ (53) by the route illustrated in Scheme 16.[41] This labeled lysine

Scheme 11

Scheme 12

Scheme 13

Scheme 14

Scheme 15

Scheme 16

Figure 1

Shihunine 40

SHIHUNINE— natural abundance C-13 NMR (noise decoupled) spectrum

Figure 2

o-Succinyl-1-^{13}C-benzoic acid **41** → Shihunine **40**

4.4% specific incorporation

enhanced signal

SHIHUNINE— enriched sample

Scheme 17

Scheme 18
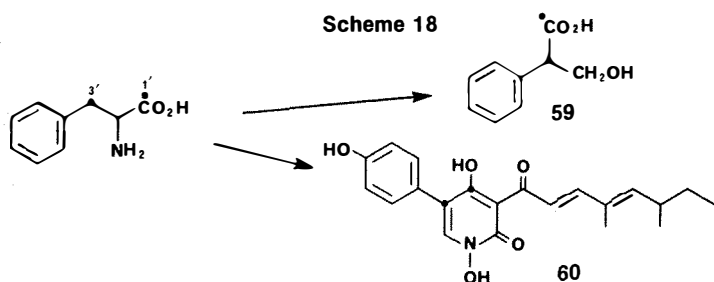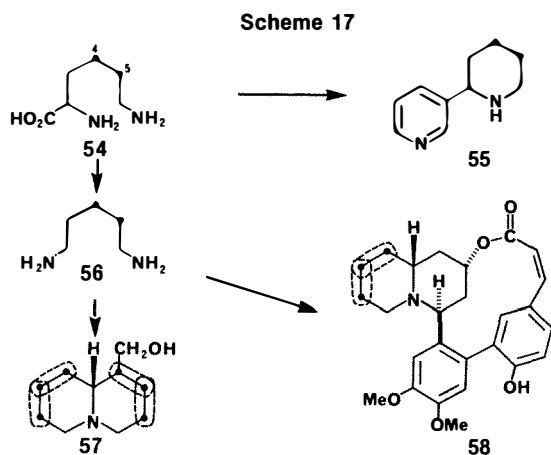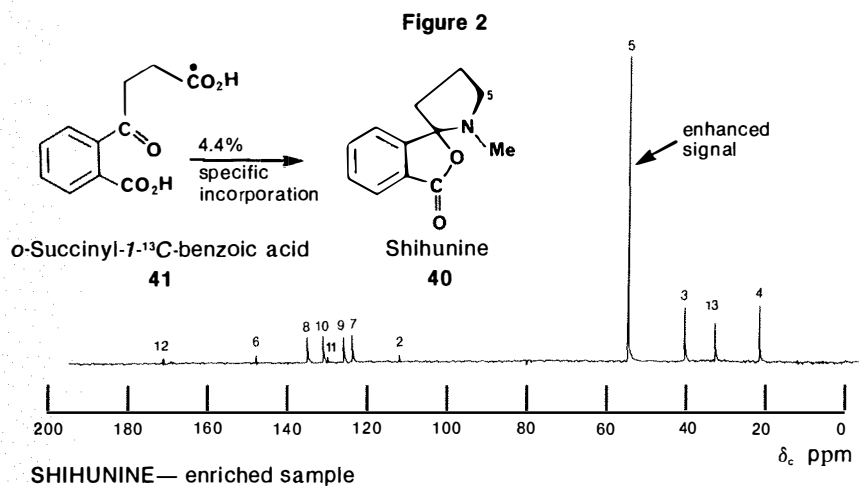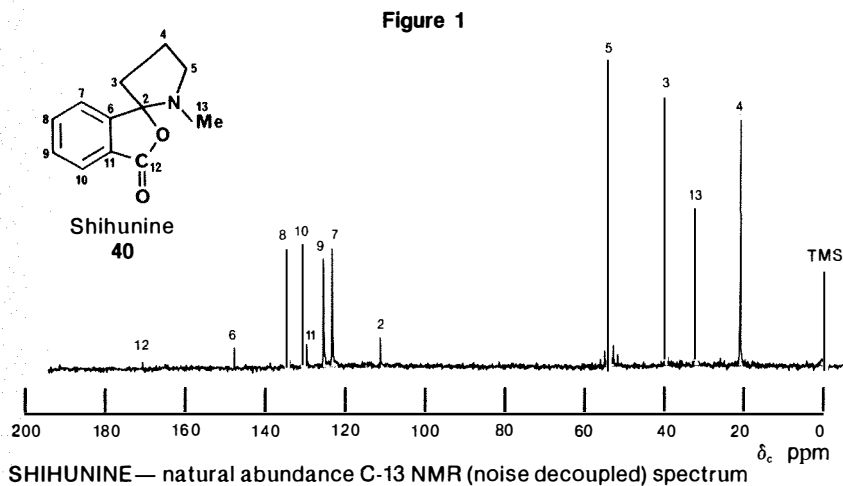
was incorporated into the piperidine ring of anabasine (**55**) unsymmetrically,[41] but its incorporation into the quinolizidine rings of lupinine (**57**)[42] and vertine (**58**)[43] proceeded via a symmetrical intermediate, presumably cadaverine (**56**). The observed coupled carbons are indicated with dashed lines in Scheme 17.

In some biosynthetic experiments, rearrangements have been detected by observing the change of remote ^{13}C atoms to contiguous as a result of an intramolecular migration. A notable example was the observation that the "switched" ring D in the natural porphyrins involves an intramolecular rearrangement.[44] This was achieved by a feeding experiment with porphobilinogen-2,11-$^{13}C_2$. The intramolecular nature of the rearrangement of the phenylalanine side chain (involving a 1,2-migration of the carboxyl group) was demonstrated in the biosynthesis of tropic acid (**59**)[45] and tenellin (**60**).[46] The rearrangement of phenylalanine-1',3'-$^{13}C_2$ results in the formation of natural products which have contiguous ^{13}C atoms, as illustrated in Scheme 18. Other doubly labeled amino acids which have been used to study the biosynthesis of natural products include phenylalanine-2',3'-$^{13}C_2$[47] and tryptophan-2',3'-$^{13}C_2$.[48]

The mechanism of enzyme action has been probed using a combination of ^{13}C-labeled substrates and NMR spectroscopy.[49] One example is illustrated in Scheme 19. Generally, it has been accepted that the mechanism of action of the enzyme aldolase, which catalyzes the aldol condensation between dihydroxyacetone phosphate and glyceraldehyde-3-phosphate to yield fructose-1,6-diphosphate, involves the initial formation of an imine between the ketone group of the dihydroxyacetone phosphate and the ε-amino group of a lysine residue in the enzyme. The formation of a carbinolamine from glycolaldehyde phosphate and aldolase has been demonstrated.[50] It was found that glycolaldehyde-1-^{2}H, 1-^{13}C phosphate (**61**) exists in water almost entirely as its hydrate (**62**). The C-1 carbon gave a signal in the ^{13}C NMR spectrum at 89.5 ppm which was split into a triplet by the adjacent deuterium ($^1J_{C,D} =$ 27.8 Hz). On addition of aldolase (from rabbit muscle) this strong signal due to the enriched position was shifted to 79.5 ppm. This new signal was assigned to the enriched carbon in the carbinolamine **63**. No signal which would correspond to the imine **64** was observed (expected at ~140 ppm). The signal at 89.5 ppm was restored on the addition of hexitol-1,6-diphosphate which displaces the glycolaldehyde phosphate from the enzyme.

Scheme 19
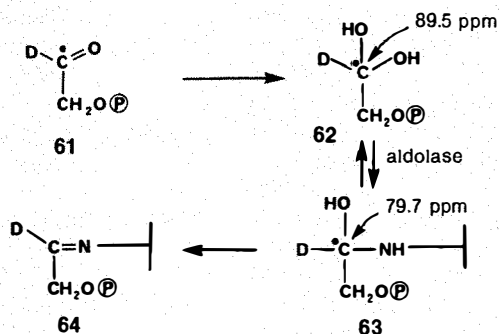
The conversion of nicotinic-2-^{13}C acid to the pyridine nucleotides (NAD$^+$, NADH) was observed *in vivo* with cells of *E. coli* by observation of the ^{13}C NMR spectrum of a cell suspension.[51]

It is now possible to examine live mammals, even humans, in the probe of an NMR spectrometer.[52] Shulman and his co-workers have pioneered much of this work.[53,54] For example, the metabolism of glucose-*1*-^{13}C in the intact rat was monitored by attaching a radio frequency coil to the outside of the rat near its liver. The initial signals of the glucose at 96.8 and 92.3 ppm (due to the C-1 position in the α- and β-anomers of glucose) were observed to decrease with time and a new signal appeared at 101 ppm. This was assigned to the C-1 position in the polysaccharide glycogen which had been produced in the rat liver from the labeled glucose. The metabolism of glucose-*1*-^{13}C in brain tissues has also been followed by ^{13}C NMR spectroscopy.[55]

The use of ^{13}C-labeled compounds for studying the metabolism of drugs and other compounds in humans is especially attractive, since one does not have to worry about potential radiation hazards which are of concern with radioactive isotopes such as carbon-14 and tritium. Probably the most sensitive method for assay of compounds labeled with stable isotopes is mass spectrometry.[56,57] It is desirable to introduce at least two ^{13}C atoms into the drug under investigation so that there will be little confusion in subsequent examination of the mass spectrum of the compound and its metabolites. For example, the natural abundance of the M + 2 peak in a compound containing 24 carbon atoms is only 2.6% of the molecular ion peak, M$^+$.[58]

The synthesis of labeled bile acids[59] and fatty acids[60] for use in human metabolism studies has been described recently. Useful information can be obtained by measuring the excess ^{13}C in the expired carbon dioxide of normal and diseased humans who have received a ^{13}C-labeled drug. One investiga-

tion showed that diabetic children metabolized glucose-$^{13}C_6$ at a slower rate than normal children.[61]

In summary, it is predicted that as ^{13}C compounds become less expensive and more available, they will be used much more extensively in studies related to human metabolism and health. In this limited space we have not mentioned many recent investigations which have used ^{13}C in conjunction with other stable isotopes such as deuterium, nitrogen-15 and the oxygen isotopes.

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Professor Edward Leete was born in Leeds, England, in 1928. He received the B.Sc. in 1948 and the Ph.D. degree in 1950 from the Department of Colour Chemistry, University of Leeds. After postdoctoral work with Leo Marion at the National Research Council Laboratories, Ottawa, Canada, he joined the faculty of the University of California, Los Angeles, in 1954 as an instructor. In 1958 he moved to the University of Minnesota, Minneapolis, where he has been a Professor of Chemistry since 1963.

He was an Alfred P. Sloan Fellow from 1962-1965 and held a Guggenheim Foundation Fellowship at the University of Oxford, England, in 1965. He was a member of the Medicinal Chemistry Study Section of the National Institutes of Health from 1962-1965. In 1965 he was awarded an honorary D.Sc. degree by the University of Leeds, and received a Distinguished Teacher Award from the University of Minnesota in 1976. He is currently a member of the editorial boards of *Phytochemistry* and the *Journal of Natural Products.*

He has published 200 scientific research papers, most of them on the biosynthesis of natural products, and is proud of the fact that he is the sole author of 86 of these, describing work carried out with his own hands.

Dr. Joseph Porwoll received the B.Sc. degree in 1976 from Moorhead State University. He received the Ph.D. degree from the University of Minnesota in 1981, having acquired extensive experience in the synthesis of ^{3}H-, ^{14}C- and ^{13}C-labeled compounds under Dr. Edward Leete. He then worked for Dr. John Wood on the total synthesis, isolation and structural determination of interesting algal metabolites at the Gray Freshwater Biological Institute, University of Minnesota. Dr. Porwoll joined Aldrich in 1983 to expand the stable isotope product line.

"Dry-Column" Flash Chromatography

This technique combines the advantages of standard flash chromatography (*e.g.*, good separation and speed) with cheapness of material and simplicity of apparatus and operation. A distinctive feature is the use of suction instead of positive pressure, thus simplifying loading of the product mixture and subsequent eluting solvents. A second feature is that the eluting solvents are added in predetermined volumes, allowing the column to run dry before the next fraction is added.

Apparatus

The apparatus is set up as for filtration using a porosity 3 cylindrical sinter (Figure 1).
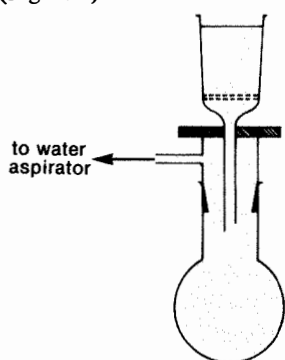

to water aspirator

Figure 1

Table 1 gives guidelines for choice of sinter size and amounts of silica, sample and solvent. Columns appreciably longer than 55mm are neither practical nor necessary, since reduction in efficiency may be observed on large-scale set-ups.

Table 1

Sinter size (diameter/-length, mm)	Silica (~wt., g)	Sample	Solvent fraction (ml)
30/45	15	15-500mg	10-15
40/50	30	500mg-3g	15-30
70/55	100	2-15g	20-50

Method

Fill the sinter to the lip with silica and apply suction, pressing the silica with extra care at the circumference. Still pressing, level the surface, tapping the sides of the sinter firmly to obtain a totally level surface and head space for the addition of product and solvents.

Under vacuum, pre-elute the column with the least polar combination of the required solvents in which the product mixture is readily soluble. If possible, use a single least-polar component (*e.g.*, use pentane for pentane/ether gradient elution). If the silica has been packed correctly, the solvent front will be seen descending in a horizontal line. If channeling occurs, suck the column dry and repeat the packing procedure. Keep the surface of the silica covered with solvent during pre-elution until solvent is seen passing into the receiver. Then allow the silica to dry under suction.

Load the sample mixture (dissolved in a minimum amount of the pre-elution system) evenly onto the surface of the silica and elute the products by adding successive portions of increasing-polarity solvent mixtures, allowing the column to be sucked dry after each addition (the silica surface is particularly stable and is only slightly disturbed on addition of solvent). Generally a solvent gradient whereby the more polar component is increased by 5-10% is the most convenient. Under these conditions, the product is usually eluted by that solvent mixture in which it would have R_f 0.5 on TLC. For quantities > 100mg, elution is often accompanied by frothing on the underside of the sinter. With a little experience, separations of the same efficiency as TLC are easily possible. There is minimal material loss and the technique is economical in time and solvents.

During prolonged chromatography with volatile solvents, atmospheric moisture may condense on the apparatus; although this does not affect the efficiency of the separation, it may be diminished by substituting less volatile solvents (*e.g.*, hexane for pentane). No solvent is particularly disfavored for this technique but combinations of pentane (hexane), ether, ethyl acetate and methanol are adequate for most separations. Low diffusion of the product bands during chromatography usually means that each component is eluted in one or two fractions, resulting in minimal loss of product in cross-contaminated fractions.

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Organozirconium Compounds as New Reagents and Intermediates

About Our Cover:

We know relatively little about artistic practice in the 17th century, so our chemist-collector was delighted to find *The Artist in His Studio* by Aert de Gelder, one of Rembrandt's last students. De Gelder probably depicted himself in his studio, and it would be fun to be able to identify the sitter. The man in the corner is grinding pigments and, apparently, the cloth hanging from the ceiling is used to control the direction and intensity of the light.

De Gelder was a genial fellow who remained faithful to Rembrandt's style for some sixty years. By the time of de Gelder's death in 1727, Rembrandt's paintings had gone completely out of fashion, yet de Gelder never became "modern". This symphony in umber, with just a few highlights of green in the chairs, must be a sketch done late in the artist's life, probably after 1700.

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

Reprints of Aldrich Catalog Covers

Eight beautiful 14×11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta*, we now offer a collection of articles selected from volumes 1-15. We chose those articles which we believe are still of interest to our readers — 354 pages of great review articles, in one beautiful hardbound volume.

Drying large glassware that will not fit into desiccators can be problematic. We have found that wrapping the male joints with Teflon® tape before placing the glassware in the drying oven is a good idea.

After a suitable drying period, the apparatus can be assembled while still hot, without fear of the joints freezing. Teflon tape withstands temperatures well over 160 °C.

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Traditionally, inexpensive chromatography columns have been made by attaching the barrel of a disposable polypropylene syringe to a suitable length of glass tubing with epoxy, butyl rubber caulking, electrical tape, or a combination thereof. The inertness of these sealants to pH extremes and organic solvents is questionable, and the time required for hardening is unacceptable when immediate use is desired. A fast, new method is suggested:

A disposable polypropylene syringe barrel is selected to fit over the outside of the glass tubing. A *gentle* flame is applied to the syringe barrel one inch from the luer lock end (Fig. 1) until the plastic softens
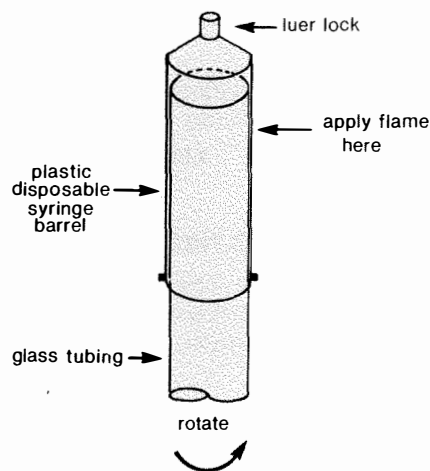

Figure 1

and becomes clear. The flame is then removed and the butt of the barrel is pulled down until the plastic separates at the point of heating (Fig. 2). The end of the barrel
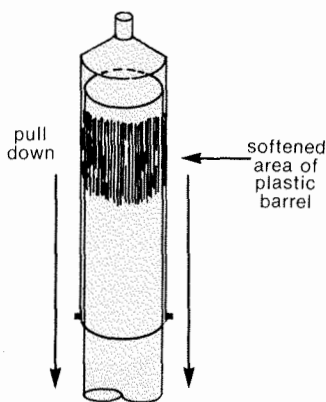

Figure 2

is removed and discarded. This leaves about one inch of the barrel with the luer lock end stuck on the glass tubing. While the plastic is still hot, two nylon wrap-it ties are tightened around the soft plastic barrel to hold it firmly against the glass (Fig. 3). As the plastic cools (water can be used
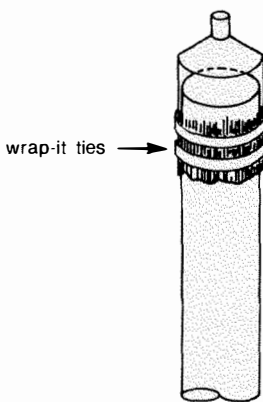
Figure 3

to speed the process) the barrel will shrink around the glass tubing creating a mechanically firm, leak-proof seal. Only polypropylene and glass are in contact with the column material. The entire process takes less than two minutes and the column can be used immediately.

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Editor's note: Consult the Equipment Section of the Aldrich Catalog/Handbook for a variety of disposable syringes and wrap-it ties.

I have found that a convenient NMR tube holder can be made in a cork ring by cutting a hole into (not through) the ring near the outer edge using a No. 2 cork borer. This holder facilitates transfer of flask contents into the NMR tube and provides a simple method for keeping flasks and NMR tubes matched.

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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 Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt.** *We reserve the right to retain all entries for consideration for future publication.*

![Please Bother Us.]

by

Alfred Bader.
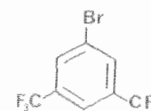
Recently Dr. Hans-Ullrich Siehl at the University of Tuebingen suggested that we offer 3,5-bis(trifluoromethyl)bromobenzene as a reagent to introduce an inductively withdrawing substituent into precursors for carbocations.

We now offer it.

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

Organozirconium Compounds as New Reagents and Intermediates

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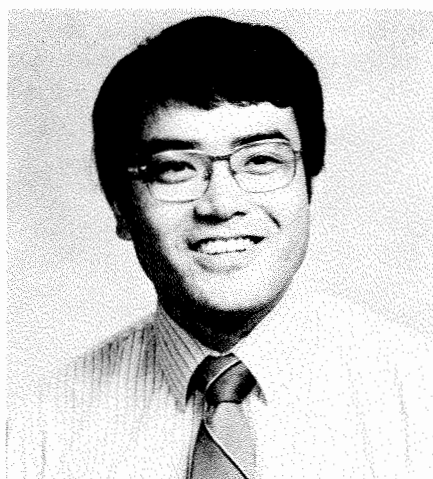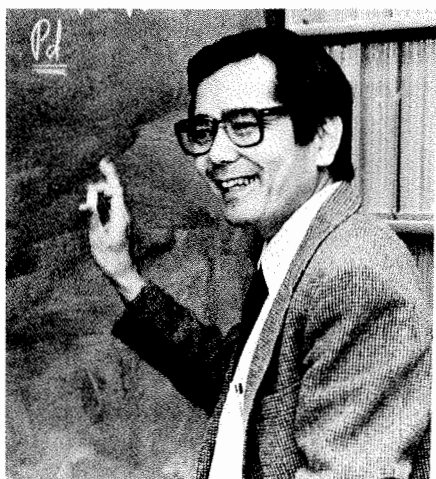
The first systematic use of zirconium in organic synthesis probably came about a decade ago when Schwartz and Hart[1] began developing *hydrozirconation*, which had been discovered earlier by Wailes and Weigold[2] in Australia. This reaction made alkyl- and alkenylzirconium derivatives readily available. These organozirconium derivatives, in turn, serve as useful intermediates for the preparation of organic halides,[1,3] alcohols,[4] and other hetero-substituted derivatives.[5] Although the initial scope of the carbon-carbon bond formation *via* organozirconiums was limited mostly to *carbonylation*[6] and *acylation* with acyl halides,[1] the development of procedures for *Pd-* or *Ni-catalyzed cross coupling* by Negishi[7] and for *Ni-catalyzed conjugate addition* by Schwartz[8] significantly increased the synthetic utility of organozirconium compounds. In general, the relatively low electronegativity of Zr permits replacement of Zr with various metals such as Al,[9] Zn,[9] Hg,[9] Sn,[9] and Cu[10] (*transmetallation*), thereby further expanding the synthetic scope of organozirconium chemistry.

The discovery and development by Negishi and Van Horn of *Zr-catalyzed carboalumination*[11] and *carbozincation*[12] represent another major breakthrough in the use of organozirconiums in organic synthesis. Organozirconium complexes also serve as effective *catalysts in hydroalumination*.[13] Alkyl and alkenyl derivatives of Al and Zn thus obtained can then serve as versatile intermediates, as detailed later.

Although organozirconiums are poor substitutes for Grignard reagents and organolithiums, *monoorganozirconium trialkoxides* have been shown by Seebach[14] to add to ketones with high addition/enolization ratios. Evans[15] and Yamamoto[16] have shown that *zirconium enolates* and related species display *high erythro selectivity in aldol-type reactions. Allylzirconium derivatives* also promise to be useful reagents for carbonyl addition.

Essentially all of the reactions mentioned above involve Zr(IV) compounds as reagents and intermediates. The carbene-like property of "Cp₂*Zr(II)" derivatives, where Cp* is either η^5-C₅H₅ or η^5-C₅Me₅, has been investigated by various workers over the past decade.[17] The reaction of these derivatives with CO investigated by Bercaw[18] and others is interesting as a homogeneous model for the Fischer-Tropsch synthesis. Generally speaking, however, Zr(II) species have not yet been used widely in the synthesis of complex

organic compounds, although this situation is rapidly changing. The propensity of Zr(II) species to undergo two-electron oxidation should make them attractive *reducing agents*. This aspect of Zr(II) chemistry deserves further investigation. Highly promising from the viewpoint of the synthesis of complex organic products is the reaction of Cp₂Zr(II) species with alkenes, alkynes, and dienes.

Since this review emphasizes the use of Zr in organic synthesis, much of the pioneering studies that do not place emphasis on organic synthesis, most notably those by J.L. Atwood, J.E. Bercaw, E.M. Brainina, K.G. Caulton, G. Erker, C. Floriani, M.F. Lappert, T.J. Marks, M.D. Rausch, G.A. Razuvaev, P.C. Wailes, and their associates are omitted. There are, however, a few comprehensive reviews covering these topics. The organometallic chemistry of Ti, Zr, and Hf through part of 1973 was surveyed by Wailes, Coutts, and Weigold.[19] More recent comprehensive reviews of the organometallic chemistry of Zr and Hf covering the literature through part of 1981 were published in 1982 by Cardin, Lappert, Raston, and Riley.[20]

Zirconium is the second member of the Group 4B Titanium triad. It occurs to the extent of 0.022% in the lithosphere. As such, it is as abundant as carbon. Unfortunately, all Zr minerals contain difficultly separable Hf, which must be a factor contributing to the current prices of pure Zr compounds. Therefore, it might be desirable to attempt to use mixtures containing both Zr and Hf. As the data summarized in Table 1 indicate, Ti, Zr, and Hf are surprisingly similar in size and electronegativity, the lanthanide contraction being mainly responsible for the similarity between Zr and Hf. Indeed, Ti and Zr do undergo similar reactions, and the chemical properties of Zr and Hf are, in most cases, almost indistinguishable. There are, however, some fundamental differences between Ti and Zr

Table 1
Some Fundamental Properties of Ti, Zr, and Hf

Element	Atomic number	Atomic weight	Electronic configuration	Covalent radius (Å)	Ionic radius (Å)	Electronegativity Pauling	Allred-Rochow
	22	47.90	$[Ar]3d^2 4s^2$	1.32	0.68 (+4)	1.5	1.32
Zr	40	91.22	$[Kr]4d^2 5s^2$	1.45	0.80 (+4)	1.4	1.22
Hf	72	178.49	$[Xe]4f^{14}5d^2 6s^2$	1.44	0.71–0.83 (+4)	1.3	1.23

that should be mentioned here. The most commonly encountered oxidation state for Ti, Zr, and Hf compounds is + 4 (d^0 configuration). Although generally less stable, these elements also readily form d^2 complexes in which the oxidation state of the metal atom is + 2. The + 3 and + 1 oxidation states are rather rare for Zr, while Ti can readily acquire the + 3 oxidation state. This property of Ti makes many of the Ti(IV) species chemically more labile than the corresponding Zr(IV) species. Contrary to what one might expect on the basis of their reported relative electronegativity values, Zr species appear to be considerably less reactive toward aldehydes and ketones than the corresponding Ti compounds. Other experimental data also suggest that Ti might, in fact, be more electropositive than Zr.

Zirconium(IV) compounds, such as $ZrCl_4$, might be viewed as tetracoordinate 8-electron species. Indeed, $ZrCl_4$ is a monomeric tetrahedral species in the vapor state. However, its sublimation point of 331° and the boiling point of $TiCl_4$ (136.4°) are both considerably higher than those of $SiCl_4$ (57.6°), $GeCl_4$ (83.1°), and $SnCl_4$ (114.1°), suggesting that there must be considerable interaction between Cl and low-lying 5 empty d orbitals of Ti or Zr. These readily available empty orbitals are also responsible for the Lewis-acid nature of Ti(IV) and Zr(IV) species. The great majority of Zr compounds discussed in this review contain $ZrCp_2$, where Cp is η^5-C_5H_5. Both the crystal and vapor-phase structures of Cp_2ZrCl_2 are similar as shown by **1**,[20] the numbers in parentheses being those of the vapor-phase structure.


1

2
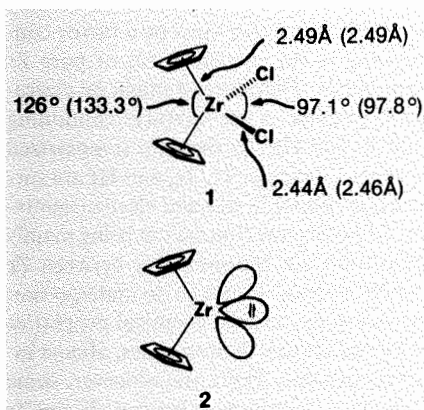
The 2 Cp and 2 Cl ligands contribute 16 (2x6 + 2x2) electrons. So, it is a 16-electron species with one empty orbital which is thought to be critically responsible for various reactions of **1** and related species. Reduction of **1** can produce a Zr(II) species that can act as "Cp_2Zr". Although its structure remains unclear, the dicarbonyl derivative has a structure similar to **1**, except that the Cp-Zr-Cp angle is much wider (143.4°). It is useful to note that the monomeric form of "$Cp_2Zr(II)$", which might be an actual reactive species in many reactions (although hypothetical), would be a 14-electron species with one filled nonbonding and two empty valence shell orbitals, as depicted in **2**. Such a species is expected to have carbene character. In summary, whether one uses $ZrCl_4$, Cp_2ZrCl_2, or "Cp_2Zr", the presence or ready availability of one or more empty orbitals appears to be crucial.

Preparation of Organozirconium Compounds

Of a dozen or so fundamentally different methods for preparing organometallics,[21] several have been applied to the preparation of organozirconiums. Using Cp_2Zr derivatives as representative cases, these methods are indicated by the following generalized equations.

1. *Transmetallation*: Zr(IV) → Zr(IV)

(eq. 1)
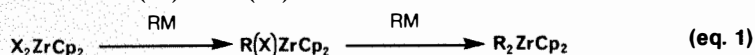
2. *Hydrozirconation*: Zr(IV) → Zr(IV)

(eq. 2)
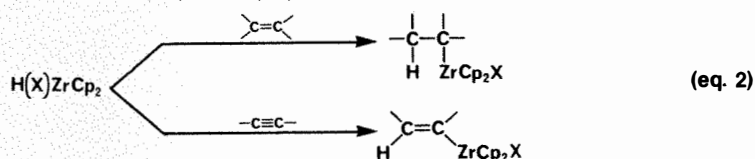
3. *Complexation*: Zr(II) → Zr(II)

L: e.g., CO

(eq. 3)

4. *Oxidative coupling*: Zr(II) → Zr(IV)

(eq. 4)
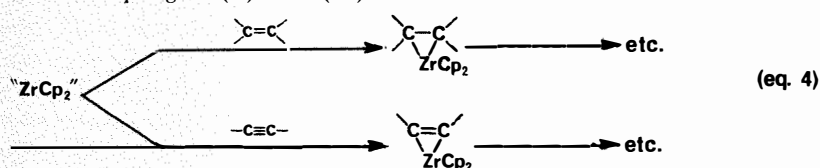
5. *Carbozirconation*: Zr(IV) → Zr(IV)

(eq. 5)

(eq. 6)

(eq. 7)
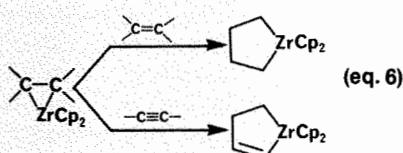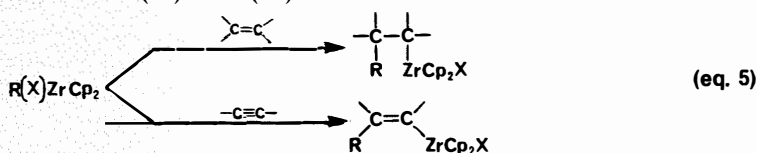
6. *Oxidative addition*: Zr(II) → Zr(IV)

(eq. 8)
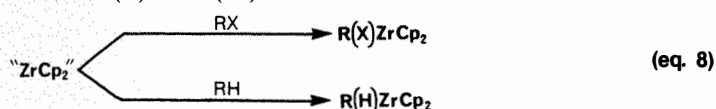
7. Metal-hydrogen exchange: Zr(IV) → Zr(IV)

$$X_2ZrCp_2 \xrightarrow[-HX]{HR} R(X)ZrCp_2 \xrightarrow[-HX]{HR} R_2ZrCp_2 \qquad \text{(eq. 9)}$$

$$O(ClZrCp_2)_2 \xrightarrow{Me_3Al} Me(Cl)ZrCp_2 \qquad \text{(eq. 10)}$$

$$\underset{R^2}{\overset{R^1}{>}}C=C\underset{AlR_2}{\overset{H}{<}} \xrightarrow[\text{2. } Cl_2ZrCp_2]{\text{1. } n\text{-BuLi}} \underset{R^2}{\overset{R^1}{>}}C=C\underset{ZrCp_2Cl}{\overset{H}{<}} \qquad \text{(eq. 11)}$$

Table 2
Scope of Hydrometallation Reactions with Respect to Substrate Structures
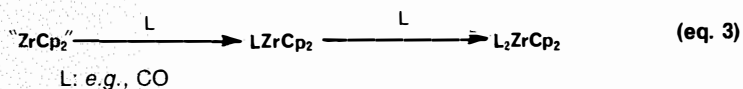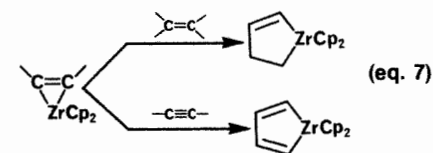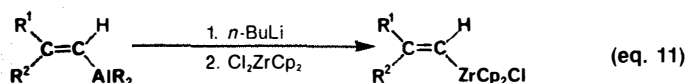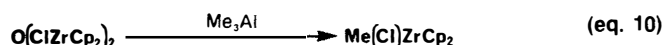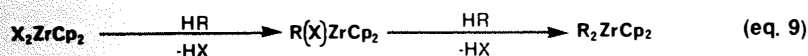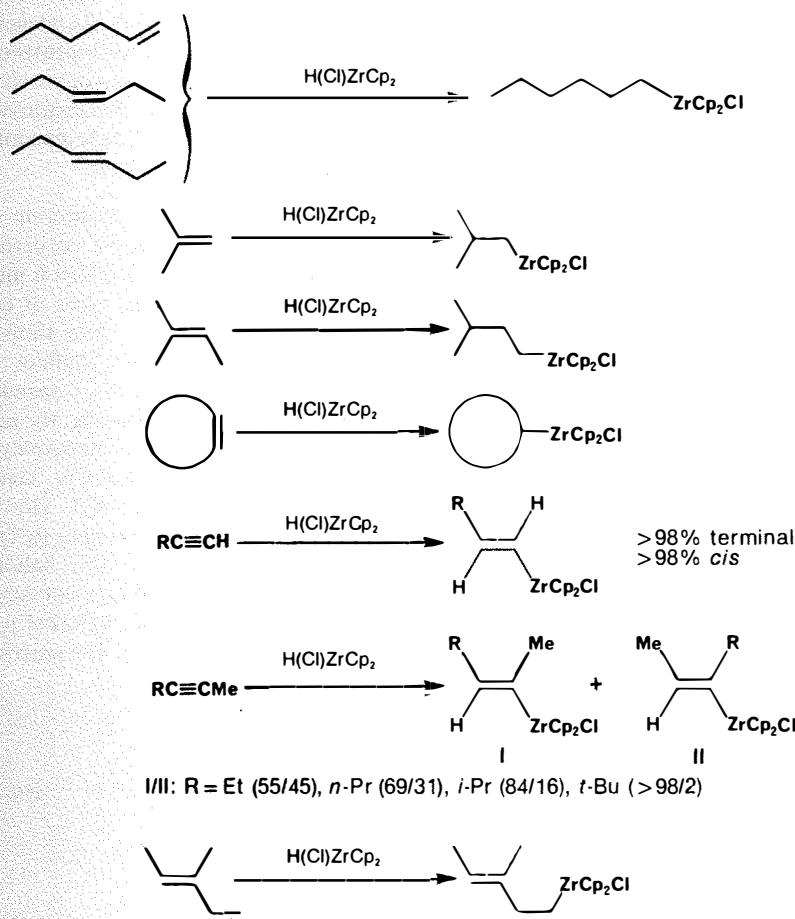
Metal	RCH=CH₂	R₂C=CH₂	RCH=CHR	R₂C=CHR	R₂C=CR₂	RC≡CH	RC≡CR
B	+	+	+	+	+	+	+
Zr	+	+	+[a]	+[a]	−	+	+
Al	+[b]	sluggish	sluggish	?	?	+	+

[a]Accompanied by Zr migration.
[b]Sluggish unless catalyzed by Zr or Ni complexes.

Scheme 1
Hydrozirconation

I/II: R = Et (55/45), n-Pr (69/31), i-Pr (84/16), t-Bu (>98/2)

Transmetallation. This is by far the most general, if not the most desirable, method for preparing organozirconiums. Zirconocene dichloride itself is commonly prepared by treating ZrCl₄ with NaCp.[22] Treatment of X₂ZrCp₂, where X is Cl, Br, I, etc., with organometallics containing highly electropositive metals, such as Li, Na, K, and Mg, appears to be a general and dependable method for preparing R₂ZrCp₂, where R is alkyl, allyl, benzyl, alkenyl, aryl, alkynyl, etc. On the other hand, the preparation of R(X)ZrCp₂ *via* transmetallation usually requires carefully chosen reagents and reaction conditions to avoid the formation of R₂ZrCp₂. Some important factors affecting the extent of substitution include (i) the steric requirement of R, (ii) the leaving group X, and (iii) the gegenion M of MR. Aluminum is also useful in this reaction. The transformations shown in eqs. 10[23] and 11[24] represent the currently most satisfactory routes to the indicated products.

Hydrozirconation.[25] This reaction is most cleanly achieved by heating olefins or acetylenes with preformed and purified H(Cl)ZrCp₂ prepared by treating Cl₂ZrCp₂ with either LiAlH(OBu-t)₃[2a] or NaAlH₂-(OCH₂CH₂OMe)₂.[1] The reaction shares some synthetically important characteristics with other facile and clean hydrometallation reactions, such as hydroboration[26] and hydroalumination.[27] Thus, the reaction is generally clean and high-yielding and involves nearly 100% *cis* addition. When it is applicable, it is usually the method of choice for preparing alkyl and alkenyl derivatives of Zr. There are, however, a few noteworthy differences among hydrometallation reactions of Zr, B, and Al. The scope of hydrozirconation with respect to both substrate structure (Table 2, Scheme 1) and chemoselectivity lies somewhere between those of hydroboration and hydroalumination. The facile isomerization of secondary alkylzirconium derivatives into primary alkyl derivatives can occur even at or below room temperature[1] and is far more facile than the corresponding reactions of B and Al. Alkenylzirconium derivatives can also isomerize in the presence of a catalytic amount of H(Cl)ZrCp₂, and a regioselectivity of ≥90% has been attained in the reaction of MeC≡CR, where R is primary, secondary, or tertiary alkyl.[3a] Hydrozirconation of conjugated dienes can produce isomerically pure homoallyl derivatives by placing Zr at the least hindered terminal position.[3b] Halogens, ethers, and metal-substituted alkoxides are tolerated in hydrozirconation. Carbonyl compounds, such as aldehydes, ketones, carboxylic acids, and esters are reduced to alcohols, while nitriles are reduced to aldehydes.[25]

Despite the facile isomerization of alkylzirconium species, the equilibrium strongly favors the adduct side. It is therefore difficult to free terminal alkenes from alkylzirconiums, although their treatment with Ph₃CBF₄ in benzene at 20° does produce terminal alkenes.[25]

Hydrozirconation can also be achieved with other reagents. The reaction of H₂ZrCp₂ with terminal acetylenes gives dialkenyl derivatives of ZrCp₂.[2b] In principle, hydrozirconation with H₂ZrCp₂ can first produce R(H)ZrCp₂, which readily decomposes[28] to generate "ZrCp₂." This Zr(II) species can then induce various side reactions. For example, the reaction of diphenylacetylene with H₂ZrCp₂ produces **3**

in an unspecified yield.[2b] One plausible path for its formation is shown in eq. 12.

Since the preparation of H(Cl)ZrCp$_2$ involves filtration of an air- and moisture-sensitive compound, it would be more convenient to generate it *in situ* and carry out hydrozirconation in the same vessel. The use of NaAlH$_2$(OCH$_2$CH$_2$OMe)$_2$ or LiAlH(OBu-*t*)$_3$ in conjunction with Cl$_2$ZrCp$_2$ appears to permit this *in situ* hydrozirconation.[29] *tert*-Butylmagnesium chloride also serves as a satisfactory hydride source.[29] Since this reagent can be derived from isobutylene, HCl, and Mg, and since isobutylene can be recycled, it could be an economical hydride source. It should be mentioned, however, that these modified procedures may not always give the same results as those observed with pure H(Cl)ZrCp$_2$.

Another attractive possibility is to promote other sluggish hydrometallation reactions with zirconium complexes. Somewhat unexpectedly, the reaction of olefins with *i*-Bu$_2$AlH cannot be catalyzed by Cl$_2$ZrCp$_2$, even though the use of 1 equivalent of Cl$_2$ZrCp$_2$ does induce a facile hydrometallation reaction.[13] Far more attractive is the reaction of olefins with *i*-Bu$_3$Al, which can indeed be markedly accelerated by a catalytic amount of Cl$_2$ZrCp$_2$.[13] This reaction most probably involves two transmetallation steps that are opposite to each other (Scheme 2). Its applicability at the present time is limited to hydroalumination of monosubstituted terminal olefins.
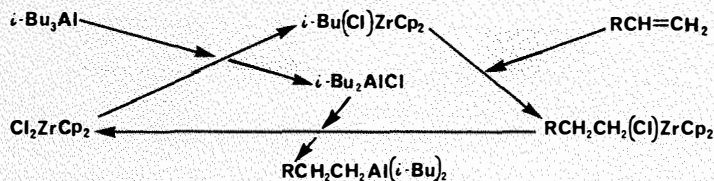
Complexation and Oxidative Coupling. The distinction between complexation and oxidative coupling is often a matter of convenience and semantics and, in most cases, these two terms should be viewed as two convenient extremes of a continuous spectrum of chemical processes. The reaction of "ZrCp$_2$" with neutral carbon compounds (L) can lead to L$_2$ZrCp$_2$. In addition to (CO)$_2$ZrCp$_2$ mentioned above, (1,3-butadiene)ZrCp$_2$ (4) represents another example of Zr(II) complexes obtainable *via* complexation of "ZrCp$_2$." Interestingly,

4a   **4b**   **5**
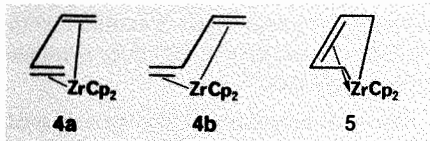
the same complex can also be prepared, perhaps more conveniently, by the reaction of Cl$_2$ZrCp$_2$ with (CH$_2$CH=CHCH$_2$)Mg[30a] which may be thought to give **5** instead of **4**. Theoretical studies[30b] indicate the *s-cis* isomer obtained by thermal processes is indeed better represented by **5** rather than **4a**, while the *s-trans* isomer obtained by
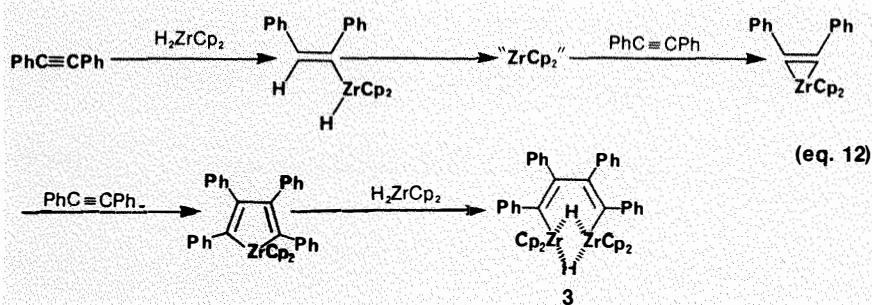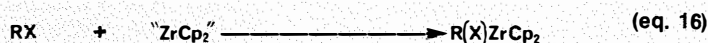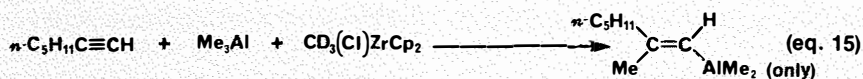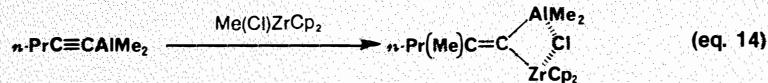
photolysis of Ph$_2$ZrCp$_2$ in the presence of butadiene[31] must be **4b**. The formation of **5** by the reaction of butadiene with "ZrCp$_2$" may be conveniently explained in terms of a combination of complexation and oxidative coupling (eq. 13).

Carbometallation. Although carbozirconation processes have been implicated in the Ziegler-Natta polymerization reaction catalyzed by Zr complexes,[19,20] unequivocal examples of straightforward carbozirconation of olefins and acetylenes are very few. The reaction of dimethylaluminoacetylenes with Me(Cl)ZrCp$_2$[32] (eq. 14) is one such example. On the other hand, the reaction of terminal and ordinary internal acetylenes with Al-Zr reagents involves a Zr-assisted direct carboalumination[33] (eq. 15). Despite all these, carbozirconation may still be an ubiquitous process especially in an intramolecular manner. Thus, a crucial step in the formation of **3** (eq. 12) and **5** from butadiene (eq. 13) may be viewed as a car-

bometallation reaction. Furthermore, conversion of olefins and acetylenes into zirconacyclopentanes, -cyclopentenes, and -cyclopentadienes may also be viewed as an oxidative coupling (eq. 4)-carbozirconation (eqs. 6 and 7) process. These reactions will be discussed in detail later.

Oxidative Addition. Inspection of the hypothetical monomeric structure of "ZrCp$_2$", *i.e.,* **2**, suggests that it might be reactive toward various types of organic halides. Indeed, it has been shown that "ZrCp$_2$" reacts with alkyl halides to produce R(X)ZrCp$_2$[34] (eq. 16). Depending on the structure of RX, however, the reaction can also produce either competitively or exclusively undesirable X$_2$ZrCp$_2$. Generally speaking, primary alkyl chlorides, bromides, and iodides produce R(X)ZrCp$_2$ cleanly, whereas tertiary alkyl halides give exclusively X$_2$ZrCp$_2$. With secondary alkyl halides, mixtures of R(X)ZrCp$_2$ and X$_2$ZrCp$_2$ are obtained.[34] The reaction has

(eq. 12)

3

Scheme 2
Zirconium-Catalyzed Hydroalumination

(eq. 13)

5

(eq. 14)

(eq. 15)

$$RX \quad + \quad \text{"ZrCp}_2\text{"} \longrightarrow R(X)ZrCp_2 \qquad \text{(eq. 16)}$$
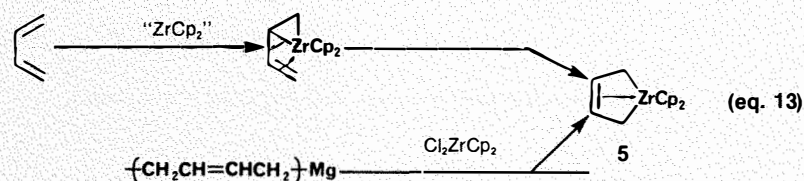
been shown to proceed by radical processes involving paramagnetic Zr(III) species, *i.e.*, X(L)ZrCp$_2$ and R(L)ZrCp$_2$[35] (eq. 17).

Zirconium(II) species can also react with arenes *via* oxidative addition to produce Ar(H)Zr(IV) derivatives[36] (eq. 18). Although promising, the scope and limitations of the reaction have not yet been delineated.

Metal-Hydrogen Exchange. Relatively acidic carbon acids, such as acetylenes, can undergo zirconium-hydrogen exchange, *e.g.*, eq. 19.[37] Although the scope of this reaction has not been delineated, it is expected to be rather narrow.
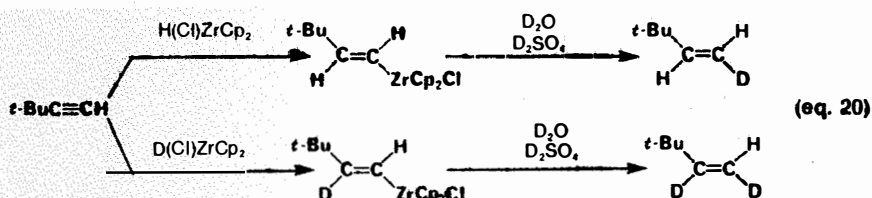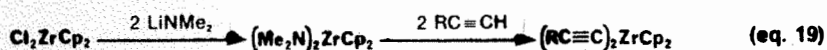
Reactions of Organozirconium Compounds

Organozirconium compounds may be used in various ways to synthesize organic compounds. In cases where the organic moieties are incorporated into the organic products, such organozirconium compounds will be considered as *intermediates*. In the other cases, they will be called *reagents*. When organozirconiums are used as intermediates, scission of one or more C-Zr bonds must take place, and Zr must be replaced by C, H(D), heteroatoms, such as Cl, Br, I, O, S, Se, N, and P, or metals, *i.e.*, transmetallation. Once transmetallated, new organometallics thus formed can undergo reactions that are characteristic of them. Transmetallation thus provides an attractive way of substantially expanding the synthetic utility of organozirconiums or, for that matter, any organometallic compounds.

Formation of Carbon-Hydrogen and Carbon-Heteroatom Bonds via Organozirconiums.

(a) *Protonolysis (Deuterolysis).* Cleavage of *sigma* Zr-C bonds occurs readily upon treatment with H$_2$O or dilute acids, although multiple bonds, such as the Zr-Cp bonds, are much less reactive and can survive various protonolysis conditions. The use of D$_2$O or D$_2$SO$_4$ permits replacement of Zr with D. Together with iodinolysis, deuterolysis provides a generally reliable method for establishing the presence of the Zr-C bond. Protonolysis or deuterolysis of Zr-C$_{sp^2}$ bonds occurs with clean retention of configuration[6b] (eq. 20). The stereochemistry of protonolysis or deuterolysis of the Zr-C$_{sp^3}$ bond does not appear to have been established, although it may also proceed with retention.

(b) *Halogenolysis.* Iodinolysis of various *sigma* Zr-C bonds with I$_2$, as well as brominolysis of Zr-C$_{sp^3}$ bonds with Br$_2$, occurs readily with retention at or below room temperature.[1,3a] Brominolysis of Zr-C$_{sp^2}$ bonds or even Zr-C$_{sp^3}$ bonds may be

(eq. 17)

(eq. 18)

$o : m : p = 0 : 67 : 33$

$$Cl_2ZrCp_2 \xrightarrow{2\ LiNMe_2} (Me_2N)_2ZrCp_2 \xrightarrow{2\ RC\equiv CH} (RC\equiv C)_2ZrCp_2 \quad \text{(eq. 19)}$$

(eq. 20)
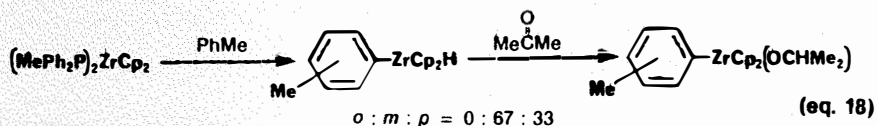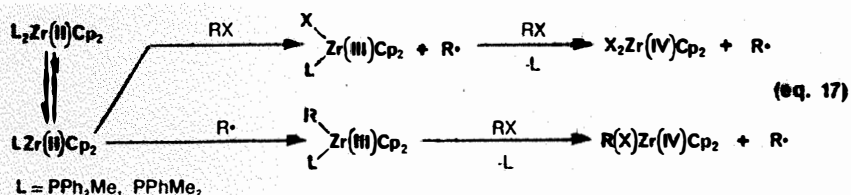
Scheme 3
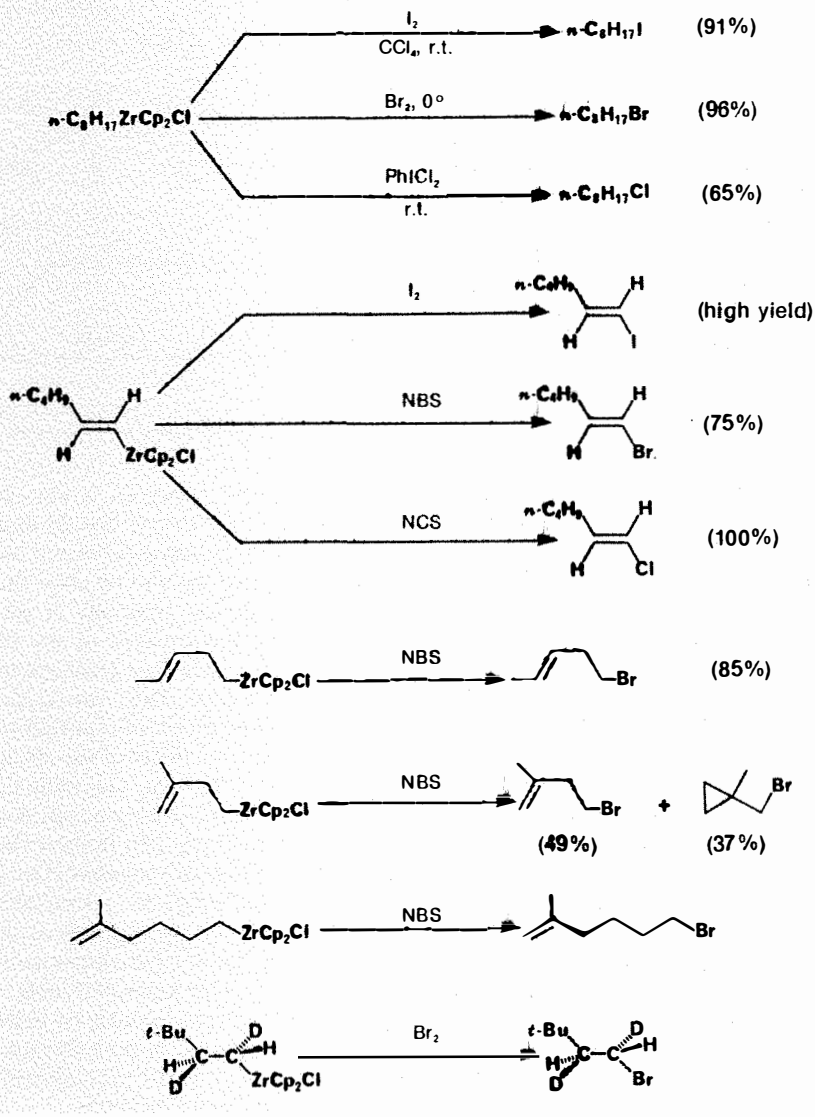
conveniently achieved with N-bromosuccinimide (NBS).[3a] The reaction of homoallylzirconiums with NBS may be accompanied by skeletal rearrangements.[3b] Chlorinolysis of Zr-C bonds is more sluggish and is usually achieved with N-chlorosuccinimide (NCS)[3a] or PhICl$_2$.[1] Some representative results are shown in Scheme 3.

(c) *Oxidation.* Alkylzirconium derivatives can be converted into alcohols with H$_2$O$_2$-NaOH, t-BuOOH, m-chloroperbenzoic acid (MCPBA), or O$_2$.[4] Unfortunately, the yields of alcohols are at best modest ($\leqslant 80\%$) and are often rather poor. Oxidation with O$_2$ appears to proceed *via* alkylperoxy derivatives[4] (eq. 21). In accord with eq. 21, the reaction proceeds with ca. 50% retention and *ca.* 50% racemization. Oxidation of alkenylzirconium derivatives with the above-mentioned oxidizing agents does not give aldehydes or ketones in any significant yield.[1]

(d) *Replacement of Zirconium with Other Heteroatoms.* The reactions involving replacement of Zr with other heteroatoms, such as S, Se, N, and P, are still very rare. The reactions shown in eqs. 22 and 23 are examples involving S and N, respectively.[5]

(e) *Transmetallation.* Zirconium is more electronegative than alkali and alkaline earth metals including Mg, as well as Group 3B metals including Sc, Y, lanthanides and actinides. On the other hand, it is as electronegative as or more electropositive than virtually all of the other metals with the possible exception of Ti and Hf (*vide supra*.) Thermodynamically, replacement of Zr in organozirconiums with a metal that is more electronegative than Zr should be favorable. In reality, however, the scope of favorable transmetallation is much narrower, because high kinetic barriers may hinder otherwise favorable processes. Although transmetallation may proceed by a variety of mechanisms, a four-center process requiring the availability of an empty orbital on each metal (eq. 24) appears to represent the dominant path. This mechanism predicts transfer of organic groups with retention of configuration.

Based on the above considerations, we may expect transmetallation of organozirconiums with Lewis-acid species with low-lying empty orbitals containing electronegative metals to be both kinetically and thermodynamically favorable. Clean and essentially quantitative transmetallation reactions of R(X)ZrCp$_2$ have been observed with haloaluminum derivatives,[9,13] such as R$_2$AlCl and AlCl$_3$, and most probably with HgCl$_2$.[9] Transmetallation reactions with ZnCl$_2$,[24] SnCl$_4$,[24] CuCl[10] and PdCl$_2$[10] have also been claimed. The exact nature
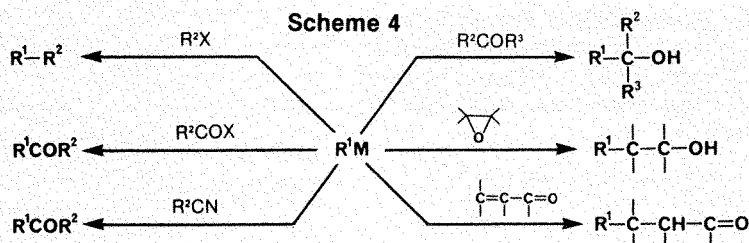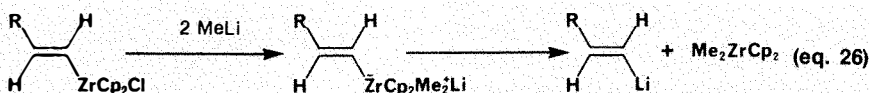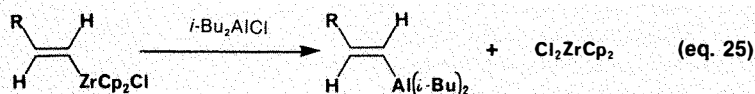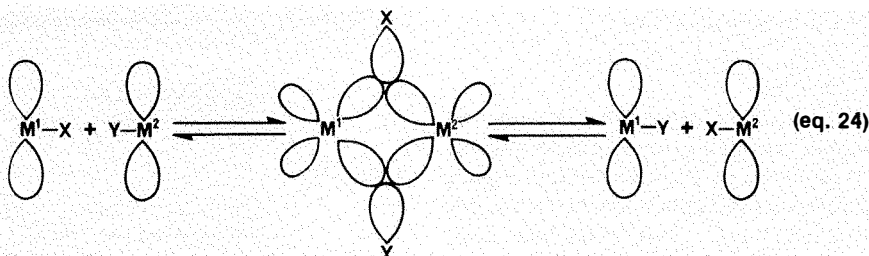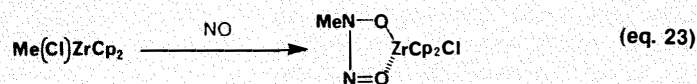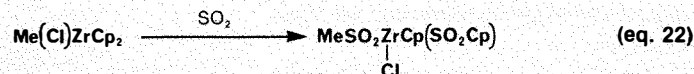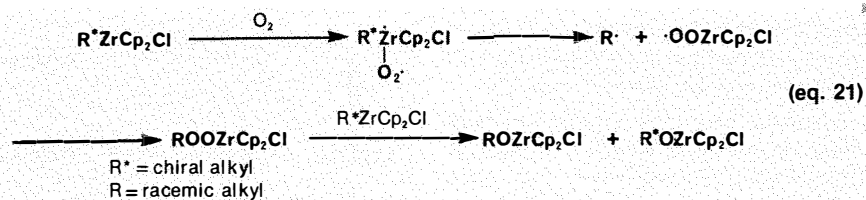
of these reactions, however, is not very clear. It is important to note that the direction of transmetallation depends not only on the metals used but also on other factors, such as ligands, especially in cases where the electronegativities of the two metals are comparable. The Zr-Al systems fall into this category. Thus, the reaction of Cl$_2$ZrCp$_2$ with lithium alkenyltrialkylaluminates involves transfer of the alkenyl group from Al to Zr[25] (eq. 11), while that of R'(X)ZrCp$_2$ with R$_2$AlCl proceeds in the opposite direction[9] (eq. 25). In these reactions, alkenyl groups are transferred exclusively. Both Al→Zr and Zr→Al transmetallation processes are believed to be involved in the Zr-catalyzed hydroalumination[13] (Scheme 2), and these kinds of double- or multiple-metal systems capable of undergoing transmetallation in both directions will further prove to be of use in developing various catalytic procedures.

It has been claimed that transfer of an alkenyl group from Zr to Li is also feasible according to eq. 26.[24] Unfortunately, the experimental details have not been published. In light of the failure to generate alkenyllithiums from the corresponding alkenyl aluminates,[38] the above claim is somewhat surprising. Although unknown, transfer of an organic group from Zr to B, Ga, In, and Tl should be facile. It is also likely that relatively electronegative transition metals can readily produce at least equilibrium quantities of their organic derivatives on reaction with organozirconiums. Such species are undoubtedly involved in the Ni- or Pd-catalyzed carbon-carbon bond formation reactions of organozirconiums,[7,8] as discussed later.

Carbon-Carbon Bond Formation via Organozirconiums

The electronegativity of Zr suggests that organozirconiums might, in general, be less

$$R^*ZrCp_2Cl \xrightarrow{O_2} R^*ZrCp_2Cl \longrightarrow R\cdot + \cdot OOZrCp_2Cl$$

$$\xrightarrow{R^*ZrCp_2Cl} ROOZrCp_2Cl \longrightarrow ROZrCp_2Cl + R^*OZrCp_2Cl$$

R* = chiral alkyl
R = racemic alkyl

(eq. 21)

$$Me(Cl)ZrCp_2 \xrightarrow{SO_2} MeSO_2ZrCp(SO_2Cp) \quad \text{(eq. 22)}$$

$$Me(Cl)ZrCp_2 \xrightarrow{NO} \quad \text{(eq. 23)}$$

$$M^1-X + Y-M^2 \rightleftharpoons \rightleftharpoons M^1-Y + X-M^2 \quad \text{(eq. 24)}$$

(eq. 25)

(eq. 26)

Scheme 4

nucleophilic toward carbon electrophiles than the corresponding organometals containing Li, Na, K, or Mg but perhaps more nucleophilic than those containing Al or Zn. In reality, however, RZrCp$_2$ seem to be much less reactive toward carbon electrophiles than organoaluminum or organozinc compounds. High steric requirements around the Zr atom of RZrCp$_2$ must be responsible, in part, for their low nucleophilicity.

When organometallics are used as nucleophiles in the carbon-carbon bond formation, the reactions shown in Scheme 4 and their variations are usually considered. Unfortunately, organozirconiums are generally unreactive toward organic halides, carboxylic acids and their derivatives except acyl halides, nitriles, epoxides, and α,β-unsaturated carbonyl compounds. Only acyl halides react directly with RZrCp$_2$X^9, but the scope of the reaction is very limited. Although RZrCp$_2$X appear to be unreactive toward aldehydes and ketones, RZr(OR^1)$_3$ are reactive and display some useful features, ^{14} as discussed later. Various potential solutions to the abovementioned difficulties may be considered, and the following either have been demonstrated or appear promising:

i. use of organozirconiums as formal electrophiles rather than nucleophiles

ii. conversion of organozirconiums into other organometals via transmetallation

iii. generation and use of organozirconiums of low steric requirements, and

iv. generation and use of organozirconates.

Through these considerations and manipulations, organozirconiums can now be used as versatile intermediates in carbon-carbon bond formation.

(a) *Carbonylation.* Although CO does not appear to react with (PhCH$_2$)$_2$ZrCp$_2$ even at 100° and 40 atm,^{39} R(X)ZrCp$_2$ containing alkyl, homoallyl, and alkenyl groups are readily carbonylated with CO at *ca.* 20 psi and room temperature.^{6} Relative rates for CO insertion decrease in the order: cyclohexyl > *n*-alkyl ≅ alkenyl.^{6} The carbonylation products, *i.e.*, RCOZrCp$_2$Cl, can be isolated and identified.^{6} In carbonylation, organozirconiums react as formal electrophiles. The complexation-migratory insertion mechanism shown in eq. 27 appears plausible.

Acylzirconium derivatives obtained as shown above can be treated with dilute HCl to give aldehydes or converted into carboxylic acids and methyl esters upon treatment with NaOH/H$_2$O$_2$ and Br$_2$/MeOH,
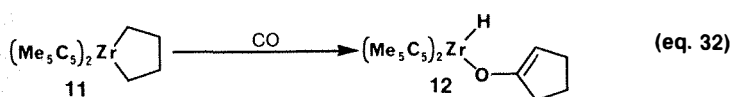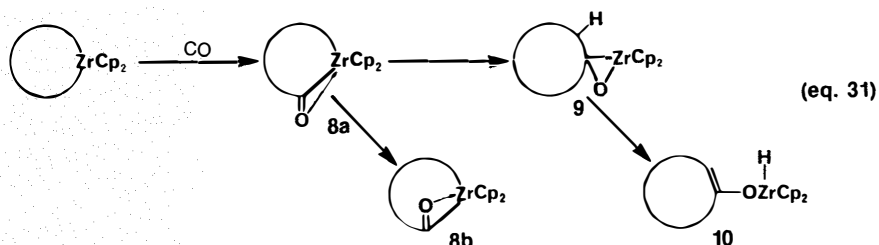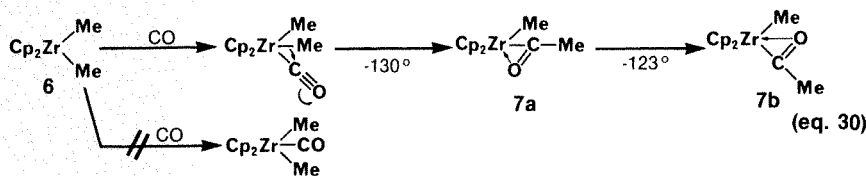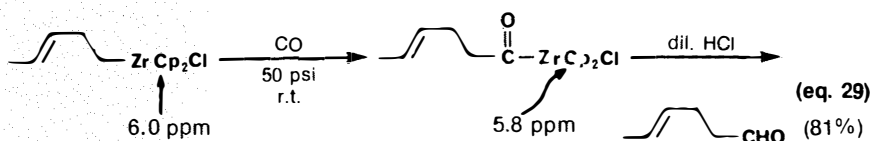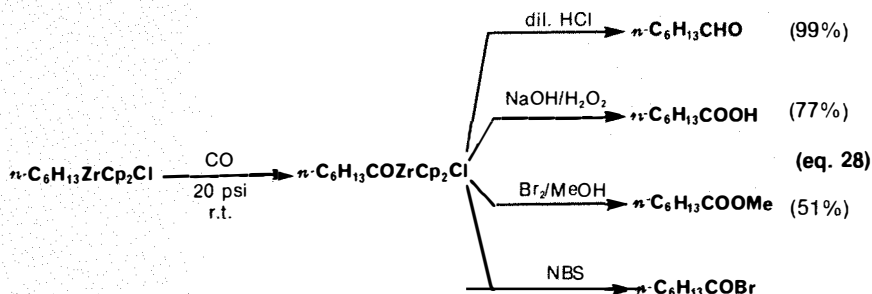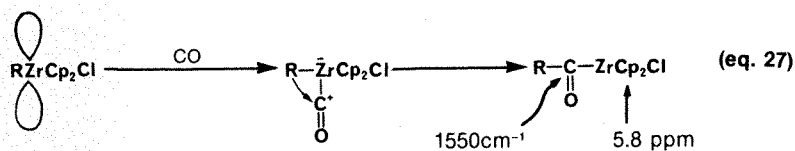
respectively.^{6} Their treatment with NBS permits isolation of acyl bromides. Some representative results of carbonylation of RZrCp$_2$X are shown in eqs. 28 and 29.

A detailed study of carbonylation of Me$_2$ZrCp$_2$ (6) indicates that it first produces 7a at temperatures as low as -130°. At -123° it rearranges to 7b.^{40} The reaction is believed to involve complexation of CO at a lateral coordination side of 6, suggesting that the empty orbital of 6 lies as shown in 6a rather than occupy a central position as in 6b^{41} (eq. 30).

In the carbonylation reaction of zirconacycles, isomerization of 8a to 8b is unfavorable unless the zirconacycles are very large. This inhibition of isomerization presumably promotes migration of the second organic group from Zr to the acyl carbon atom (eq. 31). Except for the final step producing zirconium enolates via dehydrozirconation, conversion of zirconacycles into 9 is very analogous to the reaction of boracycles with CO.^{42} Specifically, the bis(pentamethylcyclopentadienyl) derivative of zirconacyclopentane (11) gives 12^{43} (eq. 32).

Scheme 5

Depending on the structure of the zircon-acycle and reaction conditions, the course of the reaction can be considerably more complicated than that indicated in eq. 31. Thus, a zirconaindan derivative **13**, that can be obtained (presumably *via* a Zr-benzyne complex)[44] by heating Ph_2ZrCp_2 to 70° in the presence of ethylene, reacts with CO to produce a mixture of indanone (42%), indane (21%), tetralone (19%), and 3-phenylpropanol.[45] A triple-path mechanism is consistent with the results (Scheme 5). Two probable intermediates **14** and **15** react to form a key dimeric intermediate **16**, which presumably decomposes *via* three different paths. It is important to note that conversion of **13** into **14** involves clean migration of the alkyl group in preference to the aryl group.

In sharp contrast with the complex results obtained with **13**, treatment of bicyclic zirconacyclopentene derivatives **17** with CO (1.1 atm) at room temperature produces the corresponding cyclopentenones unaccompanied by closely boiling by-products, such as cyclopentene and cyclohexanone derivatives,[46] although their yields are somewhat modest. Since the required intermediates **17** are readily available, the bicyclization-carbonylation procedure provides a highly efficient and selective route to bicyclic enones (eq. 33). One general route to bicyclic cyclo-pentenones makes use of the Ti-promoted conjugate allylation[47] and conversion of methyl ketones into acetylenes[48] (eq. 34). Iodinolysis of **17** gives **18**, which, on treatment with *n*-BuLi,[49] provides **19** in 70% yield[46] (eq. 35).

Although stoichiometric, conversion of CO and H_2 into methanol promoted by Zr complexes can proceed cleanly and quantitatively according to eq. 36, thereby providing a homogeneous model for CO reduction with H_2.[50] The mechanistic details are not yet clear. However, Scheme 6 has been proposed as a plausible mechanism for the reaction of Cp_2*ZrH_2 with CO.[18] Depending on the reaction conditions, **20**, **21**, or a mixture of the two is obtained.

(b) *Acylation.* Alkylzirconium derivatives react with MeCOCl to give the corresponding ketones, but alkenylzirconium derivatives fail to produce ketones.[9] Far more favorable results are obtained by treating $RZrCp_2Cl$ first with $AlCl_3$ and then with $R'COCl$.[9] The reaction proceeds *via* $RAlCl_2$. Some representative results are shown in eqs. 37-39.

(c) *Ni- or Pd-Catalyzed Cross Coupling.* Organozirconiums themselves appear to be totally unreactive toward organic halides. However, alkenylzirconium derivatives re-
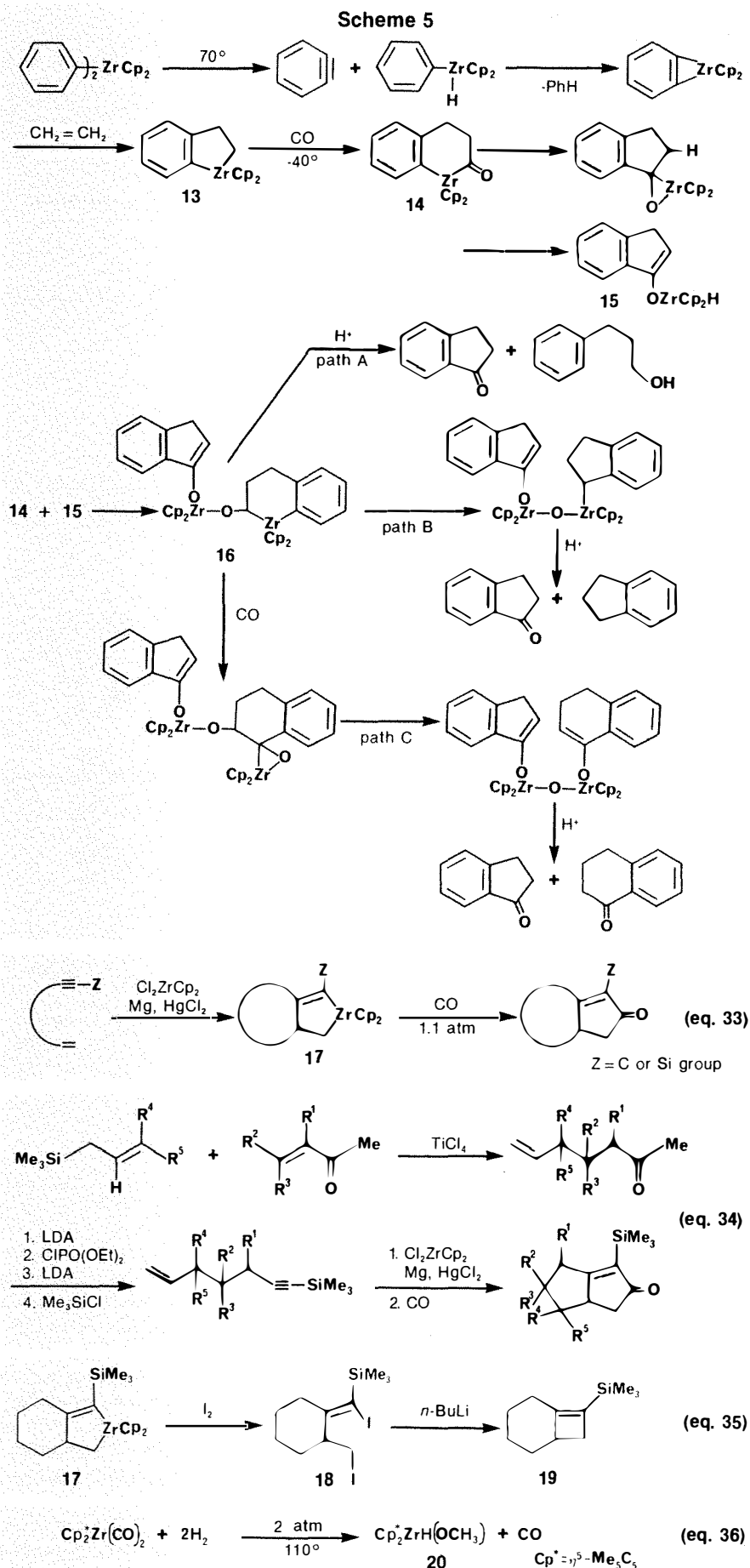

$$(eq. 33)$$

Z = C or Si group

$$(eq. 34)$$

$$(eq. 35)$$

$$Cp_2^*Zr(CO)_2 + 2H_2 \xrightarrow[110°]{2\ atm} Cp_2^*ZrH(OCH_3) + CO \qquad (eq.\ 36)$$

20 $\qquad Cp^* = \eta^5\text{-}Me_5C_5$

Table 3
Zirconium-Promoted Bicyclization of Enynes

Enyne (CH$_2$=CHR^{1}C≡CZ) R^1	Z	Zirconacyclopentene Time (h)[a]	Yield (%)	Cyclopentenone Time (h)[b]	Yield (%)[c]
-(CH$_2$)$_3$-	SiMe$_3$	12	95[d]	1	55-65 (65-75)
-CMe$_2$(CH$_2$)$_2$-	SiMe$_3$	18	e	4	62
-CH$_2$CMe$_2$CH$_2$-	SiMe$_3$	18	e	4	50
-(CH$_2$)$_4$-	SiMe$_3$	12	90-100[d]	3	60
-(CH$_2$)$_3$-	H	12	0	e	e
-(CH$_2$)$_3$-	Me	24	53[f]	e	e
-CH(OSiMe$_3$)(CH$_2$)$_2$-	SiMe$_3$	24	64[f]	e	e

[a]At room temperature. [b]At 0 °C. [c]Isolated yield. The number in parentheses is a GLC yield. [d]Isolated yield. [e]The corresponding figure was not observed. [f]Isolated yield of the protonolysis product.

Scheme 6

Scheme 7

$$\text{(eq. 37)} \quad (98\%)$$

$$\text{(eq. 38)} \quad (64\%)$$

$$\text{(eq. 39)} \quad (97\%)$$

Scheme 8

(80%)

(79%)
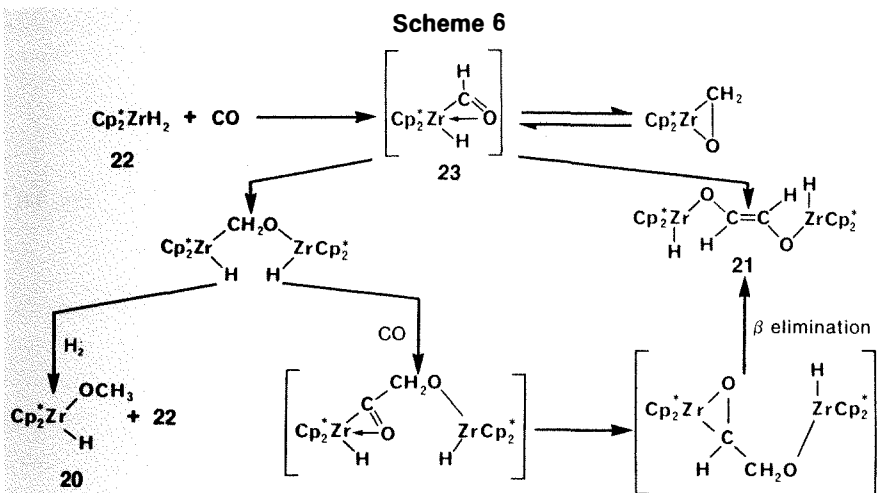
act readily with aryl,[7a] alkenyl,[7b] and alkynyl[7c] halides in the presence of a catalytic amount (≤5%) of a Ni- or Pd-phosphine complex, e.g., Pd(PPh$_3$)$_4$. This reaction used in conjunction with hydrozirconation of acetylenes provides an efficient and selective route to arylated alkenes, conjugated dienes, and enynes. Although both Ni and Pd are satisfactory for the alkenyl-aryl coupling, the alkenyl-alkynyl, and alkenyl-alkenyl cases generally require Pd complexes. When the alkenylzirconium reagent is sterically hindered, it is advantageous or often necessary to use ZnCl$_2$ or ZnBr$_2$ as a cocatalyst (the zinc effect).[7c] In such cases, double metal transfer, i.e., Zr→ Zn → Pd, may be involved. Some representative results are summarized in Scheme 7.

For the Ni-catalyzed alkenyl-aryl coupling reactions, a mechanism involving Ni(I) and Ni(III) species has been proposed.[51] For the Pd-catalyzed reactions, however, the following mechanism involving Pd(0) and Pd(II) species still appears to be plausible[52] (Scheme 8).

Alkenylzirconium derivatives also react with either allylic electrophiles[53,54] in the presence of a Pd catalyst, e.g., Pd(PPh$_3$)$_4$, or preformed allylpalladium complexes[55] (Scheme 7). A wide variety of leaving
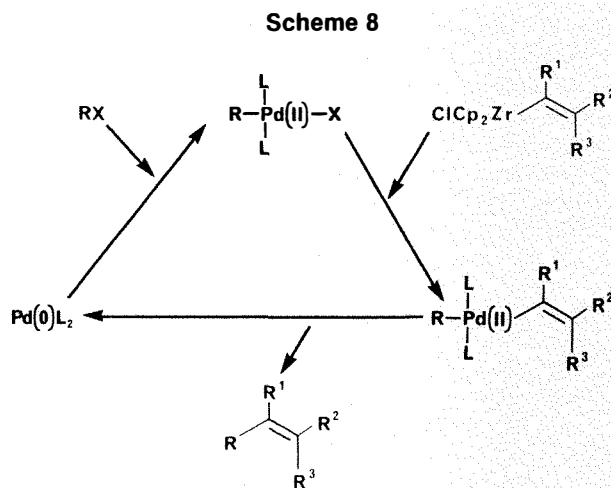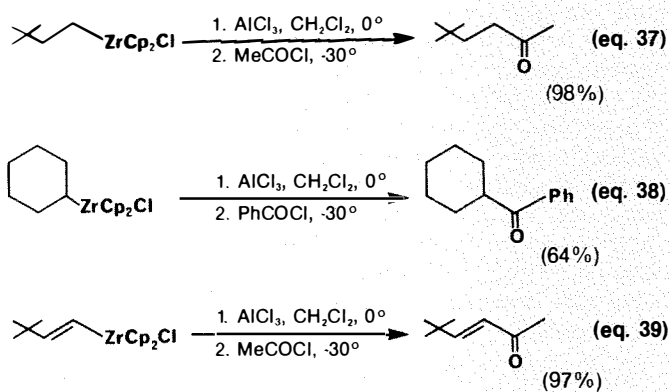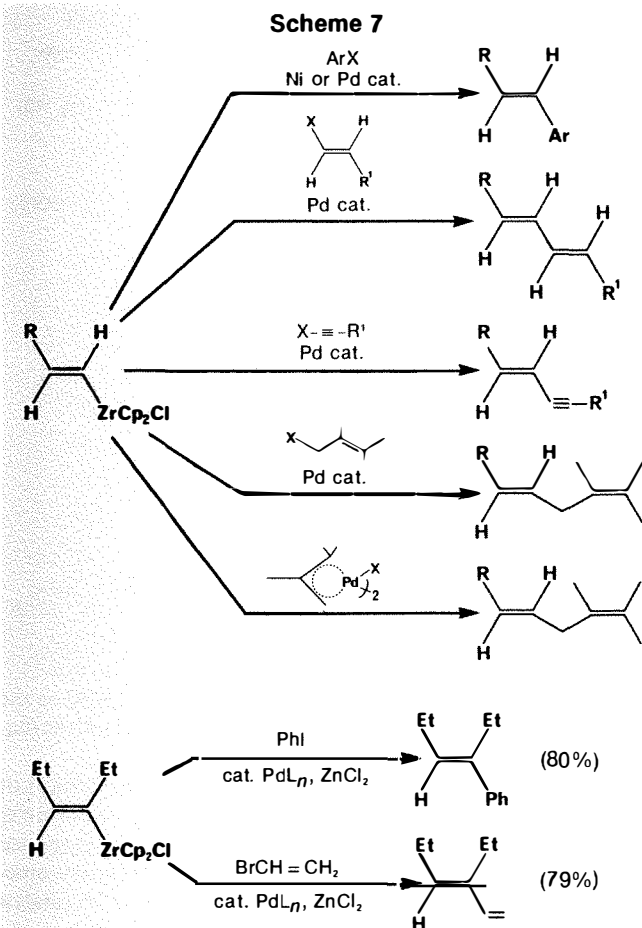
groups, such as Br, Cl, OAc, OAlMe$_2$, OPO(OEt)$_2$, and even OSiMe$_3$, can be used in the catalytic allylation reaction.[53b] The stoichiometric reaction has been applied to the synthesis of 25-hydroxycholesterol[56] (**24**) (eq. 40).

It should be mentioned here that, once organozirconiums are converted into the corresponding halides, they may then be used in cross-coupling reactions with a wide variety of organometals, such as those containing Li,[57] Mg,[57] Zn,[57] B,[57] Al,[57] and Cu,[58] either in the presence or in the absence of a Ni or Pd catalyst.[59] Alternatively, organozirconiums may be subjected to stoichiometric transmetallation prior to cross coupling. In this connection, Schwartz' claim[24] that treatment of alkenylzirconocene chlorides with 2 equivalents of MeLi generates alkenyllithiums is of interest, since alkenyllithiums readily cross-couple with a variety of alkyl halides.

(**d**) *Ni- or Cu-Promoted Conjugate Addition.* Treatment of alkenylzirconium derivatives with CuCl in THF provides new organometallic species which act as alkenylcoppers.[10] Thus, the thermal decomposition of the initial product at room temperature gives homocoupled conjugated dienes in excellent yields[10] (eq. 41). The organocopper species derived from organozirconiums can also be used for conjugate addition.[10] Since the chemical properties of organocoppers are very much dependent on the original metal in the starting compounds, the scope and limitations of the conjugate addition reaction involving Zr-derived organocoppers might be vastly different from those observed with conventional LiCuR$_2$[60] or the more recently developed LiCuR$_2$(CN).[61] However, this point is not clear because the available data are very limited.

Much more widely investigated is the conjugate addition reaction of alkenylzirconium derivatives with enones in the presence of a Ni catalyst prepared by treating Ni(acac)$_2$, (acac = 2,4-pentanedionato), with i-Bu$_2$AlH in THF[8] (eq. 42). β-Monosubstituted alkenylzirconiums provide conjugate addition products in moderate yields, but α,β-disubstituted ones give much poorer results. The scope of the reaction is indicated by the yields (in parentheses) of the following products.

(eq. 40)

(**24**, 94%; 66% overall)

(eq. 41)

(eq. 42)

(eq. 43)

Scheme 9

Z = SiMe$_2$-t-Bu
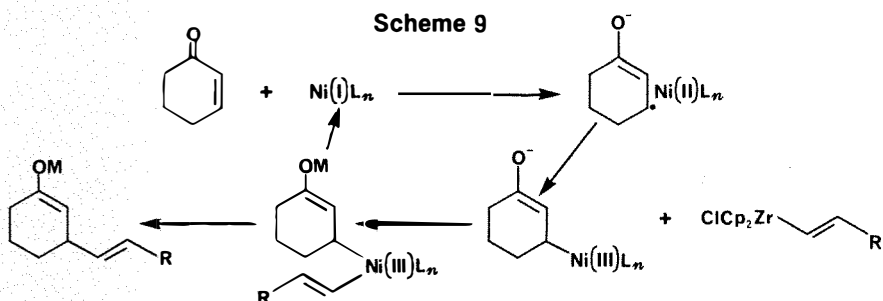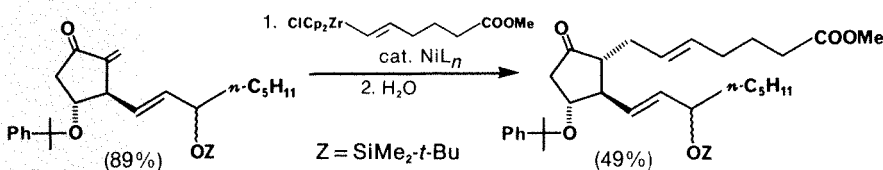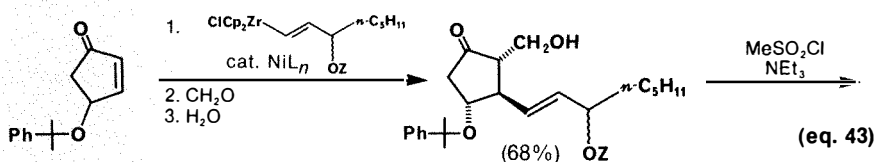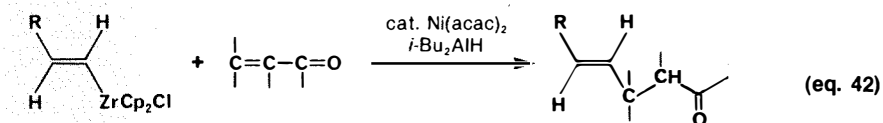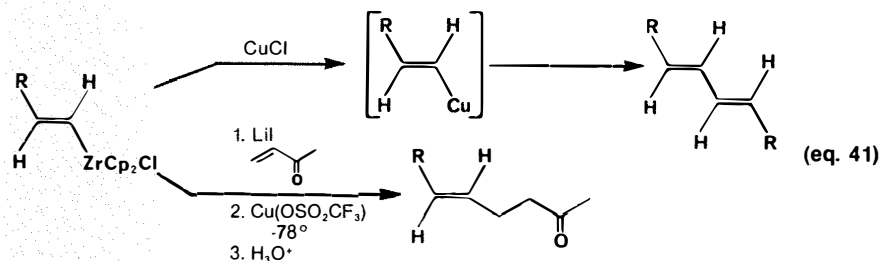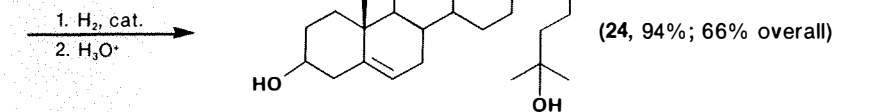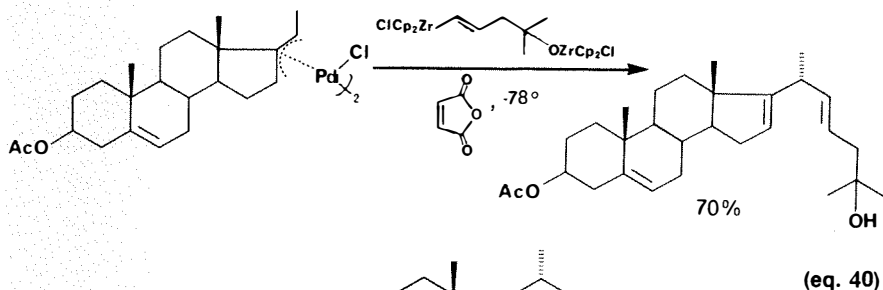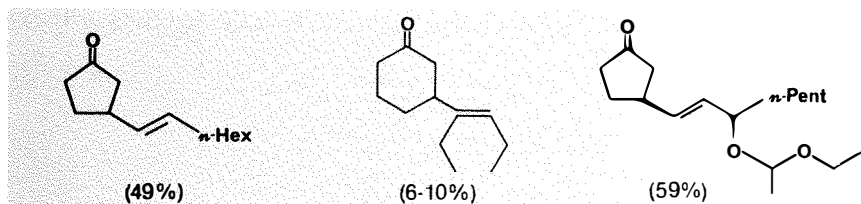
This procedure has been applied to the synthesis of prostaglandin derivatives (eq. 43).

As in the case of conjugate addition of organocuprates,[62] the one-electron transfer mechanism (Scheme 9) has been proposed and supported mainly by a cyclic voltametry study of the Ni(acac)$_2$-i-Bu$_2$AlH catalyst system.[51]

(49%)   (6-10%)   (59%)

(e) *Carbonyl Addition Reactions.* Alkyl- or alkenylzirconocene derivatives are quite inert toward aldehydes and ketones. On the other hand, alkyl-, aryl-, and alkenylzirconium trialkoxides, *e.g.*, *n*-BuZr(OBu-*n*)₃, readily add to aldehydes and ketones.[14,63] One synthetically useful characteristic of such organozirconium reagents relative to those of conventional organometals containing Li or Mg or the more recently developed organotitaniums,[64] is the high addition/enolization ratio.[65] This primarily stems from the low basicity of the organozirconium compounds. This chara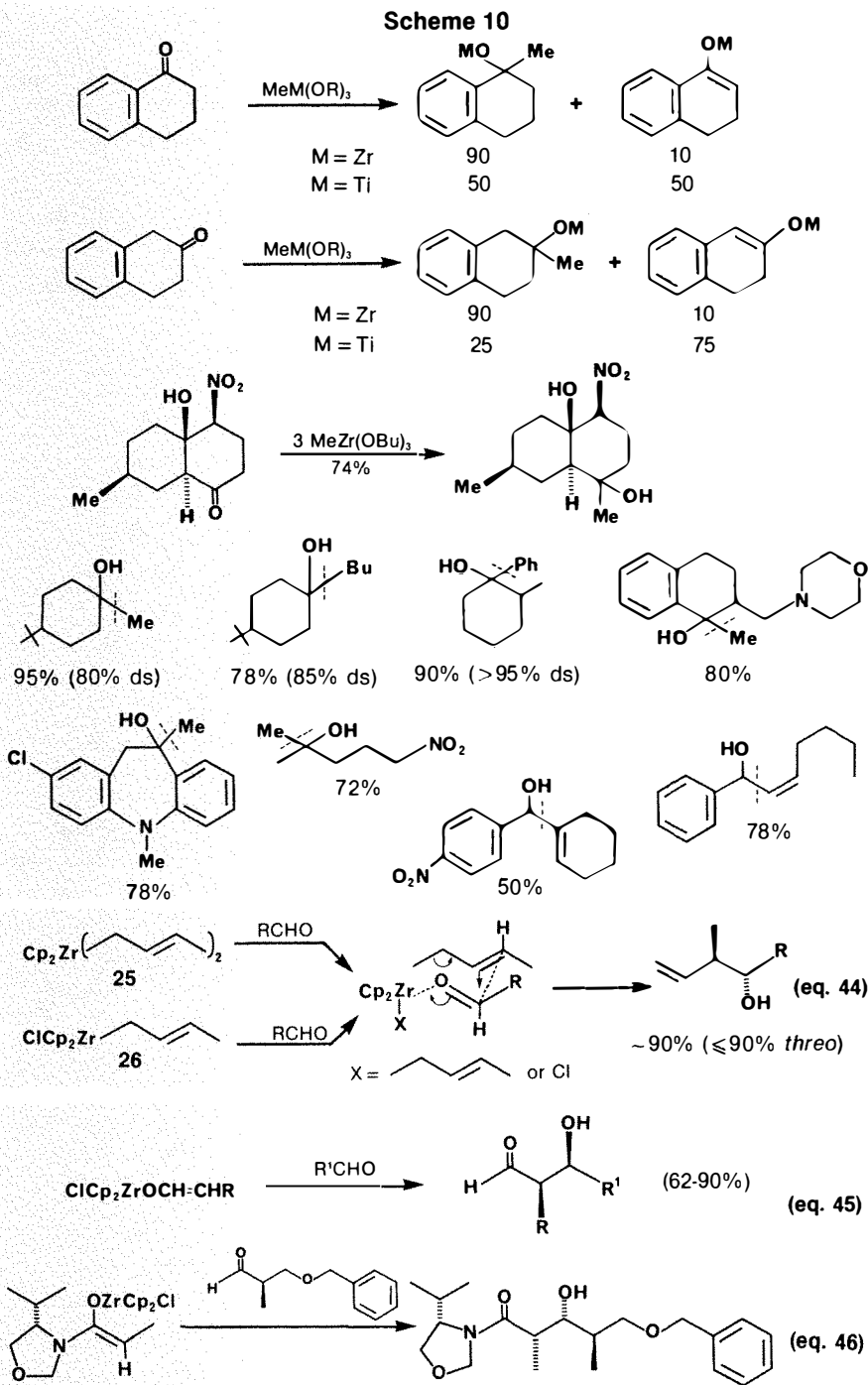cteristic resembles that of organoceriums and other organolanthanides.[66] Some representative results are summarized in Scheme 10.

Allylzirconiums and structurally related zirconium enolates are evidently more reactive toward carbonyl compounds than their alkyl, alkenyl, and aryl counterparts. Even allylzirconocene[67] and enoxyzirconocene[15,16] derivatives react readily with aldehydes. Both **25** and **26**, which exist essentially as the *E* isomers at -78°, exhibit up to **90%** *threo* selectivity (eq. 44). The preparation of **25** merely involves *in situ* treatment of Cl₂ZrCp₂ with 2 equivalents of crotyl Grignard reagent,[67a] while **26** is prepared by heating **25** with 1 equivalent of Cl₂ZrCp₂.[67b] The use of crotylzirconium trialkoxides is equally satisfactory.[67b] Interestingly, the use of zirconium enolates in place of allylzirconiums selectively produces *erythro* aldols[15,16] (eqs. 45 and 46).

As discussed earlier, *s-cis*-(1,3-diene) ZrCp₂ complexes may be viewed as allylzirconium derivatives (**5**). It is therefore not surprising that they react readily with aldehydes,[68] ketones,[68] nitriles,[68] and esters[69] (Scheme 11). Their treatment in succession with carbonyl compounds and/or nitriles produces 1,4-disubstituted derivatives[70] (Scheme 12). These compounds also undergo carbometallation with olefins and acetylenes to produce new allylic organozirconium derivatives **27** and **28**,[71] respectively, which in turn react with carbonyl compounds and nitriles[70] (Scheme 13). What is somewhat surprising is the high regioselectivity (95-98%) they display with unsymmetrical dienes, *e.g.*, isoprene, and they promise to provide selective routes to natural products of terpenoid origin.

1,1-Dimetallo alkanes[72] and alkenes[32] containing Ti and Al act as "super" Wittig-like reagents. Whereas Zr analogs of the alkene derivatives do not react with carbonyl compounds,[32] those of the alkane derivatives (Tebbe reagent) do react to produce olefins[73] (Scheme 14). Unlike Ti, Zr can accommodate alkyl groups containing β hydrogens. The synthetic scope of the

Scheme 10

Scheme 11

(eq. 44) ~90% (⩽90% *threo*)

ClCp₂ZrOCH=CHR →(R'CHO) (62-90%) (eq. 45)

(eq. 46)

R'R²CO → (90-95%)

RCN → (90-95%)

RCOOR' → (85-98%)

Scheme 12

Scheme 13

Scheme 14

$$RC\equiv CH \xrightarrow[\text{cat. } Cl_2ZrCp_2]{Me_3Al} \quad \text{(eq. 47)}$$

$$RC\equiv CH \xrightarrow[Cl_2ZrCp_2]{AIR'_2} \cdots \xrightarrow{I_2 \ (0.6\text{-}0.7 \ \text{equiv.})} \quad \text{(eq. 48)}$$

+ isomer   (~98% regioselective)
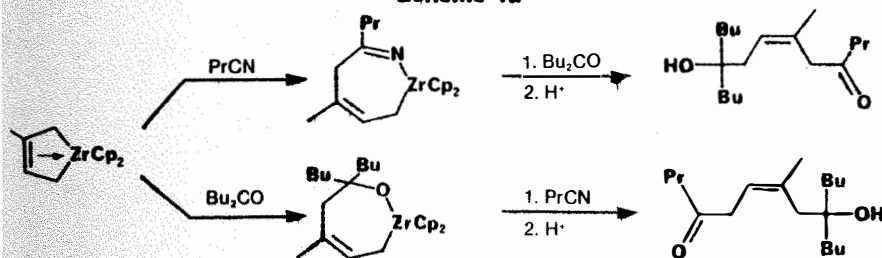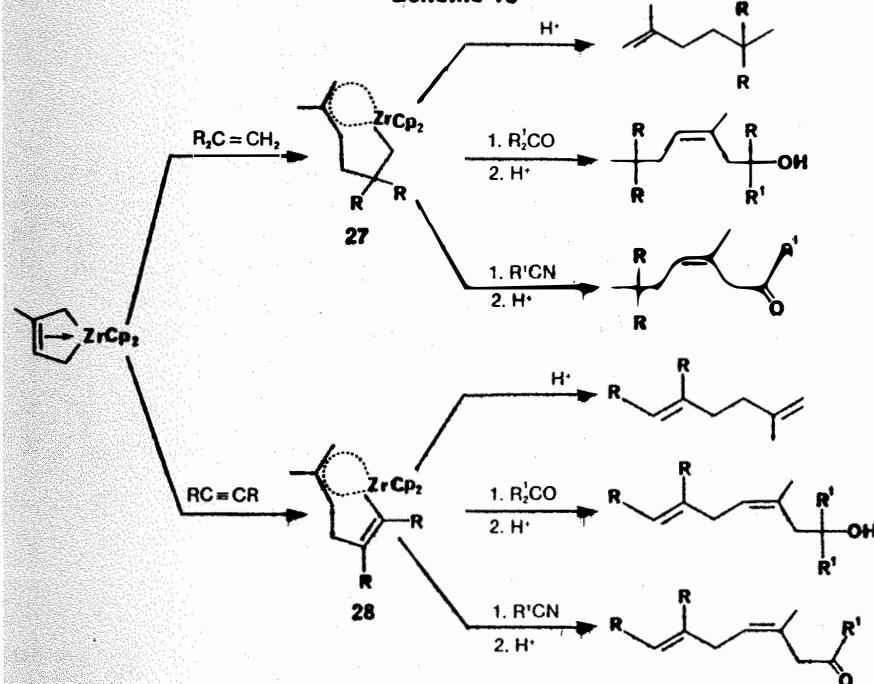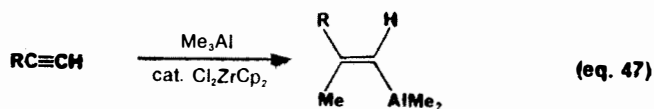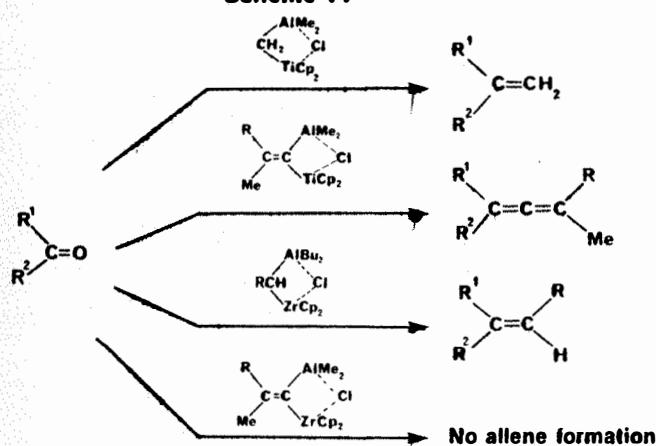
reaction, however, needs to be delineated further.

Organozirconium Compounds as Reagents

When organozirconiums are used as "reagents," no organic moiety of such organozirconiums is incorporated into the organic products. These reagents may be used catalytically or stoichiometrically. Probably the most widely investigated use of organozirconiums as catalysts is seen in the area of the Ziegler-Natta polymerization of olefins. Its discussion, however, is beyond the scope of this review, and interested readers are referred to reviews and monographs covering this subject.[19,74]

(a) Zr-Catalyzed Carboalumination and Carbozincation of Acetylenes. The reaction of acetylenes with Me_3Al-Cl_2ZrCp_2 gives (E)-2-methyl-1-alkenylalanes[11] (eq. 47). The reaction proceeds via essentially 100% cis addition. The regioselectivity of methylalumination is typically ca. 95%, and the combined yields often approach 100%. The simultaneous presence of Zr and Al appears to be essential, and the reaction is catalytic in Zr. The early results were reviewed in 1981.[75] Although a similar reaction occurs with Cl_2TiCp_2,[76] the Zr-catalyzed reaction is often substantially cleaner and of wider applicability.

The reaction can accommodate various functionalities in acetylenes, such as conjugated and isolated alkenyl, [76,53] Cl, Br, I, OH, SPh, and SiR_3.[77] Unbranched primary alkylalanes, allylalanes and benzylalanes also participate in the reaction. With these organoalanes, however, the regioselectivity is 70-80%.[33] Alkylalanes containing β hydrogens tend to undergo competitive hydroalumination. With $(i\text{-}Bu)_3Al$-Cl_2ZrCp_2, hydroalumination occurs exclusively,[13] as discussed earlier (Scheme 2). The competitive hydroalumination reaction can be completely suppressed by the use of R_2AlCl-Cl_2ZrCp_2 or R_3Al-$R(Cl)ZrCp_2$, which does not readily undergo alkyl-Cl exchange.[33] Alternatively, the Zr-catalyzed carbozincation reaction may be used.[78] The Zr-catalyzed allylalumination is the only r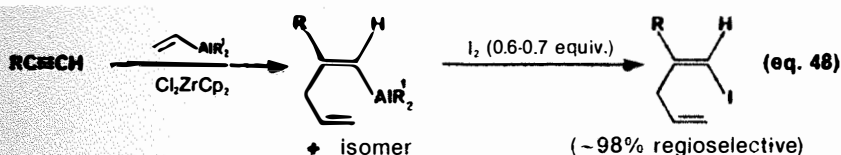eliable method for allylmetallating terminal acetylenes in a controlled and satisfactory manner[79] (eq. 48), although allylzincation of silylated acetylenes[80] and Zr-catalyzed allylzincation of internal acetylenes[80] are satisfactory. The use of a limited amount of an electrophilic reagent, e.g., I_2, will selectively produce one regioisomer (eq. 48). For other related controlled carbometallations of acetylenes, such as carbocupration and allylboration, a recent review[81] on the topic should be consulted.

Alkenylalanes obtained by Zr-catalyzed

carboalumination may be subjected to a wide variety of reactions that organoaluminum compounds undergo.[21,27,75] Some representative reactions are shown in Schemes 15-17 for comparison with those of organozirconiums. In this connection, it should be recalled that an alkenyl group can be transferred cleanly in either Al → Zr[25] or Zr → Al[9] direction (eqs. 11 and 25).
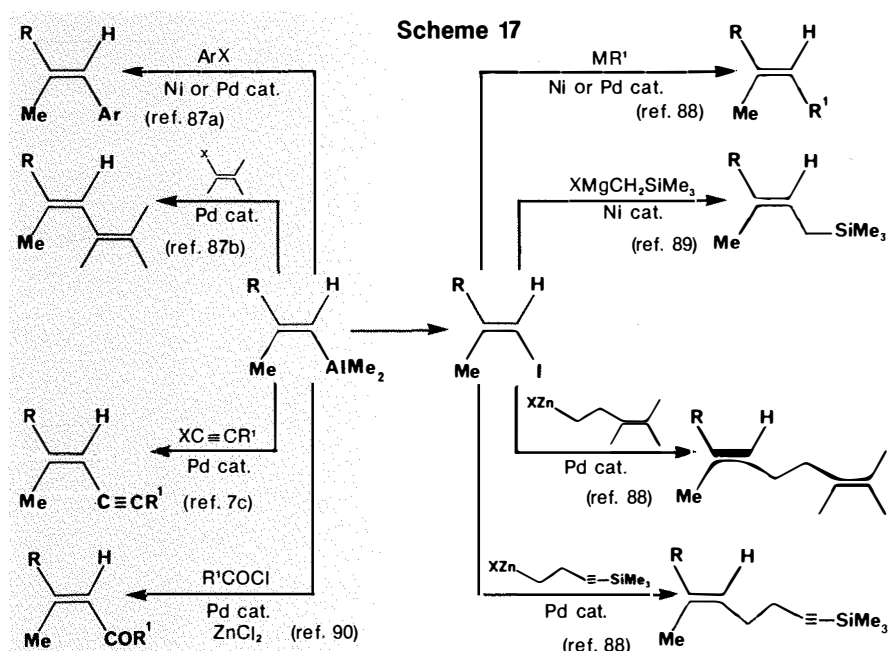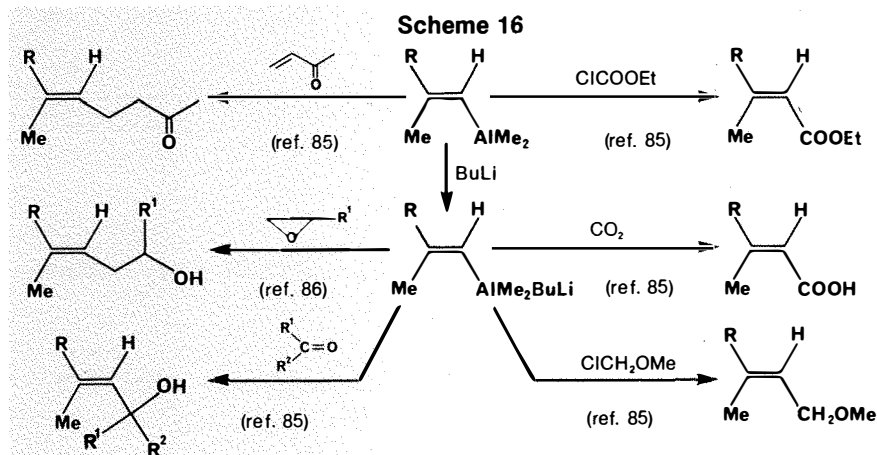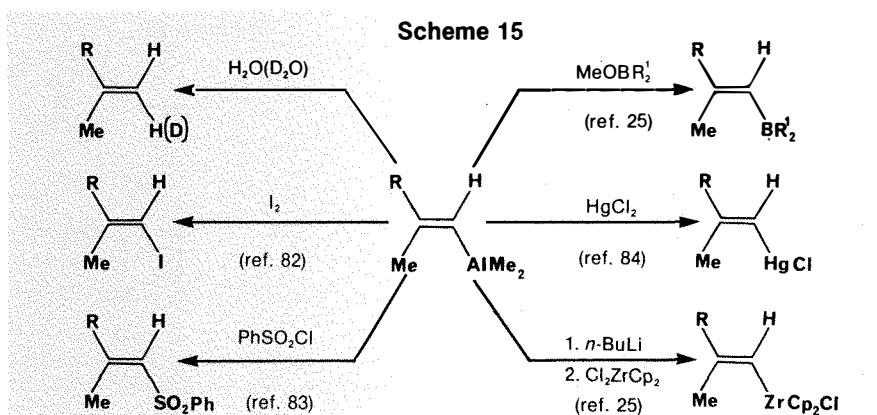
Using the Zr-catalyzed carboalumination reaction in conjunction with organoaluminum chemistry, various terpenoids have been synthesized selectively. Some representative examples are shown in Scheme 18.

The mechanism of the Zr-catalyzed carboalumination is not very clear. However, certain aspects have been clarified.[33] In some special cases, such as the one shown in eq. 14,[32] addition to the Zr-C bond occurs. In more representative cases, however, direct addition of the Al-C bond occurs,[33] as in eq. 15. Methyl-Cl exchange, rapid in the $Me_3Al-Cl_2ZrCp_2$ system, is not essential to the Zr-catalyzed carboalumination. The simultaneous presence of both Al and Zr appears necessary. The clean and facile *cis* addition strongly suggests that a coordinatively unsaturated species interacts with acetylenes in a concerted manner. One likely mechanism is shown in Scheme 19. Further clarification of the mechanism, however, requires additional studies.

(b) *Cyclization via Zr-Catalyzed Hydroalumination, Carboalumination and Carbozincation.* Intramolecular carbometallation of acetylenes is a potentially attractive route to stereo-defined exocyclic alkenes (eq. 49). However, generation of the required alkynyl-containing organometals without radical intermediates capable of undergoing nonstereoselective radical cyclization has been difficult.

Treatment of **41** with *i*-Bu₃Al-cat. Cl_2ZrCp_2 proceeds *via* Zr-catalyzed hydroalumination followed by intramolecular carboalumination to produce **42** in 85% yield.[96] Likewise, **43** is converted into **44** in 72% yield. Unfortunately, carbometallation of silylalkynes tends to be nonstereoselective, and the reaction of **45** with *i*-Bu₃Al-cat. Cl_2ZrCp_2 gives an *ca.* 20:80 mixture of the two stereoisomers of **46**. By taking advantage of the configurational instability of the 1-silyl-1-alkenylmetals, however, a highly stereoselective (97%) conversion of **47** into **48** can be achieved.[96] These results are summarized in Scheme 20.

The reaction of **49** with $Me_3Al-Cl_2ZrCp_2$ does not produce the expected carbometallation product **(50)**. Instead, it gives a 1-cyclobutenylsilane derivative **51** in 92% yield.[49] The reaction has been shown to in-

volve the novel π-type cyclization process shown in Scheme 21.[97] In accord with the above mechanism, the reaction can be highly regioselective but nonregiospecific[97] (eq. 50).

A more straightforward σ-type cyclization process can also occur, as in eq. 51.[49] A systematic investigation has indicated that the σ- and π-cyclization reactions of ω-halo-1-alkenylmetals display highly con-

trasting features, as summarized in Table 4.[97]

The role of Si in the σ-process (eq. 51) is merely to induce a facile configurational isomerization,[99] and the σ-cyclization step itself does not require Si or any second metal (M^2).[97] On the other hand, the π-process seems to require M^2, whose role appears to be to increase the nucleophilicity of the alkenyl group through σ donation.

Scheme 15

Scheme 16

Scheme 17

Scheme 18
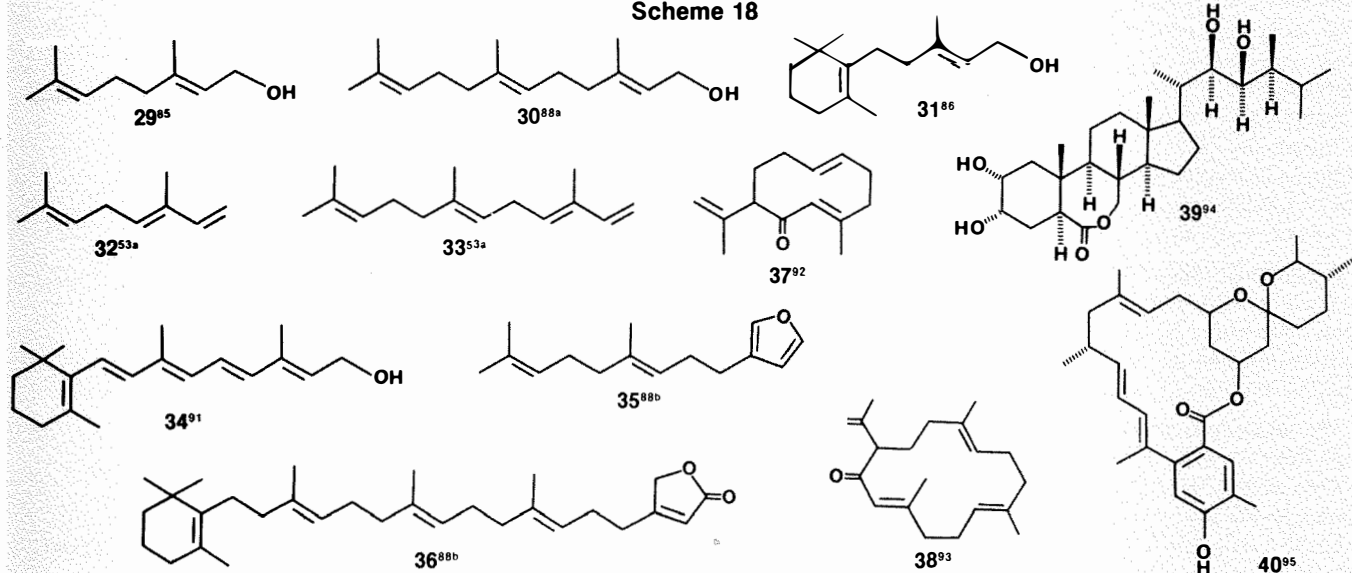
Scheme 19

$$RC \equiv C \overset{Z}{-} M \quad \xrightarrow{?} \quad \overset{R}{\underset{M}{\diagdown}} C = \overset{Z}{\bigcirc} \qquad \textbf{(eq. 49)}$$
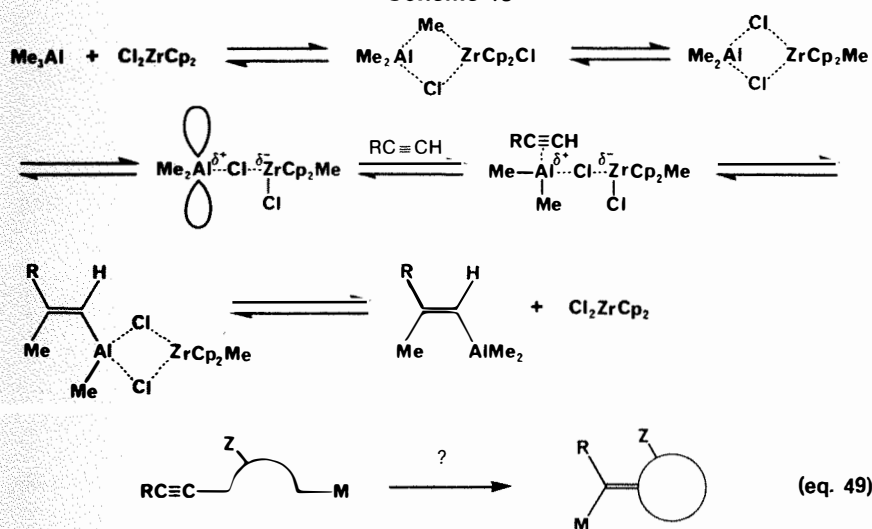
Scheme 20
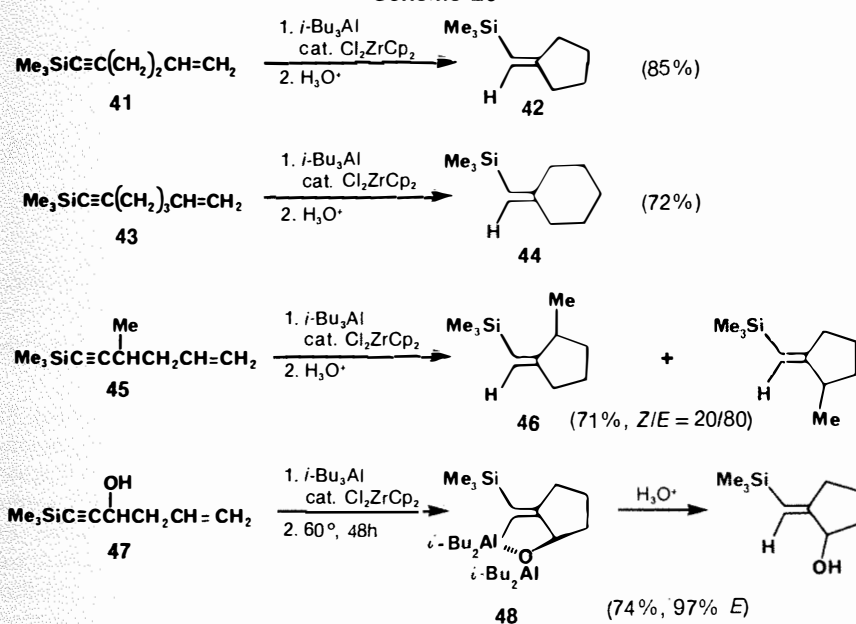
Indeed, certain metals other than Si, such as Al and Zn, can be used as M^2, as in eq. 52.[97]

More recent results indicate that certain metals, *e.g.*, Al and Zn, can participate in either σ- or π-processes depending on various parameters and reaction conditions. Thus, for example, **52** does not show any sign of cyclization to produce the expected cyclopentene derivative under the same conditions as in eq. 52. Replacement of CH_2Cl_2 with THF, however, induces the desired cyclization at moderate rates.[98] This reaction can be accelerated further by adding 1 equivalent of *n*-BuLi, and the results are more favorable. Similarly, allylzincation in THF gives a cyclopentenylzinc derivative in 86% yield (Scheme 22). Although not yet established, it is likely that the reactions shown in Scheme 22 involve σ-processes. This reaction is applicable to six-membered-ring formation as well.

The synthesis of cycloalkenyl iodides by treating cycloalkanone tosylhydrazones with BuLi (the Shapiro reaction[99]) and I_2 gives those products that correspond to the "kinetic" enolates of the starting cycloalkanones or regioisomeric mixtures. The procedure described above gives exclusively those products corresponding to the "thermodynamic" enolates. 1-Trimethyl-silyl-2-methylcyclobutene (**51**) has been converted into grandisol (**54**),[49] as shown in eq. 53. Numerous other applications of regio-defined cycloalkenylmetals to the synthesis of natural products appear to be feasible.

(c) *Reduction, Hydrogenation, Isomerization, and Disproportionation.* Organo-zirconiums can be good sources of zirconium hydrides, as in Scheme 2. Either organozirconiums or preformed zirconium

Scheme 21

$\mathbf{49}$ (X = Cl, Br, I)

50

51

(eq. 50)

(eq. 51)

(90%)

Table 4

Some Notable Features of σ- and π-Cycloalkylation Reactions of ω-Halo-1-alkenylmetals

Feature	σ-Process	π-Process
M^1 (to be lost)	Li, Al(?), Zn(?)	Al, Zn, Zr, Si
M^2 (to be retained)	unnecessary	Al, Zn, Si
Alkene stereochemistry	Z configuration required	unimportant
Regiochemistry	regiospecific	can be regioselective but nonregiospecific
Ease of cyclization with respect to ring size	4 - 7 facile	3,4> >5<6
Solvent	polar solvents, e.g., THF, favored	nonpolar solvents favored

(74%)

(eq. 52)

(70%)

Scheme 22

no cyclization

(78%)

52

53

(86%)

hydrides can act as reducing agents, and some reducing properties of $HZrCp_2Cl$[25] were described earlier in this review. Similarly, $ClCp_2ZrBH_4$ reduces aldehydes and ketones to alcohols in benzene.[100] At present, its merits and demerits relative to other metal hydrides are not clear.

The strong tendency of Zr(II) species to be oxidized to Zr(IV) compounds should make certain Zr(II) species good reducing agents. Of course, all of the Zr(II) → Zr(IV) reactions discussed earlier involve reduction of organic substrates. Treatment of propene oxide with Cl_2ZrCp_2-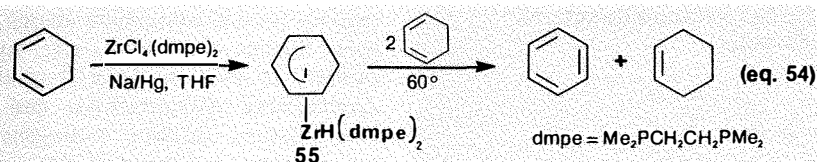Na/Hg achieves deoxygenation to give propene.[101] Many other new reduction reactions of Zr(II) species will be developed in the future. Unfortunately, however, the high oxophilicity of Zr(IV) species will make development of catalytic procedures for reduction of oxygenated organic compounds or similar polar derivatives very difficult, if not impossible.

Perhaps more promising is the use of Zr reagents for interconversions among nonpolar organic compounds, e.g., hydrocarbons. In addition to the Zr-catalyzed Ziegler-Natta polymerization and carbometallation, catalytic hydrogenation, isomerization, and disproportionation of unsaturated hydrocarbons have been reported. Homogeneous hydrogenation using H_2ZrCp_2 was reported in 1972.[2b] The catalytic cycle may involve hydrozirconation followed by hydrogenation of $R(H)ZrCp_2$. The latter step has been shown to proceed by a mechanism shown in Scheme 23.[28]

Isomerization of 1-alkenes into (E)-2-alkenes can be achieved with either Ti or Zr complexes as catalysts. Although i-PrMgBr-Cl_2ZrCp_2 does induce the desired transformation selectively, $NaC_{10}H_8$-Cl_2-$Ti(C_5Me_5)_2$ is far superior to the Mg-Zr system.[101] Disproportionation of 1,3- or 1,4-cyclohexadiene into cyclohexene and benzene occurs at 60° in the presence of **55**, which can be prepared by treating 1,3-cyclohexadiene with $ZrCl_4(dmpe)_2$ and Na/Hg in THF[102] (eq. 54). As such, these catalytic procedures for interconversions of hydrocarbons may not be practical or competitive with other known procedures. Future investigations, however, may reveal some uniquely advantageous features associated with Zr reagents.

Conclusion

A decade ago, the use of organozirconiums in organic synthesis was virtually unknown. Today, there is little doubt about their synthetic usefulness as described in the 100 or so publications cited in this review.

51 → (1. MeCOCl, AlCl₃; 2. NaOH) → 88% → (Li₂Cu(allyl)₂CN) → 91% **(eq. 53)**

1. Me₃SiCH₂MgCl
2. H₃O⁺
3. Sia₂BH
4. H₂O₂-NaOH
5. KH
→ **54** (50%)

Scheme 23

$$Cp_2Zr\begin{smallmatrix}H\\R\end{smallmatrix} \xrightarrow{D_2} Cp_2Zr{-}R\ (D{-}{-}D) \quad + \quad Cp_2Zr{-}H\ (D{-}{-}D)$$

$$Cp_2Zr\begin{smallmatrix}H\\D\end{smallmatrix} + RD \qquad Cp_2Zr\begin{smallmatrix}D\\R\end{smallmatrix} + HD$$

etc.   etc.

$$\text{cyclohexadiene} \xrightarrow[\text{Na/Hg, THF}]{ZrCl_4(dmpe)_2} \mathbf{55}\ ZrH(dmpe)_2 \xrightarrow[60°]{2\ \text{diene}} \text{benzene} + \text{cyclohexene}\quad \textbf{(eq. 54)}$$

dmpe = Me₂PCH₂CH₂PMe₂
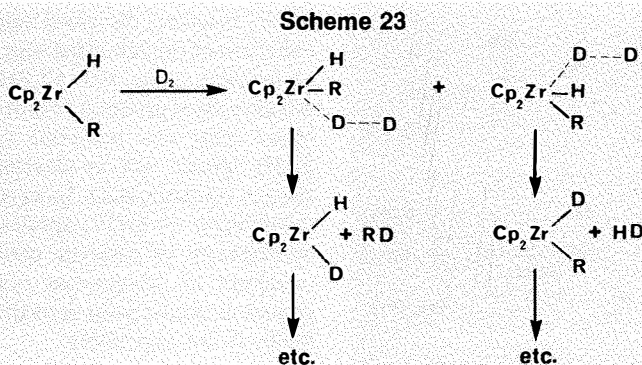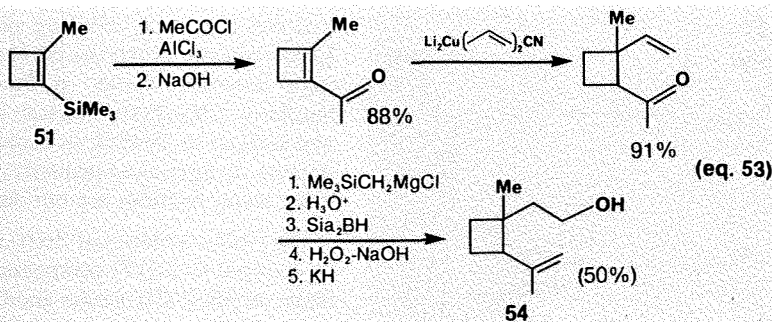
Basic investigations must still continue. In this review, we have tried to point out certain areas that need to be investigated further. More developmental studies are also greatly needed. In view of the current costs of Zr derivatives, the stoichiometric use of Zr should be practised to allow the economical recovery or recycling of active Zr compounds. The use of Zr compounds as catalysts is still of very limited scope. Clearly, much more work needs to be carried out in this area.

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About the Authors

Professor Ei-ichi Negishi received the bachelor's degree from the University of Tokyo in 1958. While he was a research chemist at Teijin, Ltd., Japan, he came to the University of Pennsylvania as a Fulbright Scholar in 1960 and received his Ph.D. degree in 1963. He joined Professor H.C. Brown's research group at Purdue University as a postdoctoral associate in 1966 and became his assistant in 1968. In 1972 he moved to Syracuse University as Assistant Professor and was promoted to Associate Professor in 1976. He returned to Purdue University as Professor in 1979.

Dr. Negishi is the author of about 150 scientific publications, including a book entitled, "*Organometallics in Organic Synthesis*" (Wiley-Interscience, New York, 1980, Volume 1). His recent work has centered on the use of transition-metal complexes as catalytic reagents in organic synthesis. Some transition metal-catalyzed reactions developed by him and his students include Pd- or Ni-catalyzed cross-coupling and Zr- or Ti-catalyzed carbometallation reactions.

Dr. Tamotsu Takahashi received the bachelor's and Ph.D. degrees from the University of Tokyo in 1978 and 1983, respectively. He has been a research associate at the same university since 1983. He is currently on a leave of absence and is engaged in postdoctoral research in Professor Negishi's laboratories at Purdue University.

Sharpless Chemistry

In 1980, Professor Barry Sharpless and Dr. Tsutomu Katsuki introduced the titanium alkoxide/tartrate-catalyzed epoxidation of prochiral allylic alcohols as a versatile and highly enantioselective method for the preparation of homochiral 2,3-epoxy alcohols.[1] The numerous publications which appeared within a few years following this initial report attest to its usefulness for the syntheses of biologically important organic compounds (*e.g.*, leucotrienes,[2] pheromones,[3] terpenes,[4] anthracyclines,[5] and carbohydrates[6]). The utility of the Sharpless Asymmetric Epoxidation is limited only by the development of new applications for the derived homochiral 2,3-epoxy alcohols. Thus, to extend the scope of the reaction, Sharpless and co-workers have since investigated the selectivity of nucleophilic ring-opening reactions of these substrates.[7] The following paragraphs highlight some exciting recent developments in this area.

Titanium isopropoxide has been found to mediate the ring opening of 2,3-epoxy alcohols with a variety of nucleophiles under mild experimental conditions with fair to excellent C-3 regioselectivity.[8] In the absence of titanium alkoxide no reaction was observed under otherwise identical conditions.
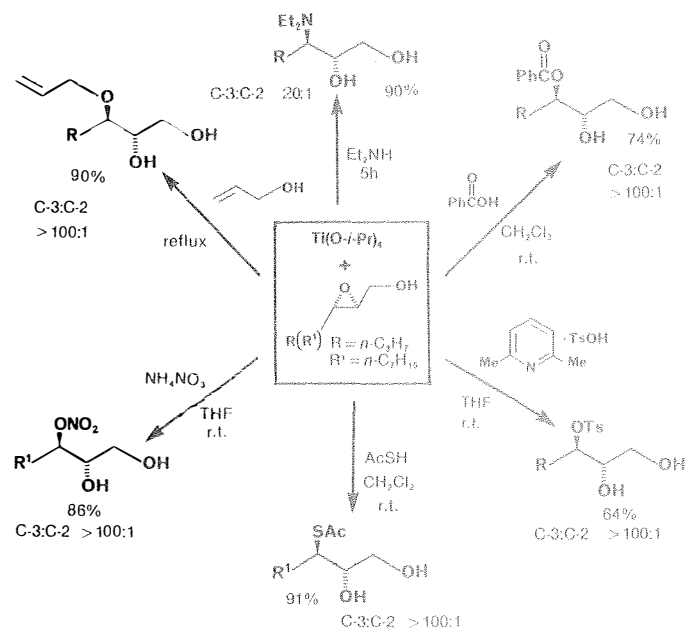
Titanium alkoxide has also been found to catalyze the ring opening of 2,3-epoxy carboxylic acids (glycidic acids) with high C-3 regioselectivity.[9] The acids are readily available through RuO$_4$ oxidation of the corresponding homochiral epoxy alcohols,[10] themselves derived from asymmetric epoxidation.
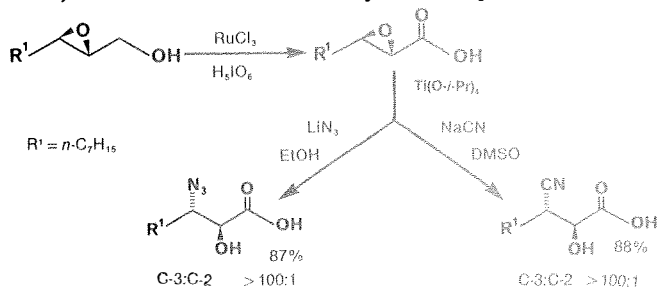
Application of the Sharpless Asymmetric Epoxidation/RuO$_4$ oxidation in conjunction with the titanium isopropoxide-induced ring opening of the derived glycidic acids has afforded selectively *all four stereoisomers* of the unusual N-terminal amino acid of amastatin, a tripeptide competitive inhibitor of aminopepsidases, from readily available achiral materials.[11]
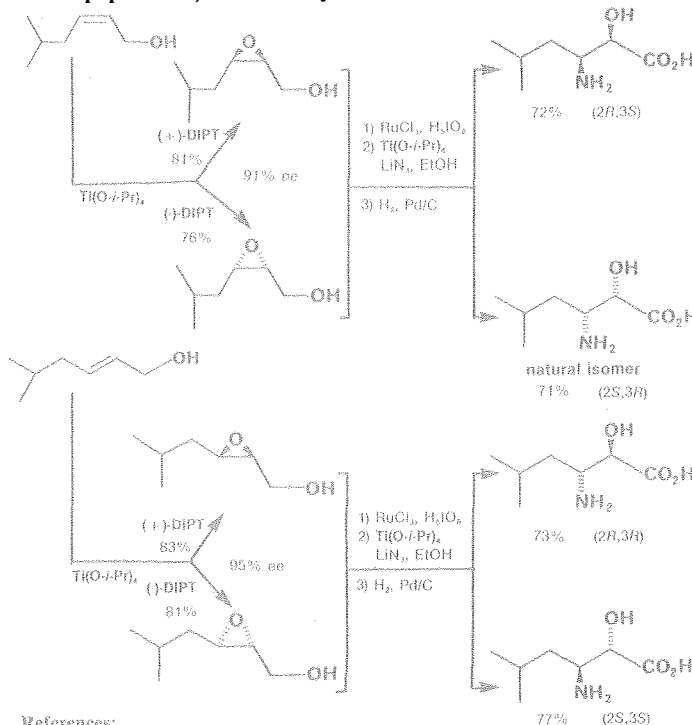
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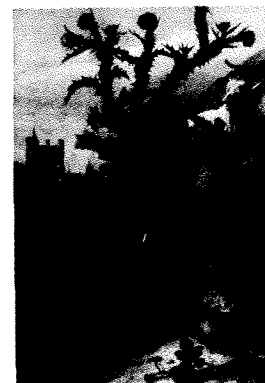FAX: (07329) 87-39

About Our Cover:

Fig. 1

Fig. 2

There are thousands of portraits of men, women and children, and quite a few of cats, dogs and horses — but who has ever seen a real portrait of goats? Our chemist-collector loves to acquire paintings the likes of which he has never seen before — particularly by artists who were close to Rembrandt. So he tried for years to acquire this 'portrait' (oil on canvas, 27 x 36 inches) by one of Rembrandt's good friends, Lambert Doomer.

Doomer was one of the great draftsmen of the Golden Age; his many landscape drawings are superb. His paintings are rare, though one has appeared on an *Acta* (Vol. 9, No. 2, 1976). Doomer must really have been intrigued by these animals; there is a drawing (Fig. 1) of one of them in the Albertina in Vienna, and the same appears in a painting (Fig. 2) in the museum in Copenhagen. Doomer's biographer calls our collector's painting Doomer's finest animal painting;[1] Doomer thought so highly of it that he mentioned it in his will of 1677, and in 1700 it was recorded in the inventory of his estate.

1) W. Schultz, *Lambert Doomer, 1624-1700, Leben und Werke*, Berlin, 1972, pp 101-102 and p 468, G57.

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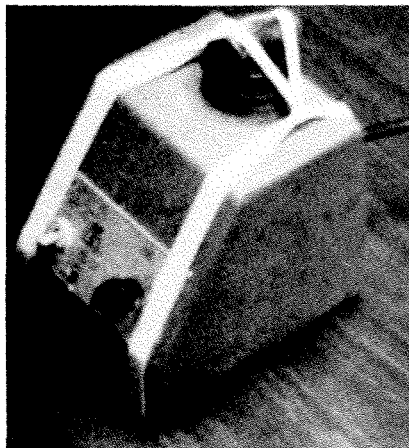
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Editor's note: We are grateful to Dr. Ronald Wolfe, Sigma Chemical Company, for helpful suggestions regarding this technique.

The sharp water peak at $\sim \delta$ 1.5 in CDCl₃ solution is familiar to organic chemists who work with ¹H NMR samples in the microgram range (*e.g.*, ref. 1). Chemists who carry out deuterium-exchange experiments with D₂O in the milligram range are familiar with the HOD peak at $\sim \delta$ 4.7 (*e.g.*, ref. 2). Since speculation failed to provide a convincing explanation of the nature of these two "water" peaks, we did the following simple experiments:

1. A 150-μl aliquot of Aldrich " 100 atom % D" CDCl₃ was transferred from a freshly opened 0.5-ml ampule to a dry 150-μl cavity cell. This sample showed a peak at δ 1.52 of approximately the same intensity as the residual CHCl₃ peak. The remaining 350μl was dried over 4Å molecular sieves (activated at 350°C); this treatment decreased the intensity of the δ 1.52 peak by about one-half.

2. Aldrich 99.8 atom % CDCl₃ was saturated with water by shaking, and the mixture was centrifuged. The CDCl₃ layer was removed by syringe and placed in a dry 150-μl cavity cell. The NMR spectrum showed a greatly increased (slightly shifted) peak at δ 1.55, which was approximately 3.4 times the intensity of the residual (0.2 atom %) CHCl₃ peak, and a small peak at $\sim \delta$ 4.75 ($\sim \frac{1}{3}$ the intensity of the residual CHCl₃ peak). This solution was shaken *in situ* to saturation with water and centrifuged, but the CDCl₃ solution was not transferred to another cell; these are the usual conditions for the deuterium-exchange experiment. The δ 4.75 peak was greatly increased in intensity ($\sim$ 2 times that

of the residual CHCl₃ peak). The peak at δ 1.55 was unchanged.

We draw the following conclusions:

1. The "δ 1.5" peak represents "monomeric" dissolved water in CDCl₃. In "dry" CDCl₃ it occurs at δ 1.52. Even at satura-

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"Please Bother Us."

by *Alfred Bader*.
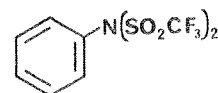
Recently Professor W.D. Wulff at the University of Chicago suggested that we offer N-phenyltrifluoromethanesulfonimide which has been used in the synthesis of enol triflates,[1] precursors to vinyl cations[2] and vinyl carbenes.[3] Professor Wulff has used this reagent in a regioselective entry to vinyl lithiums from unsymmetrical ketones.[4]

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2) For leading references, see Ladika, M.; Stang, P.J.; Schiavelli, M.D.; Kowalski, M.H. *J. Am. Chem. Soc.* **1984**, *106*, 6372.
3) For leading references, see Krageloh, K.; Anderson, G.H.; Stang, P.J. *J. Am. Chem. Soc.* **1984**, *106*, 6015.
4) Wulff, W.D. *et al.* 190th National Meeting of the American Chemical Society, Chicago, Sept. 1985; Abstract No. ORGN 173.

Naturally we made it.

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

Formamidines as Precursors to α-Amino Carbanions and Their Application to Asymmetric C-C Bond-Forming Reactions*

Albert I. Meyers
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Introduction

In the past decade, organic chemists have met the challenge of uncovering useful asymmetric syntheses admirably, where virtually none existed prior to the 1970's. The monograph "Asymmetric Organic Reactions" by J.D. Morrison and H.S. Mosher,[1] published in 1971, outlines many of the frustrated attempts by earlier investigators to develop useful C-C bond-forming reactions with simultaneous enantioselectivity. This monograph was probably the major impetus for recent studies assessing the factors required to achieve useful asymmetric syntheses. It should not be construed that the earlier chemists lacked the insight and intellect to succeed, only that the current generation of synthetic chemists is able to see the problem more clearly. In the words of Sir Isaac Newton, "If (we) have seen farther than others, it is because (we) have stood on the shoulders of giants". Today, one only has to glance through current periodicals to find a steady stream of reports on useful asymmetric C-C bond-forming reactions. The five-volume treatise[2] "Asymmetric Synthesis", edited by Professor James D. Morrison (University of New Hampshire), is a tribute to the many laboratories which have successfully developed useful methodology — methodology that hardly existed in 1971. Other summaries of the successes in this field have also appeared.[3] Furthermore, it should not go unnoticed that three of the past four ACS Awards for Creative Work in Synthetic Organic Chemistry, presented to D.A. Evans (1982), K.B. Sharpless (1983), and the author (1985), have been given for work with novel approaches to asymmetric synthesis. The works of the first two are described in *Aldrichim. Acta* **1982**, *15*(2), 23 and **1983**,

Professor Albert I. Meyers (right) receiving the A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich, from Dr. Alfred Bader, Chairman of the Board, Sigma-Aldrich Corporation.
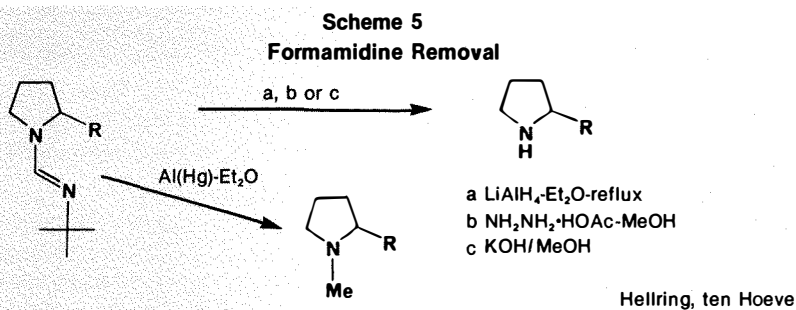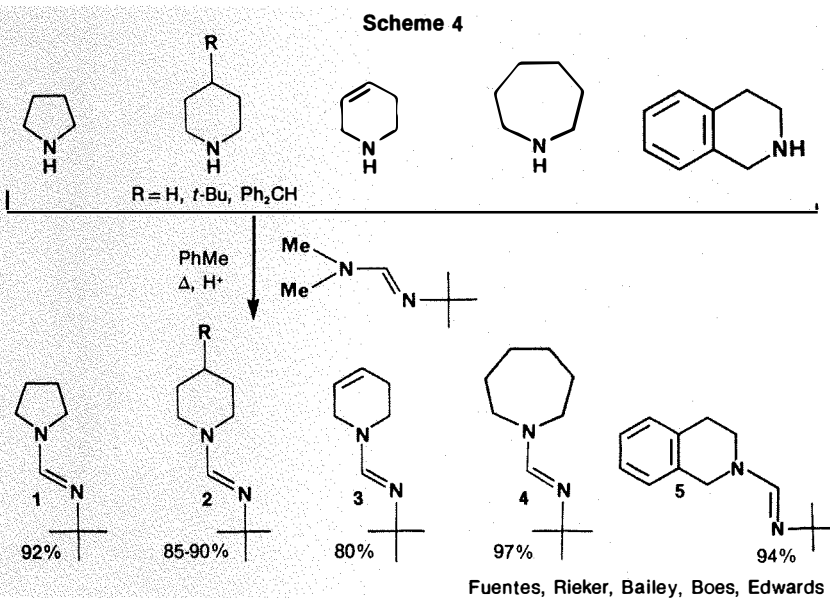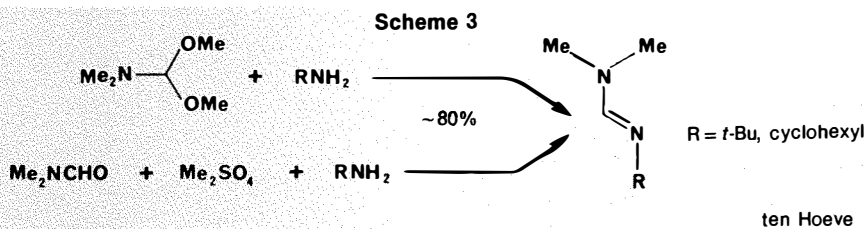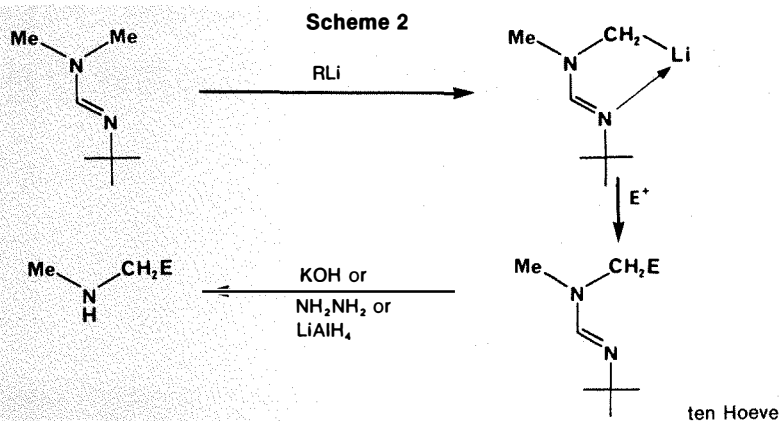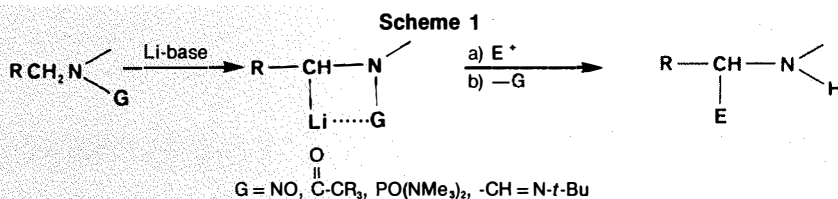
16(4), 67, respectively.

This report describes the efforts and results of a novel C-C bond-forming process which not only leads to new chemistry, but also to a potentially powerful and un-precedented asymmetric synthesis. The following will chronicle the use of formamidines, both chiral and achiral, as precursors to α-amino carbanions and their application to a variety of natural products.

Achiral Formamidines - Synthesis, Metallation and Alkylation. The formation of a carbanion adjacent to nitrogen has been a long-sought-after process whose successful implementation would allow alkylation of a variety of amines. The generalized process (Scheme 1) depicts the manner in which an "activating" group (G) on nitrogen increases the kinetic acidity of an α-proton such that a lithio salt would result. The latter is then capable of reacting with electrophilic reagents to form a new C-C bond and, after removal of G, leads to an α-alkylated amine. Indeed, in recent years, this process has been successfully demonstrated by the elegant studies of Seebach[4] and Beak,[5] and has been reviewed by Beak[6] and Krief.[7] The activating group utilized in Scheme 1 is nitroso, phosphoryl, hindered acyl or, as this report shows, a formamidine. Our studies began in 1980 when we found[8] that formamidines (Scheme 2) readily gave α-lithio anions when treated with various organolithium compounds and that these could be alkylated efficiently to the elaborated derivatives.[3] Removal of the formamidine moiety by hydrolysis, hydrazinolysis, or reduction gave the unsymmetrically alkylated N-methyl amine. The ease with which this two-step process occurred stirred our interest in assessing its scope and utility. In view of the extensive studies by Seebach[4] and Beak,[5] it was necessary to evaluate whether the formamidines indeed provided a convenient alternative. As it turned out, formamidines derived from dimethylamine were prepared readily from dimethylformamide or its acetal according to the routes in Scheme 3. Since the dimethylamino formamidine and its resulting carbanion in Scheme 3 are of limited synthetic value, the acquisition of the formamidine made it possible to transform a number of secondary amines (Scheme 4) into their formamidines (1-5) by simple exchange in refluxing toluene, with or without an acid catalyst.[9] Finally, it was deemed important that the formamidine, after metallation and alkylation, be easily removed to regenerate the parent amino group. This was done routinely by adding hydrazine solution (25-50°) and stirring 12-18h, or refluxing with methanolic KOH, or treating with ethereal lithium aluminum hydride.[9] In some cases, the formamidine was removed by shaking with aluminum amalgam in moist ether, leaving an N-methyl group (Scheme 5).
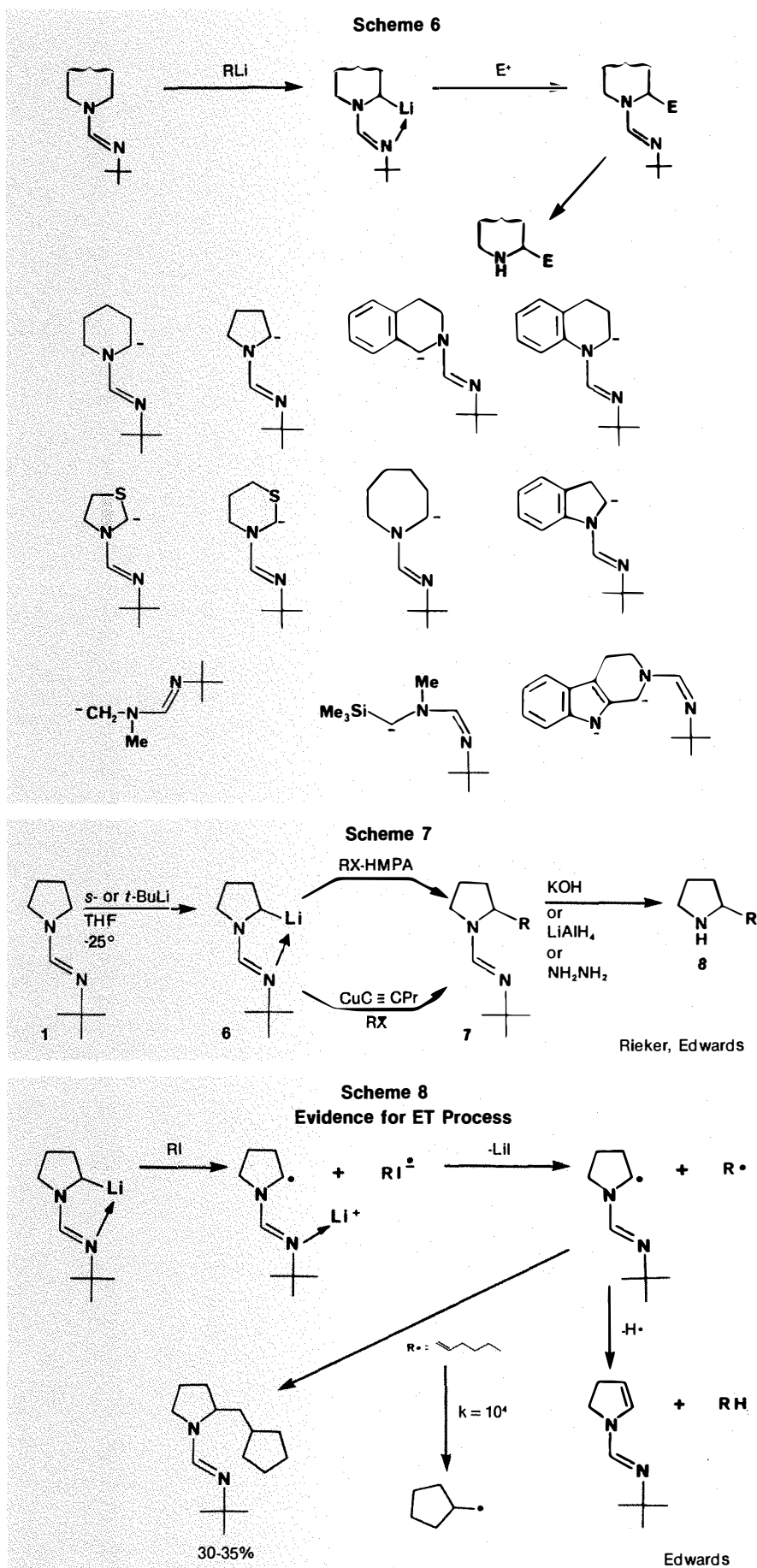
With the knowledge that secondary amines could be transformed easily into their N-*tert*-butyl formamidines (TBF) and the starting amine regenerated under mild conditions, we proceeded to survey the

Scheme 1

$$R\,CH_2\,N{<}^{}_{G} \xrightarrow{\text{Li-base}} R{-}CH{-}N{<} \xrightarrow[\text{b) } -G]{\text{a) } E^+} R{-}CH{-}N{<}^{}_{H}$$

G = NO, C-CR₃, PO(NMe₃)₂, -CH = N-*t*-Bu

Scheme 2

ten Hoeve

Scheme 3

$$Me_2N{-}{<}^{OMe}_{OMe} + RNH_2 \longrightarrow$$

~80%

$$Me_2NCHO + Me_2SO_4 + RNH_2 \longrightarrow$$

R = *t*-Bu, cyclohexyl

ten Hoeve

Scheme 4

R = H, *t*-Bu, Ph₂CH

PhMe, Δ, H⁺

1 92%   2 85-90%   3 80%   4 97%   5 94%

Fuentes, Rieker, Bailey, Boes, Edwards

Scheme 5
Formamidine Removal

a, b or c

Al(Hg)-Et₂O

a LiAlH₄-Et₂O-reflux
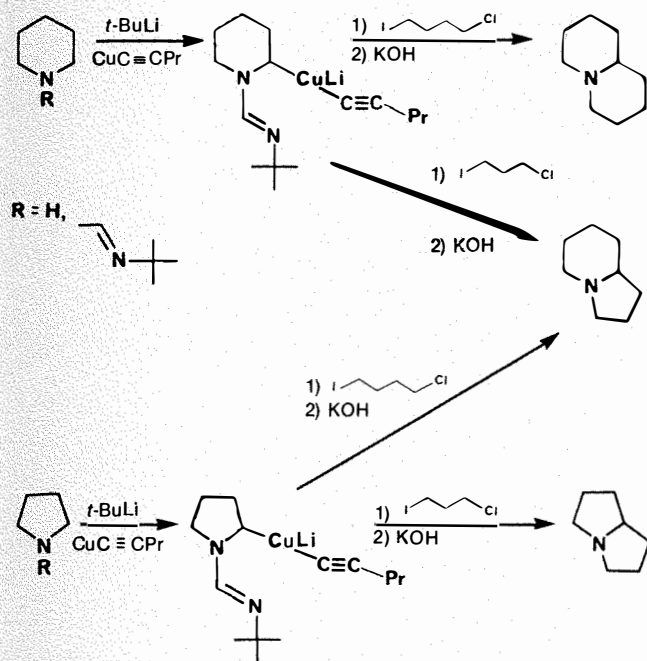b NH₂NH₂·HOAc-MeOH
c KOH/MeOH

Hellring, ten Hoeve

scope of α-amino carbanion chemistry and found that it was applicable to a large number of systems (Scheme 6).

Although metallation of the systems in Scheme 6 was carried out using *n*-, *s*-, or *t*-butyllithium, the lithiated piperidines and pyrrolidines presented a unique problem when the electrophiles employed were alkyl halides. The THF solution of lithio pyrrolidines **6**, when treated with alkyl bromides or iodides, gave alkylated products **7** only if HMPA was added or the corresponding cuprate was prepared (Scheme 7).[9] The yields of alkylation, as the cuprate or in the presence of HMPA, were generally above 80% and provided, after formamidine removal, α-alkyl pyrrolidines **8** in good yield. In the absence of HMPA or the pentynyl cuprate, oxidation to the 4,5-dihydropyrroles took place, which was suggestive of an electron-transfer process (Scheme 8). Use of 6-hexenyl iodide as the electrophile verified electron transfer; we isolated the (cyclopentylmethyl)pyrrolidine, obviously the result of radical rearrangement. A similar problem was encountered when piperidine formamidines were metallated as shown in Scheme 9. Once again, the mixed cuprates were prepared and when α,ω-dihaloalkanes were employed, the 1-azabicycloalkanes were obtained in good yields.[10] It is noteworthy that the cyclization to the 1-azabicyclics took place spontaneously during the hydrolysis step to remove the formamidine. This methodology for alkylation adjacent to the amino group was demonstrated by the synthesis of 2-ethyl-5-heptylpyrrolidine **9** which, as a 60:40 mixture, is identical with the fire ant venom (Scheme 10).[9]
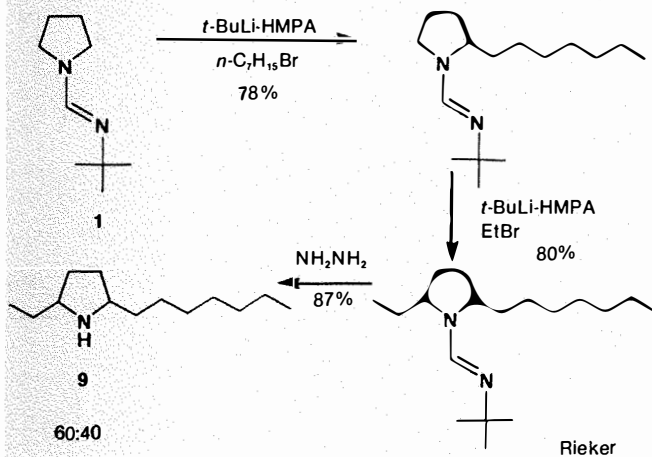
Another interesting and synthetically useful transformation was shown when the α-lithio anions in Scheme 11 were treated with diphenyl diselenide. The resulting α-phenyl selenides were easily transformed into the enamidines by treatment with aqueous bicarbonate.[11] These systems further exhibited their synthetic significance by cleanly metallating at the 2-vinyl position, which was followed by reaction with a variety of alkyl and silyl halides (Scheme 12). Allylic halides reacted best if the α-lithio enamidines were first transformed into their mixed cuprates.[11] After alkylation of the 2-vinyl position, subsequent metallation using *tert*-butyllithium-TMEDA took place at the α-methylene group affording the dialkyl product in good yield (Scheme 13). Of further interest is the fact that removal of the formamidine gave the cyclic imine which was reduced to either the *trans* or *cis* 2,6-dialkylpiperidines using lithium aluminum hydride or DIBAL,
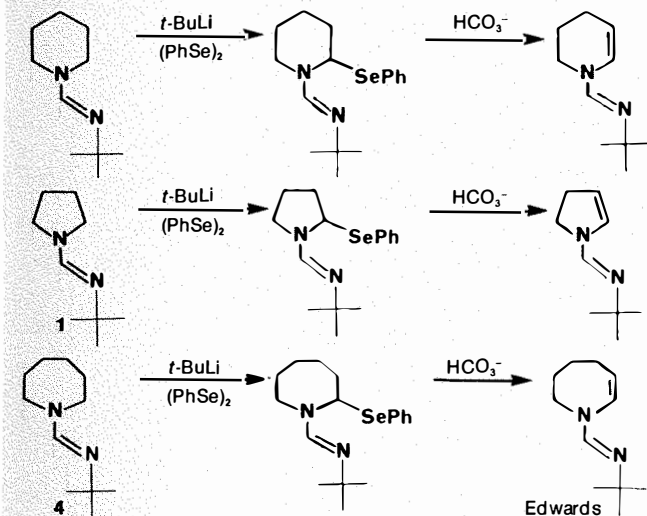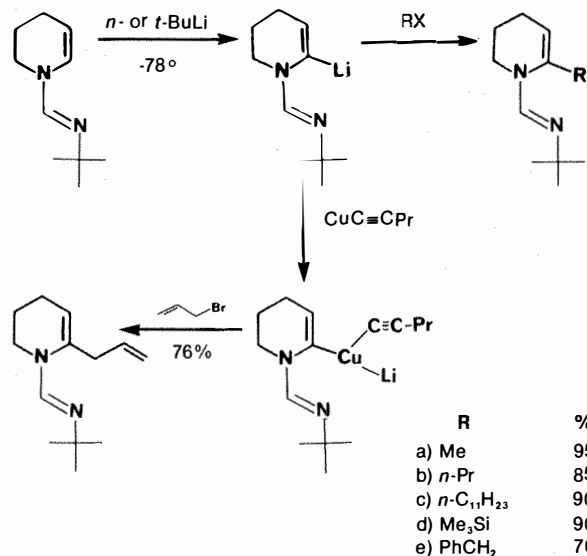

Scheme 6

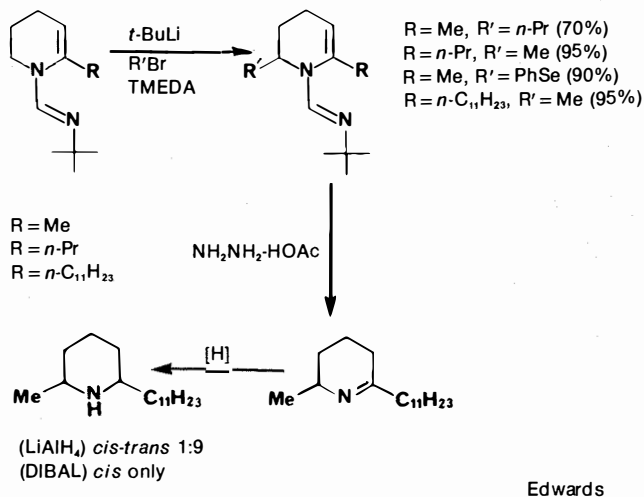**Scheme 7**

Rieker, Edwards

Scheme 8
Evidence for ET Process

$k = 10^4$

30-35%

Edwards

Scheme 9

R = H,

1) ![pentyl chloride] 2) KOH

Edwards

Scheme 10

t-BuLi·HMPA / n-C$_7$H$_{15}$Br / 78%

t-BuLi·HMPA / EtBr / 80%

NH$_2$NH$_2$ / 87%

9

60:40

Rieker

Scheme 11

t-BuLi / (PhSe)$_2$

HCO$_3^-$

t-BuLi / (PhSe)$_2$

HCO$_3^-$

1

t-BuLi / (PhSe)$_2$

HCO$_3^-$

4

Edwards

Scheme 12

n- or t-BuLi / -78°

RX

CuC≡CPr

Br / 76%

R	%
a) Me	95
b) n-Pr	85
c) n-C$_{11}$H$_{23}$	90
d) Me$_3$Si	90
e) PhCH$_2$	76

Edwards

Scheme 13

t-BuLi / R'Br / TMEDA

R = Me, R' = n-Pr (70%)
R = n-Pr, R' = Me (95%)
R = Me, R' = PhSe (90%)
R = n-C$_{11}$H$_{23}$, R' = Me (95%)

R = Me
R = n-Pr
R = n-C$_{11}$H$_{23}$

NH$_2$NH$_2$·HOAc

[H]

Me — $C_{11}H_{23}$ Me — $C_{11}H_{23}$

(LiAlH$_4$) cis-trans 1:9
(DIBAL) cis only

Edwards

Scheme 14

Me$_2$N—N—R / Me$_2$NH

R = t-Bu
R = C$_6$H$_{11}$

a) R = t-Bu (89%)
b) R = C$_6$H$_{11}$ (95%)

1) R'Li THF
2) E$^+$

hydrolysis or reduction

78-84% overall

Hellring

respectively.[11]

We also examined the metallation-alkylation of 1,2,3,4-tetrahydroisoquinolines by transforming the unsubstituted base into its formamidine (Scheme 14). By use of either *n*-BuLi or LDA, the α-lithio anions were smoothly generated and 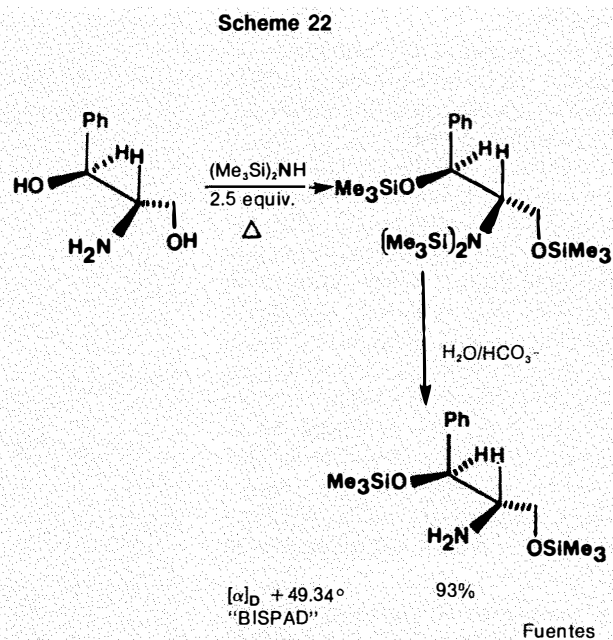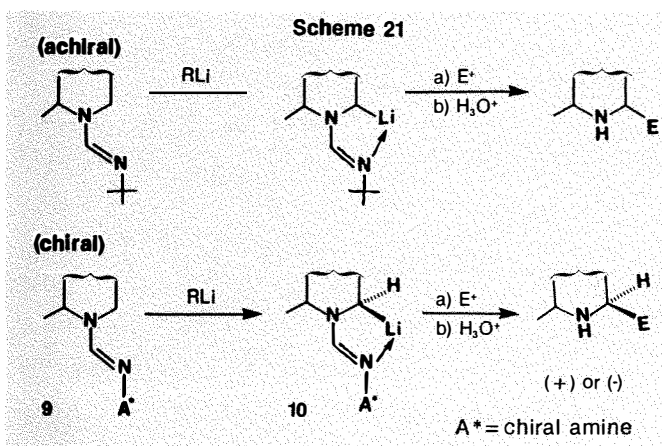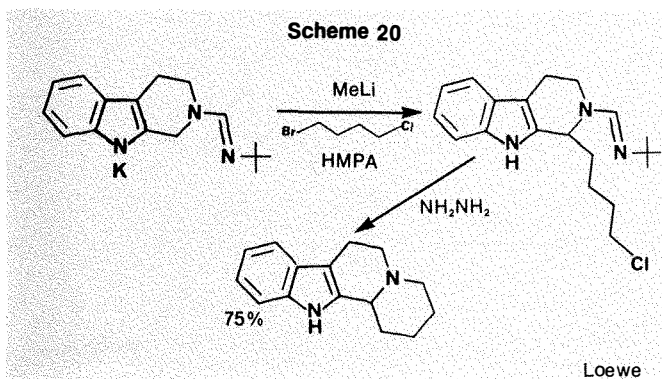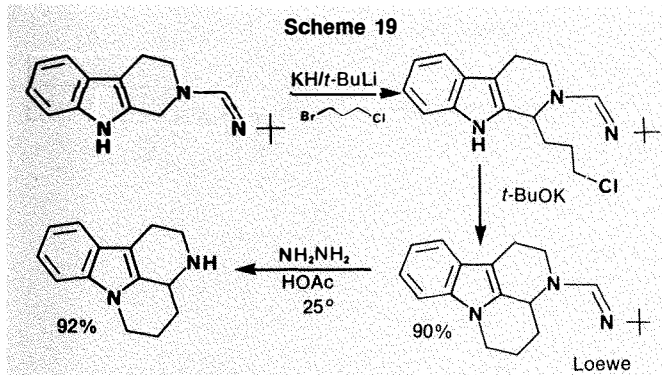a variety of electrophiles introduced to give, after formamidine removal, the 1-substituted tetrahydroisoquinolines.[12] When bifunctional electrophiles were employed, a route to benzoquinolizines and dibenzo derivatives was opened (Scheme 15). It is of interest that the bifunctional electrophile, 2-(carboethoxy)benzyl chloride, alkylated the lithiated isoquinoline exclusively at the benzyl carbon. Furthermore, the monoalkylated isoquinoline can be alkylated again[12] to give 1,1-disubstituted derivatives (Scheme 16).

The metallation of indolines and their subsequent alkylation to 2-substituted derivatives were also studied and proved satisfactory (Scheme 17). Addition of benzaldehyde gave, after reductive removal of the formamidine, a 97:3 ratio of diastereomers.[13] Similarly, 1,2,3,4-tetrahydroquinolines were metallated and alkylated in good yield[13] to give the elaborated derivatives (Scheme 18). It is important to note two procedural changes when the indoline and tetrahydroquinolines were examined. First, direct exchange of these heterocycles was not possible with the dimethylamino *t*-butyl formamidines. This is due to the poor nucleophilicity of these "aniline-type" amines. Thus, the formamides were prepared first and treated with Meerwein's reagent and *t*-butylamine[13] as shown in Scheme 18. Secondly, only *t*-butyllithium was sufficiently basic for deprotonation, due to the poor kinetic acidity of the α-protons.[13]

Another system of considerable significance with respect to its α-amino carbanion involved the β-carbolines and their alkylation to indole alkaloids (Scheme 19). Starting with unsubstituted β-carboline, exchange with the dimethylamino *t*-butyl formamidine as previously described (Scheme 4) gave the carboline formamidine. The indole nitrogen was either protected (chloromethyl methyl ether)[14] or merely transformed into its potassium salt.[15] Treatment with MeLi, *n*-, *s*-, or *t*-BuLi gave the dianion which, when treated with 1-chloro-3-bromopropane afforded the chloropropyl derivative in Scheme 19. After quenching and reforming the indole-potassium derivative, cyclization toward the indole nitrogen ensued smoothly to give the tetracyclic indole derivative in high yields. The dilithio derivative of β-carboline could not be pro-

Scheme 15

Hellring

Scheme 16

Hellring

Scheme 17

E	%
Me	83
Et	77
Ph⟍OH	78 (97:3)

Hellring

Scheme 18

1) HCO₂Et
2) Me₃O⁺BF₄⁻
3) *t*-BuNH₂

97%

E	%
Me	92
n-Bu	84
Ph⟍OH	75 (1:1)

Hellring

Scheme 19

KH/*t*-BuLi

t-BuOK

NH₂NH₂
HOAc
25°

92%

90%

Loewe

Scheme 20

MeLi

HMPA

NH₂NH₂

75%

Loewe

Scheme 21

(achiral)

RLi

a) E⁺
b) H₃O⁺

(chiral)

RLi

a) E⁺
b) H₃O⁺

9   10   (+) or (-)

A* = chiral amine

Scheme 22

$(Me_3Si)_2NH$
2.5 equiv.
Δ

H_2O/HCO_3^-

$[\alpha]_D$ + 49.34°
"BISPAD"

93%

Fuentes

Scheme 23

$BH_3 \cdot Me_2S$
or
$LiAlH_4$

$(Me_3Si)_2NH$
H_2O/HCO_3^-

11

90-97%   >99%

Fuentes, Kubota

---

duced and, therefore, the mixed potassio-lithio salt was employed. On the other hand, the alkylated β-carboline could be induced to cyclize to the naturally occurring indolo[*b*]quinolizine as described in Scheme 20. In this case, hydrazinolysis at room temperature produced the indole alkaloid without isolation or indication of any intermediates.[15]

The foregoing is a summary of the rich chemistry exhibited by simple, achiral formamidines. It now remains to describe our recent efforts involving chiral formamidines and to revisit some of the above chemistry with regard to asymmetric C-C bond-forming processes.
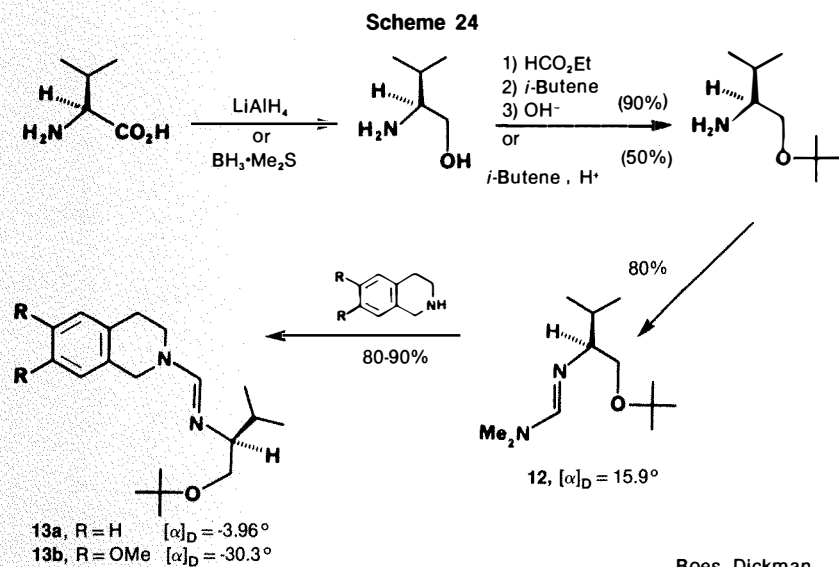
Chiral Formamidines - Synthesis, Metallation and Alkylation. In the previous section we discussed the synthesis, metallation

and alkylation of achiral formamidines; in this portion of our survey, we will make the simple shift to formamidines containing a chiral amine, A (Scheme 21). We hoped to metallate the α-carbon in these chiral systems so that the carbon-lithium bond would reside in an environment of absolute stereochemistry wherein this lithio intermediate was chiral (provided that the C-Li bond was predominantly covalent) or, alternatively, that the approach vector for the electrophile was determined by the topography of the lithiated species. If either or both of these characteristics were important, one could expect a high degree of diastereoselection. Removal of the chiral auxiliary would then provide the α-alkylated amine in high enantiomeric excess. A glance at the chiral formamidine 9 and the lithiated species 10 raised concern over their

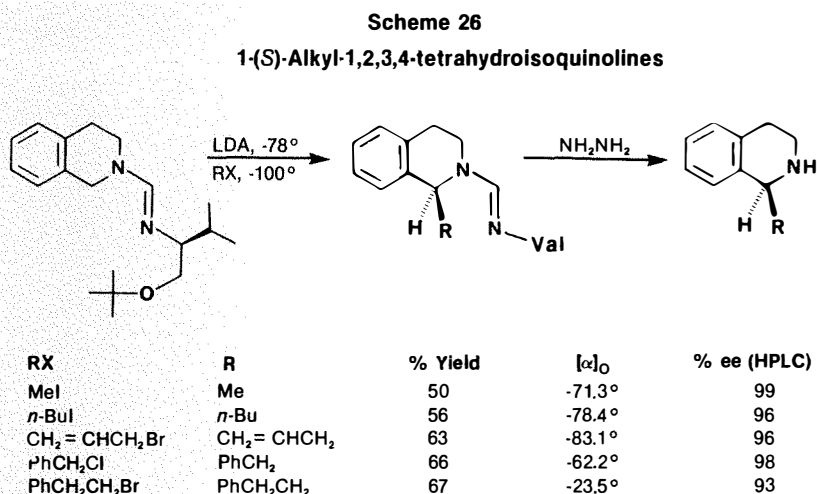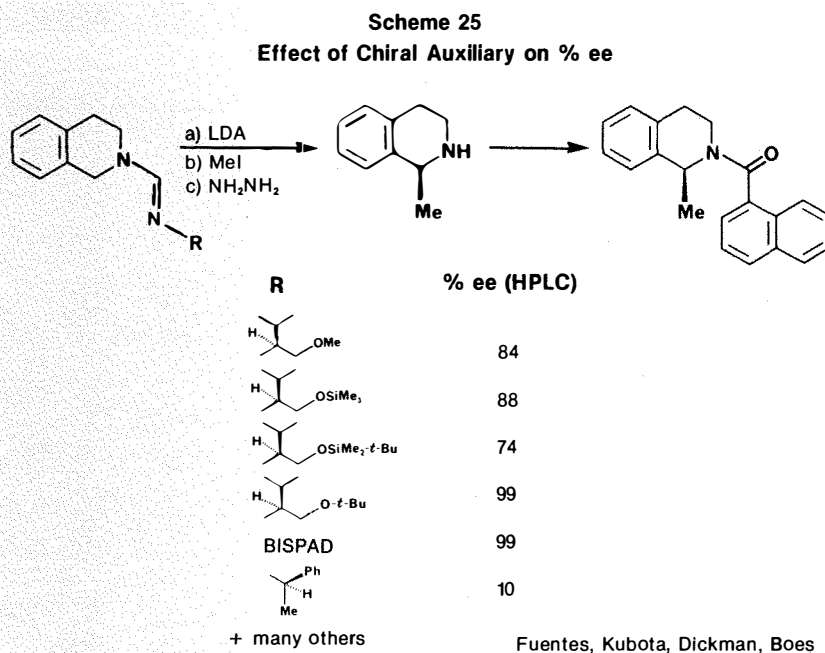ability to influence a stereoselective process in view of the apparent distance between stereocenters in A and the α-proton 9 or the α-carbanion 10. However, we felt if A contained a suitably placed ligand, coordination would result to furnish the needed geometrical arrangement for either metallation or alkylation. This concept has been used before in our laboratory with great success.[16]

Initially, a suitable chiral amine for the formamidines was the readily available (*S,S*)-2-amino-1-phenyl-1,3-propanediol which was silylated with hexamethyldisilazane to yield the bis-silylated phenyl amino diol (BISPAD) as shown in Scheme 22. Furthermore, a variety of amino acids was reduced with either borane-dimethyl sulfide or lithium aluminum hydride to the corre-

sponding amino alcohols with no racemization.[17] The hydroxyl group was then silylated or transformed into its methyl ether (KH-MeI)[18] and then treated with DMF-acetal to furnish the dimethylamino formamidine 11. (Scheme 23) A further chiral auxiliary was prepared, namely the *tert*-butyl ether of the valine dimethylamino formamidine, 12, shown in Scheme 24. Reaction by simple heating with tetrahydroisoquinolines afforded the key formamidines 13a and 13b necessary to evaluate the asymmetric alkylation. A series of isoquinoline formamidines containing various chiral amino residues was evaluated by metallation and reaction with methyl iodide (Scheme 25). After removal of the chiral formamidine, the free isoquinoline was treated with 1-naphthoyl chloride to form the naphthamide which was subjected to HPLC analysis (as was the racemic 1-methylisoquinoline) using the Pirkle column[19] to determine the enantiomeric excess. Remarkably, all the chiral formamidines in Scheme 25 possessing an oxygen function gave highly stereoselective alkylation, whereas the simple α-phenethylamino substituent gave poor ($\leqslant$10%) enantioselectivity. Because of technical problems (due mainly to decomposition) with the O-silyl ethers, we elected to focus on the *tert*-butyl ether of valinol as the optimum chiral auxiliary. Using this as our key stereochemical component, we alkylated the isoquinoline with various alkyl halides and found that the asymmetric process was excellent for all cases examined (Scheme 26).[20] It was now apparent that the asymmetric alkylation of isoquinolines *via* their chiral formamidines would proceed as well as those alkylations in the achiral series but with the added bonus of enantioselectivity. This represented the first asymmetric alkylation of α-amino carbanions and added a significant parameter to this methodology. We extended this process to bifunctional electrophiles and were successful in preparing (S)-benzoquinolizine, previously reported in the literature as a degradation product of the alkaloid securine,[21] in 99% ee (Scheme 27). Finally, in the isoquinoline series, we prepared the 6,7-dimethoxyisoquinoline formamidine by the sequence in Scheme 24 and further demonstrated the power of this technique by the total synthesis of three isoquinoline alkaloids,[20] (-)-salsolidine, (-)-norcoralydine, and (+)-homolaudanosine, in greater than 95% ee and with the correct absolute configuration (Scheme 28). The enantiomeric purities were checked by chiral HPLC analysis using the Pirkle column. (Fig. 1 depicts a typical HPLC plot for racemic and enantiomeric materials.)
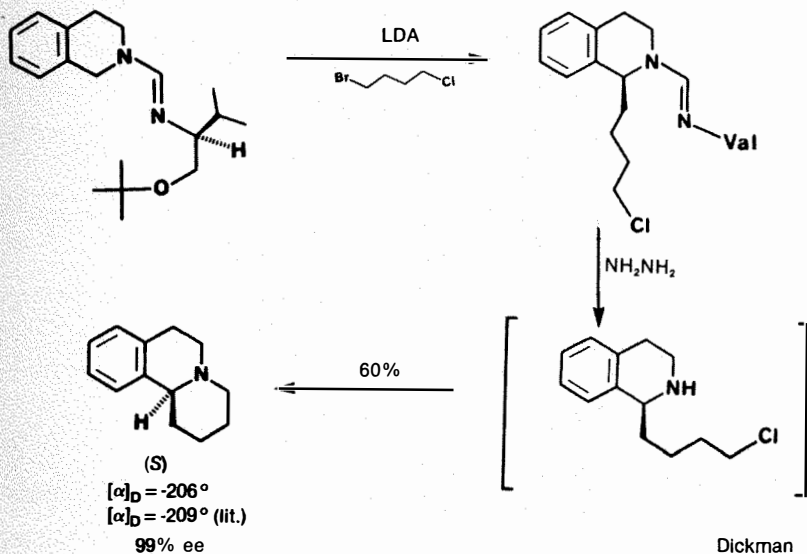
Scheme 24

13a, R = H [α]$_D$ = -3.96°
13b, R = OMe [α]$_D$ = -30.3°

12, [α]$_D$ = 15.9°

Boes, Dickman

Scheme 25
Effect of Chiral Auxiliary on % ee

R	% ee (HPLC)
OMe	84
OSiMe$_3$	88
OSiMe$_2$-t-Bu	74
O-t-Bu	99
BISPAD	99
Ph / Me	10

+ many others

Fuentes, Kubota, Dickman, Boes

Scheme 26
1-(S)-Alkyl-1,2,3,4-tetrahydroisoquinolines

RX	R	% Yield	[α]$_D$	% ee (HPLC)
MeI	Me	50	-71.3°	99
n-BuI	n-Bu	56	-78.4°	96
CH$_2$=CHCH$_2$Br	CH$_2$=CHCH$_2$	63	-83.1°	96
PhCH$_2$Cl	PhCH$_2$	66	-62.2°	98
PhCH$_2$CH$_2$Br	PhCH$_2$CH$_2$	67	-23.5°	93

Dickman

Scheme 27

LDA

NH$_2$NH$_2$

60%

(S)
$[\alpha]_D = -206°$
$[\alpha]_D = -209°$ (lit.)
99% ee

Dickman

Scheme 28

Natural Isoquinoline Alkaloids

t-BuLi

MeI

NH$_2$NH$_2$

-100°

61%

(MeO)$_2$C$_6$H$_3$CH$_2$CH$_2$Br
NH$_2$NH$_2$
CH$_2$O-HCl

70%

(MeO)$_2$C$_6$H$_3$CH$_2$CH$_2$I
NH$_2$NH$_2$ 55%
HCO$_2$Et-LiAlH$_4$

$[\alpha]_D = -56.5°$
$[\alpha]_D = -59.5°$ (lit.)
95% ee

$[\alpha]_D = -273°$
$[\alpha]_D = -277°$ (lit.)
99% ee

$[\alpha]_D = -10.4°$
$[\alpha]_D = -11.0°$ (lit.)
95% ee   Boes

Figure 1

(-)-salsolidine   (±)-salsolidine
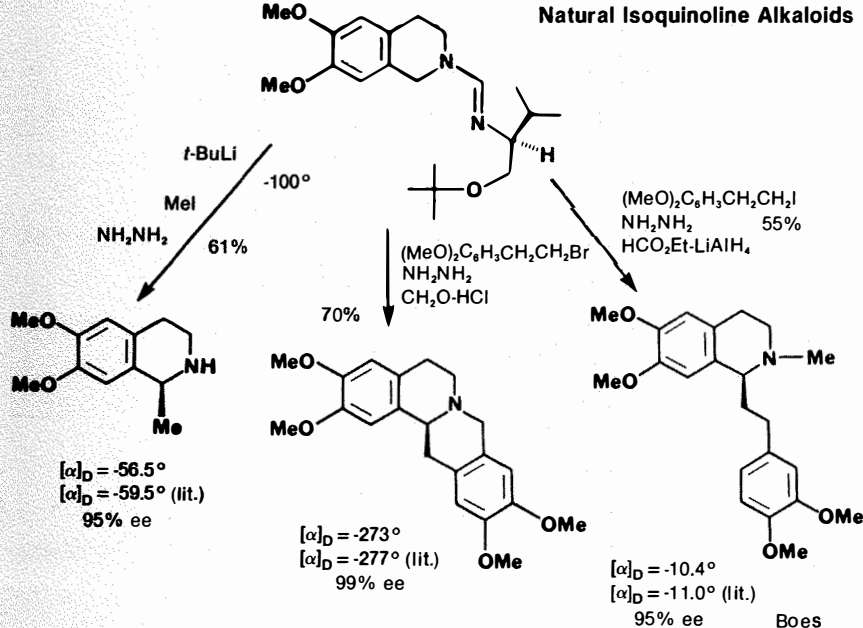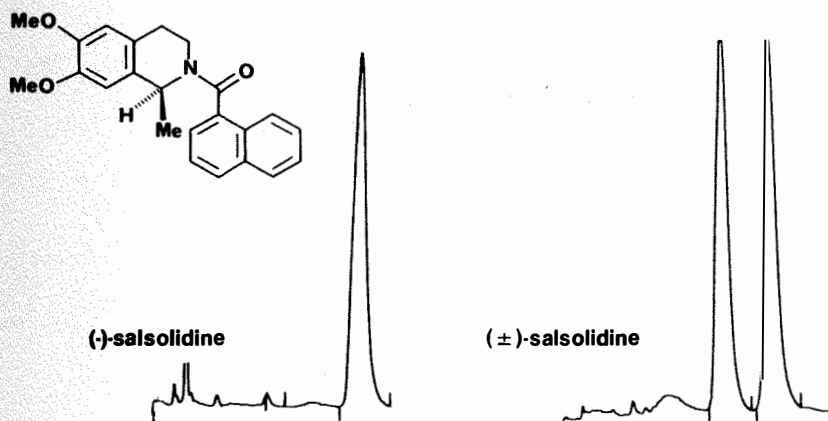
Next we turned to the β-carbolines and affixed the chiral auxiliary derived from valinol *t*-butyl ether (VBE). Attempts to duplicate the racemic methodology by initially regenerating the indole potassium salt prior to metallation with *n*-butyllithium gave poor stereoselection in the alkylation step. Therefore, we added chloromethyl methyl ether to mask the indole nitrogen and proceeded to metallate with *n*-butyllithium, alkylate with methyl iodide and, after hydrazine treatment and dilute acid, obtained the 1-methylcarboline (tetrahydroharman) in greater than 98% ee (Scheme 29).[22]
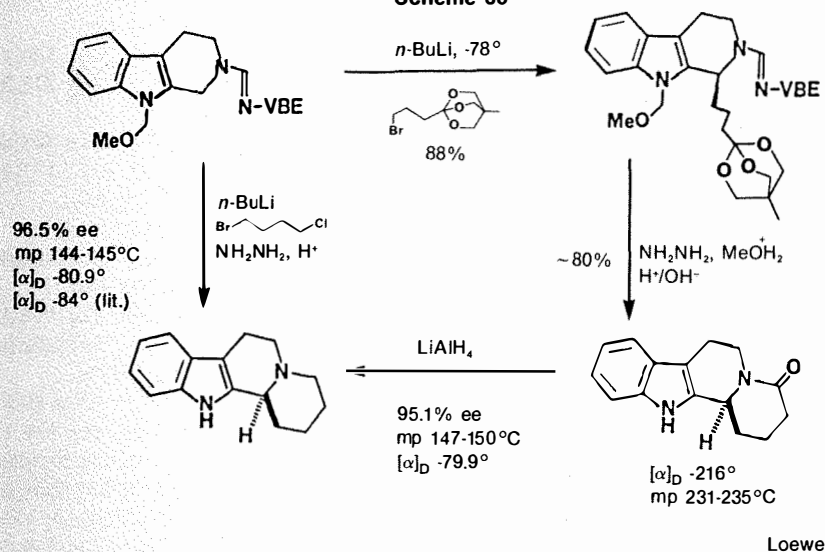
Additionally, we alkylated the chiral formamidine of β-carboline with the bifunctional electrophile 1-chloro-4-bromobutane (Scheme 30) to give the naturally occurring indoloquinolizine.[23] Alternatively, we could alkylate with the bromopropyl ortho ester[23] which could be readily transformed into the tetracyclic lactam and ultimately reduced to the indoloquinolizine.[24]

A number of other asymmetric alkylations have been performed leading to chiral pyrrolidines, piperidines, and benzomorphan derivatives, and attest to the wide generality of this approach to enantiomerically pure (or nearly so) products. Mechanistic studies on this novel alkylation are underway and we have been able to establish a reasonable working model for the underlying factors responsible for the high degree of diastereoselection in chiral formamidines.[25] Based on molecular models, we have made the assumption that **14** is the most reasonable conformation for the chiral formamidines and, in view of this, that the base removes the "axial" proton. This is considered to be the most facile entry by base for minimizing interaction with the isopropyl group and the protons at C-3 in the isoquinoline ring, **15**. Furthermore, the kinetic acidity of the axial proton should be assisted by the π-bond, the absence of which hinders deprotonation. The resulting anion, **16a** and **16b**, can be depicted as shown in Scheme 31. Alkylation with methyl iodide proceeds through **16b** with retention[26,27] to give **17**, while addition of DMSO-d_6 leads to **18** by quenching of **16a**. The chelation effects of DMSO to lithium may deliver the deuterium in an intramolecular sense. When **18**, formed exclusively by DMSO-d_6 quench, is treated again with base and methyl iodide is added, only **17** is formed. Thus, the deuterium in **18** is removed cleanly in spite of any attending isotope effect. This augurs well for stereospecific deprotonation in this process. A recent report by Seebach[27] described the X-ray structure of the 1-magnesium salt of tetra-
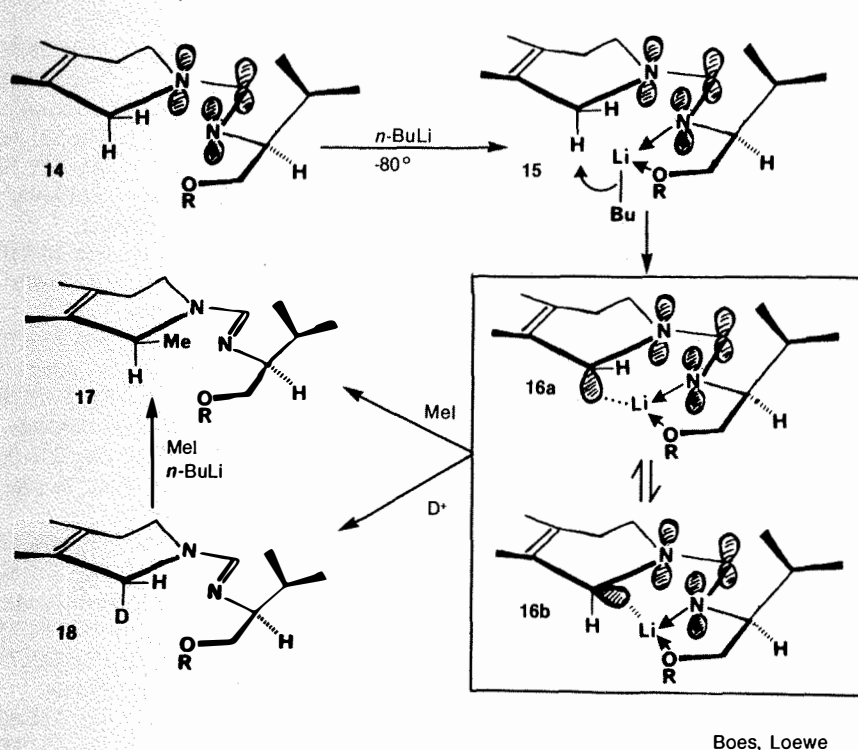
Scheme 29

Loewe

Scheme 30

96.5% ee
mp 144-145°C
[α]$_D$ -80.9°
[α]$_D$ -84° (lit.)

95.1% ee
mp 147-150°C
[α]$_D$ -79.9°

[α]$_D$ -216°
mp 231-235°C

Loewe

Scheme 31

Boes, Loewe
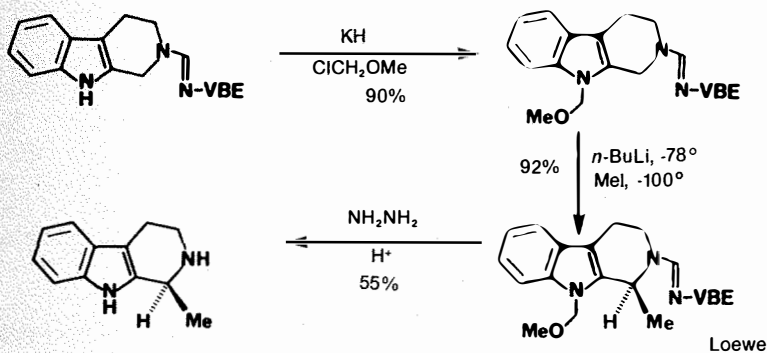
hydroisoquinoline and showed that the C-Mg bond occupies an equatorial position (**16b**). This lends support to alkylation of the carbonlithium bond with retention of configuration (**16b** to **17**). Another interesting fact is acquired from the results in Scheme 32. A mixture of epimers (1:1) was metallated using *t*-butyllithium (weaker bases do not form the tertiary carbanion) and then treated with methyl iodide. Amazingly, only the epimer with the axial proton (in the assumed favored conformation) gave alkylation, whereas the other epimer (*R*) was recovered unreacted. The details of this experiment have been reported.[25]

In summary, we have uncovered a valuable asymmetric alkylation of α-amino carbanions as well as novel alkylation of these systems in an achiral manner. We can say with some certainty that the asymmetric process is due to stereospecific deprotonation and alkylation in the presence of the chelating chiral auxiliary. Undoubtedly, future studies will lead to further extension of this novel process.

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Scheme 32

Boes

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About the Author

Albert I. Meyers was born in New York City on November 22, 1932. He received the Bachelor's and Ph.D degrees from New York University in 1954 and 1957, respectively, working with the late Professor J.J. Ritter. His thesis dealt with the Ritter Reaction which involved the condensation of carbocations with nitriles. In 1957 he joined the Cities Service Oil Co. and in 1958 joined the faculty of Louisiana State University in New Orleans (now called the University of New Orleans). In 1965-1966 he was an NIH Special Fellow at Harvard University in Professor E.J. Corey's laboratory where his interest in carbanion chemistry arose. He was promoted to Boyd Professor at LSU in 1969 and moved to Wayne State University as Professor in 1970. In 1972 he joined the faculty of Colorado State University, where he is at present.

Professor Meyers' research interests involved new synthetic reactions, the use of heterocycles as vehicles in synthetic chemistry, the total synthesis of natural products, and asymmetric synthesis. The use of oxazolines as precursors to chiral and achiral compounds and selective aromatic substitutions have been among his major areas of interest. The introduction of rigid chelation as a prerequisite to efficient asymmetric reactions has been a major topic of his recent efforts.

He has published over 250 papers, several reviews and a monograph entitled "Heterocycles in Organic Synthesis." Professor Meyers has served on the Executive Committee of the Organic Division, as chairman of the Organic Division, host for the National Organic Symposium in Fort Collins (1975), chairman of the Gordon Conference on Heterocyclic Compounds (1973) and Stereochemistry (1982). He has been on the editorial boards of *The Journal of Organic Chemistry, Journal of Heterocyclic Chemistry, Heterocycles*, and *Organic Preparations and Procedures*. He served as associate editor of the *Journal of the American Chemical Society* (1980-1985) and is currently on the NIH Study Section and on the Board of Editors for *Organic Synthesis*. Honors include an NIH Special Fellowship (1965), the Royal Society Centenary Lectureship and Silver Medal (1982), the Colorado Section ACS Award (1982), Colorado State University Distinguished

Award-Winning Chemistry*
1985 — Professor Albert I. Meyers

Albert I. Meyers, Professor of Chemistry at Colorado State University, is the 1985 recipient of the ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich. We extend our congratulations to Professor Meyers, and highlight here some of the significant developments which have come from his laboratories in recent years.

A recurring theme in Professor Meyers' research is the use of heteroatom-containing auxiliary reagents which direct the stereochemical course of carbanion reactions in a regio-, diastereo-, and/or enantioselective manner. Developments from the Meyers group include synthetic techniques based on the chemistry of formamidines and oxazolines.

Formamidines

The discovery that an α-amino carbanion is stabilized if the amine is part of a formamidine has led to the regioselective alkylation of pyrrolidines,[1] piperidines,[1] tetrahydropyridines,[1] azacycloheptanes, and tetrahydro-β-carbolines,[2] as exemplified below.
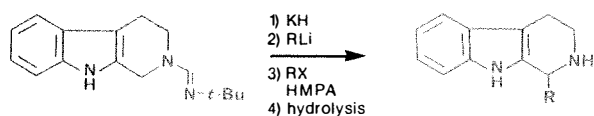
Enamidine intermediates derived from formamidines and carbonyl compounds may be converted into homologated secondary amines, aldehydes or ketones.[3]
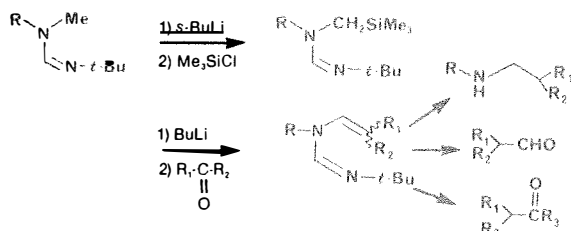

Extensions of this methodology include the synthesis of azabicycloalkanes,[4] enamidines,[5] and an enantioselective alkylation of tetrahydroisoquinolines.[6,7]
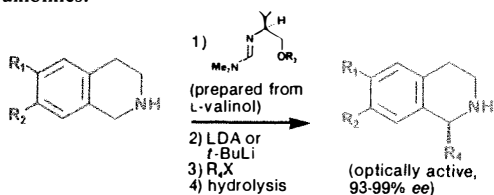

Oxazolines — chiral syntheses

The directing effects of a chiral oxazoline have been utilized in the syntheses of axially chiral biphenyls,[8] dihydronaphthalenes,[9] binaphthyls[10] and (S)-4-naphthoquinolines[11] via organometallic reactions.
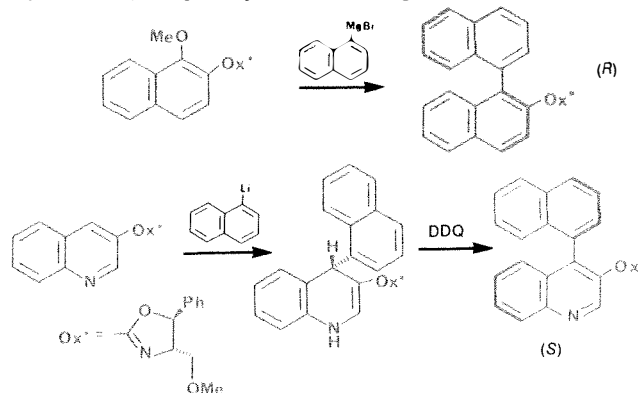
Similar methodology yields chiral phthalides.[12] Although the enantioselectivity of the addition reaction shown below is low, the diastereomeric intermediates can be separated easily by flash chromatography; after hydrolysis, the enantiomeric phthalides are isolated virtually optically pure.

(diastereomer at ★ not shown)
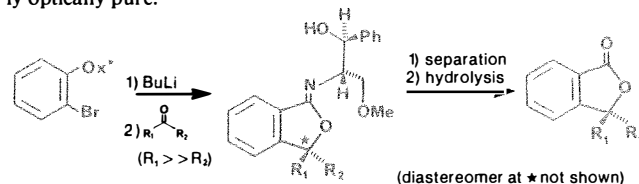
Use of a boron azenolate derived from a chiral oxazoline in the aldol condensation affords very high erythro selectivity.[13] A review by Professor Meyers on oxazolines has just appeared.[14]

95-98% erythro
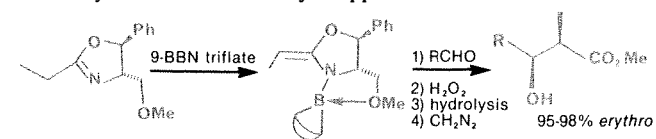
References:
(Professor Meyers is the senior author in all cases.)

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*An article based on Professor Meyers' award acceptance speech appears on page 59.

centrifugation, the wall film is still visible. The intensity of the peak depends on the amount of HOD (residual in the D_2O and produced by the exchange), on the thickness of the wall film, and on the completeness of separation of the two layers. Transfer of the centrifuged and filtered $CDCl_3$ layer to a dry tube will remove or greatly reduce the peak.

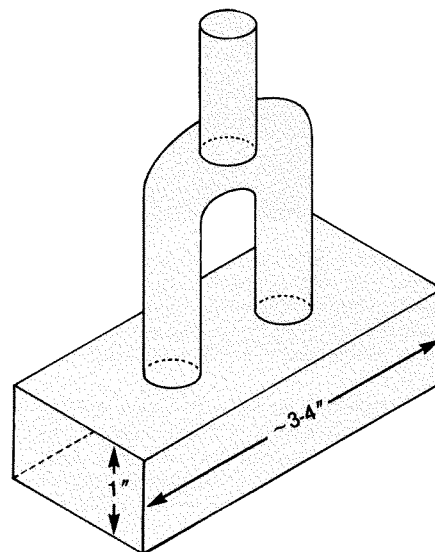Experiments were performed on a Varian XL-100 instrument.

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tion, the peak shifts only to δ 1.55 because of the low solubility of water in $CDCl_3$.

2. The HOD peak at $\sim\delta$ 4.7 (in our experiment, the H_2O peak) that appears following the usual deuterium-exchange experiment represents HOD dissolved in the film of D_2O on the wall of the cell or in minute droplets of D_2O. This peak can be quite large if the mixture is not centrifuged but merely allowed to stand. Even after

The importance of protecting the environment of the laboratory must be a primary concern of all lab workers. Many laboratories still do routine GC analyses under less-than-optimum conditions. This is especially true with older GC's using TC detectors requiring large samples ($> 5\mu l$) and large columns ($> \frac{1}{8}$" i.d.). The exhaust from such instruments can be, at best, annoying and, at worst, life-threatening over an extended period of time.

In some laboratories the GC is placed in a fume hood, but we have found a simpler method for venting the exhaust vapors. A plastic aspirator is attached to a low-pressure air line in the fume hood and the suction inlet is attached to a piece of plastic hose that is routed to the detector vents of the GC. A piece of aluminum sheeting is cut and formed into a small, open rectangular box. Two holes are cut in the box for the two narrow "legs" of a "Y" tube. Silicon rubber is used to seal the "Y" tube into the aluminum box. The plastic line from the fume hood is attached to the remaining free "leg" of the "Y". Double-sided adhesive tape is used to hold the miniature aluminum fume hood in place above the vents. An air flow is established in the aspirator to maintain suction through the "Y" tubes. Air is used as the working fluid to conserve water and to avoid the possibility of accidental flooding.

During the three years that this apparatus has been in operation, numerous odorous compounds were separated by GC, with no detectable odors escaping from the instrument.

Bob Small
Ciba-Geigy Corp.
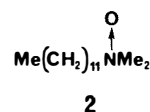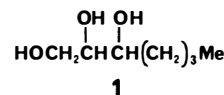*P.O. Box 113*
McIntosh, Alabama 36553

Crystallization of Membrane Proteins

$$\text{HOCH}_2\text{CH}\underset{|}{\overset{\text{OH}}{}}\text{CH}\underset{|}{\overset{\text{OH}}{}}(\text{CH}_2)_3\text{Me}$$

1

$$\text{Me}(\text{CH}_2)_{11}\overset{\text{O}}{\underset{\uparrow}{\text{N}}}\text{Me}_2$$

2

1,2,3-Heptanetriol (1) was found to enhance the crystallization of membrane proteins solubilized in detergents such as *N,N*-dimethyldodecylamine-*N*-oxide (**2**) and 1-*O*-octyl-β-D-glucopyranoside. Membrane-protein crystallization is becoming an important tool for protein-complex studies.[1-3]

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Tetrathiafulvalenes (TTF) and Their Selenium and Tellurium Analogs (TSF and TTeF): Electron Donors for Organic Metals

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Introduction

Since the first reports in the early 1970's of the high electrical conductivity in the chloride salt of tetrathiafulvalene (TTF, **1**) and in the charge-transfer complex of TTF with tetracyanoquinodimethane (TCNQ), relentless interest in organic metals has been sustained by synthetic organic chemists, physical chemists and solid-state physicists; the large volume of review articles, conference proceedings and books published on organic metals in the last decade bears testimony to this.[1-10] It quickly became clear that high conductivity and other remarkable solid-state properties are anisotropic and are associated with crystal structures in which the donor and acceptor molecules form segregated stacks with extensive π-electron overlap and delocalization along these one-dimensional stacks. Derivatives of TTF remain of paramount importance in the arena of crystalline organic conductors (Table 1) and the recent thrust of synthetic work towards the TTF system has been stimulated by the quest for new, highly conducting materials. In 1976 a review describing synthetic routes to TTF and

tetraselenafulvalene (TSF) was published;[11] the field has burgeoned vigorously since then, and the aim of this article is to highlight the major routes now available to TTF derivatives and their selenium and tellurium analogs.

Tetrathiafulvalene

TTF is a planar molecule with D_{2h} symmetry and is easily oxidized to the radical cation and the dication. As discussed at length elsewhere[4] these three properties of TTF are of particular relevance to the design of new derivatives as donors for or-

ganic metals. The most widely used routes to TTF derivatives proceed *via* coupling of 1,3-dithiolium salts (**2**) or 1,3-dithiole-2-thiones (**3**) (eq. 1). For example, TTF itself is prepared *via* the sequence outlined in eq. 2; the overall yield for this sequence is 56% and the reactions are applicable to large-scale synthesis.[27]

The chemistry of 1,3-dithiolium salts (**2**) has been reviewed.[28] The reaction **4**→**1** is considered to proceed *via* deprotonation of the dithiolium cation to yield the stabilized carbene which then reacts as a nucleophile
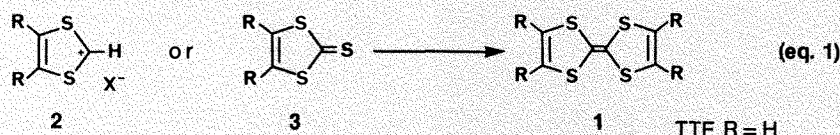
$$\text{(eq. 1)}$$

2   **3**   **1**   TTF R = H

Table 1[12]
Landmarks in the Development of Organic Metals Based on TTF

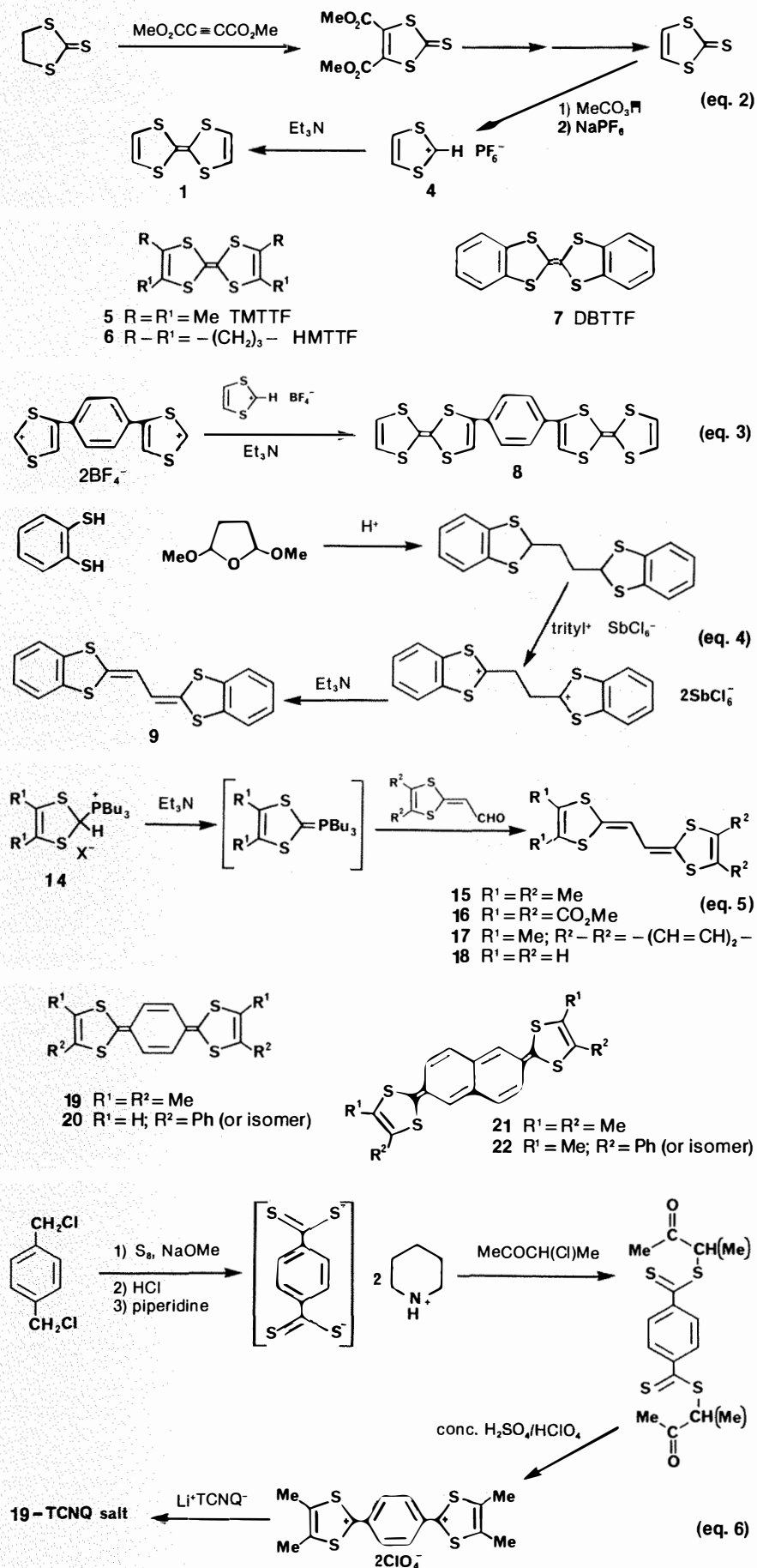| Year	Material	Property	Reference
1970	TTF	First reported synthesis	13
1972	TTF chloride	Metallic conductivity observed: σ_{rt} 0.2 $(\Omega\,cm)^{-1}$	14
1973	TTF-TCNQ	σ_{rt} 500 $(\Omega\,cm)^{-1}$ Metal-insulator transition T_{M-I} at 53°K	15
1974	TSF-TCNQ	Selenium analogs prepared Metallic state stabilized down to T_{M-I} at 28°K	16
1975	HMTSF-TCNQ	Metallic behavior observed down to T_{M-I} at 16°K	17
1976	HMTSF-TCNQ	T_{M-I} supressed under pressure	18
1978	TMTSF-DMTCNQ	T_{M-I} supressed under pressure	19
1979	TMTTF-tetrahalo-*p*-benzoquinone	First organic metals not containing TCNQ or derivative as acceptor	20
1980	(TMTSF)₂X	Organic superconductivity observed at 0.9°K at 12 kbar for X = PF₆, and at ambient pressure for X = ClO₄	21
1982	BEDT-TTF salts	Two-dimensional organic metals	22
1982	DBTTeF and HMTTeF	First Te analogs prepared	23, 24
1983	(BEDT-TTF)₂ReO₄	First sulfur-based organic superconductor	25
1983	(BEDSe-TSeF)X	Metallic salts X = ReO₄, ClO₄ prepared	26

at C-2 of another 1,3-dithiolium cation. This method (eq. 2) has been used for the preparation of symmetrically substituted derivatives TMTTF (5),[29] HMTTF (6)[30] and DBTTF (7),[31] all of which have played important roles in probing structure/property relationships in organic metals. For example, DBTTF is a weaker electron donor than TTF and forms metallic complexes only with very strong electron acceptors, e.g., TCNQF$_4$.[4] Also the bis-TTF derivative 8 has been prepared by this route (eq. 3).[32]

Dithiolium cations are also precursors of several DBTTF derivatives where there is extended conjugation between the dithiole rings. These materials are currently of interest, as the radical cations derived from them incorporate the desirable features of more widely spaced sites of maximum spin density. The route to compound 9 is shown in eq. 4.[33,34] The dithiole skeleton is assembled by condensation of an ortho-dithiol and an aldehyde, or masked aldehyde. The electron donor ability of 9 is very similar to that of TTF and markedly better than DBTTF. Approaches directly analogous to eq. 4 lead to derivatives 10,[35] 11,[36] 12[37] and 13.[38]
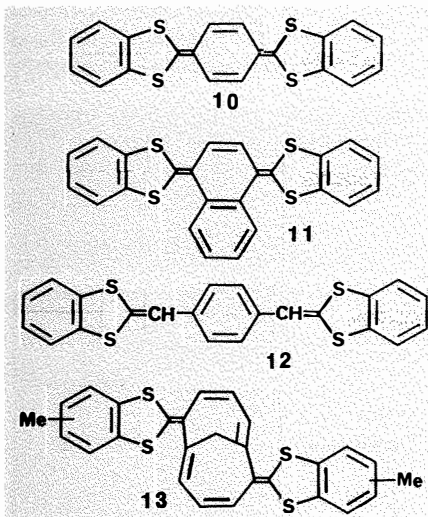
1,3-Dithiolium cations readily react with trialkylphosphines to form phosphonium salts (14) and this reaction has been utilized recently for the efficient synthesis of vinylogs of TTF (15-18) (eq. 5).[39] Compound 16 has been converted into the parent compound 18 which is a more efficient donor than TTF as judged by cyclic voltammetry.[39]

The 1,3-dithiole skeleton can also be assembled by condensation of a dithiocarboxylic acid with an appropriate halo-substituted compound, followed by acid-catalyzed cyclization. This approach has yielded highly conjugated TTF derivatives 19,[40] 20,[41] 21[31,42] and 22,[34,42] as detailed for 19 (eq. 6).

(eq. 2)

5 R = R^1 = Me TMTTF
6 R – R^1 = – (CH$_2$)$_3$ – HMTTF
7 DBTTF

(eq. 3)

(eq. 4)

(eq. 5)

15 R^1 = R^2 = Me
16 R^1 = R^2 = CO$_2$Me
17 R^1 = Me; R^2 – R^2 = – (CH = CH)$_2$ –
18 R^1 = R^2 = H

19 R^1 = R^2 = Me
20 R^1 = H; R^2 = Ph (or isomer)

21 R^1 = R^2 = Me
22 R^1 = Me; R^2 = Ph (or isomer)

19 – TCNQ salt

(eq. 6)

An alternative approach to the synthesis of tetrathiafulvalenes, *e.g.*, **26**, is the desulfurization or deoxygenation of 1,3-dithiole-2-thiones or -2-ones, *e.g.*, **23**,[43] **24**[44] or **25**[44,45] with trivalent phosphorus compounds (eq. 7). This reaction has been used widely when electron-withdrawing groups are present on the dithiole, although yields are not always good and other products are sometimes obtained.[46] One report suggests that it is preferable to use $Co_2(CO)_8$ instead of a phosphorus reagent for the coupling, as a wider range of substituents can be tolerated.[47]

The TTF derivative, BEDT-TTF (**28**), is currently at the forefront of organic-metals research as low-temperature superconductivity has been observed in certain salts of this donor. For example, $(BEDT-TTF)_2$-$ClO_4(1,1,2$-trichloroethane$)_{0.5}$ is metallic over the temperature range 300-$1.4\,°K$ with no evidence of a metal-to-semiconductor transition. Moreover, the salt shows two-dimensional metallic conduction over this temperature range, the conduction pathway resulting from close intermolecular contacts of sulfur atoms. Routes to BEDT-TTF are shown in eq. **8** and have been evaluated critically recently.[48] Thiapendione (**27**) can be readily synthesized on a large scale, and can be converted to BEDT-TTF in a two-step reaction with an overall yield of **80-90%**, making this the synthetic method of choice.

An entirely new approach to the TTF skeleton based on reactions of thiapendione has been reported recently (eq. **9**).[49] Although the final product is obtained as an isomeric mixture and a yield is not given for the last step, this method is worthy of note as it is a noncoupling method that is potentially versatile.

A nickel-complex-assisted synthesis of tetrakis(trifluoromethyl)TTF (**26**) in which the Ni(triphos) group acts as a catalyst has been reported but the scope of this reaction has not been investigated (eq. **10**).[50] Although this method affords **26** under mild conditions, the reaction is less efficient than the quantitative reaction previously reported by Hartzler from the one-step reaction of hexafluoro-2-butyne and carbon disulfide under pressure.[43]

Another recent advance in methodology for TTF synthesis is the oxidative electro-dimerization of 1,3-dithioles, probably *via* radical cation intermediates; however, in the two cases studied, yields are moderate or low.[51]

In general, the methods described above suffer limitations when applied to the synthesis of unsymmetrical TTF derivatives,
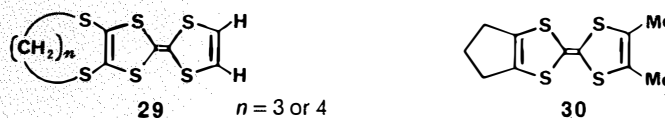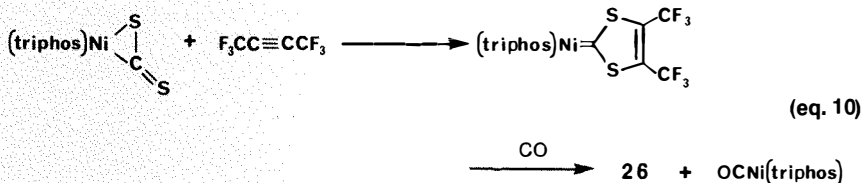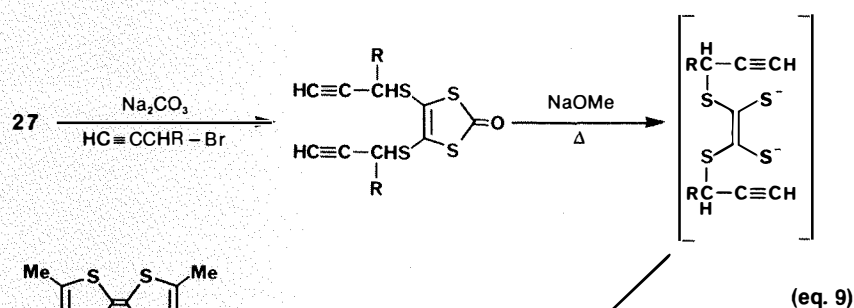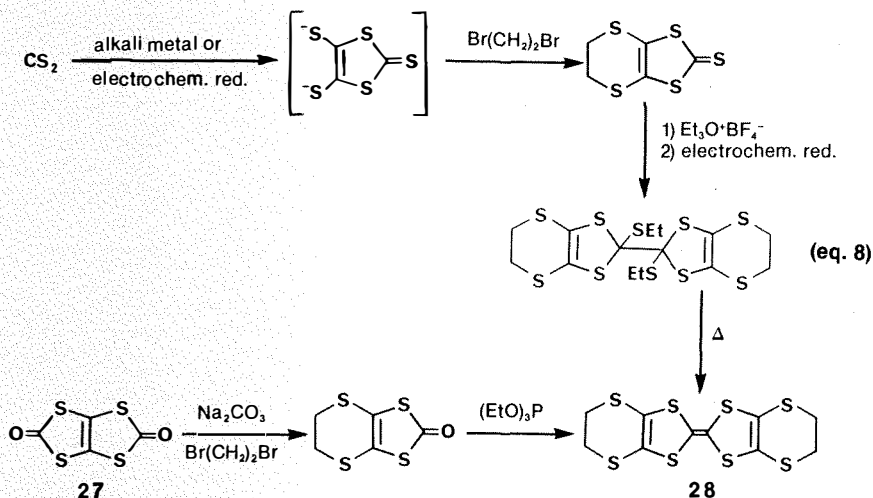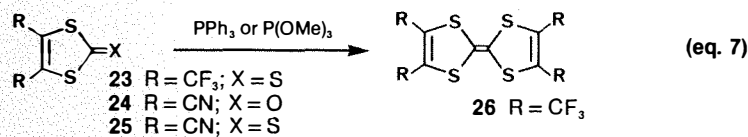
as the key cross-coupling step yields a product that is a mixture, as illustrated in the recent synthesis of hetero-ring fused derivatives **29**[52] and alkylated derivative **30**.[53] However, several solutions to this cross-coupling problem are now in hand, and it is possible that radical cation salts of some unsymmetrically alkylated TTF derivatives will show higher conductivity than symmet-

rical salts, maintaining the metallic state to lower temperature.[53] Phosphoranes (**31**) react with 1,3-dithiolium salts to form coupling products which eliminate PPh_3 in the presence of Et_3N to afford TTF derivatives (**32**). This clearly allows for the preparation of unsymmetrical tetrathiafulvalenes from two different 1,3-dithiolium moieties (eq. 11).[54]

(eq. 7)

23 R = CF₃; X = S
24 R = CN; X = O
25 R = CN; X = S

26 R = CF₃

(eq. 8)

(eq. 9)

(eq. 10)

29 n = 3 or 4

30

More recently, anions from compound **33** have been treated with 1,3-dithiole-2-thiones to give products **34** which are converted to benzotetrathiafulvalenes (**35**) in high yield (eq. 12).[55]

Tetraselenafulvalenes

The importance of sulfur '*d*' orbital overlap in bestowing metallic properties on TTF salts was quickly recognized. This directed synthetic chemists towards the tetraselenafulvalene system (TSF) with larger, more polarizable selenium '*d*' orbitals, and it is now proven that many TSF salts do show increased stability of the metallic state relative to their TTF counterparts. In 1979 Bechgaard and coworkers found that a family of salts based on TMTSF (**39**) [*viz.*, (TMTSF)$_2$X, where X=NO$_3$, PF$_6$, AsF$_6$, or SbF$_6$] possesses superconducting properties at very low temperatures.[21,56]

TSF (**38**) and TMTSF (**39**) were prepared initially using the phosphine-promoted coupling method and it was shown that selenone derivatives (**36**) couple far more efficiently than their thione analogs (**37**) (eq. 13).[16,57] A serious drawback of this early method is the use of the fetid reagent, carbon diselenide; nonetheless, this procedure, with some improvements, still gives the highest overall yields of tetraselenafulvalenes.[58] Later TMTSF was prepared *via* reaction of H$_2$Se with selenoureas or *N*,*N*-dimethylphosgeniminium chloride, and recently this procedure has been improved by using NaSeH instead of gaseous H$_2$Se (eq. 14).[58]

The ready coupling of 1,3-diselenole-2-selenones (**36**) has facilitated cross-coupling reactions to give unsymmetrically alkylated tetraselenafulvalenes[59] and diselenadithiafulvalenes (**40**),[60] although isomers have to be separated in both cases. Diselenadithiafulvalenes (**41**), isomeric with (**40**), have been prepared recently by reaction under pressure of carbon selenosulfide (CSSe) with alkynes bearing at least one electron-withdrawing group.[61] TSF derivatives with fused rings, *viz.*, **42**[62] and **44**,[26] have also been prepared by the phosphite coupling method, and derivatives with extended conjugation between the diselenole rings are accessible using methodology analogous to eq. 5.[63]

Tetratellurafulvalenes

Derivatives of tetratellurafulvalene (TTeF) were long awaited in the expectation that there would be further stabilization of the metallic state in salts derived from these donors due to increased intrachain couplings. Two derivatives of TTeF, *viz.*, DBTTeF (**43**)[23] and HMTTeF (**45**) (eq.
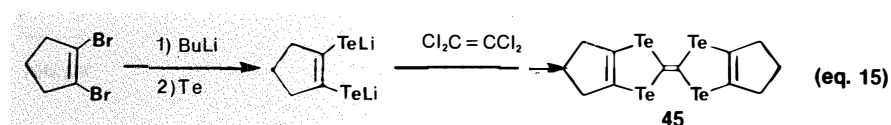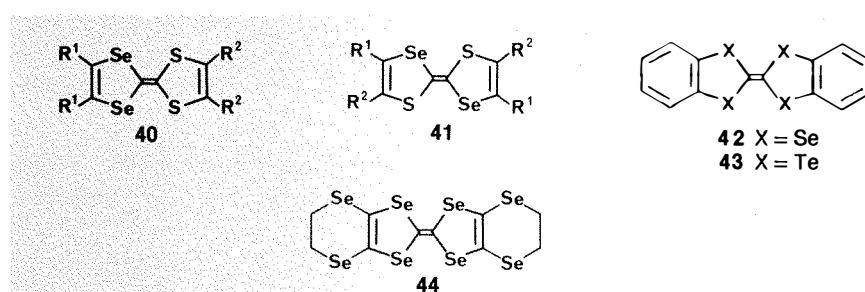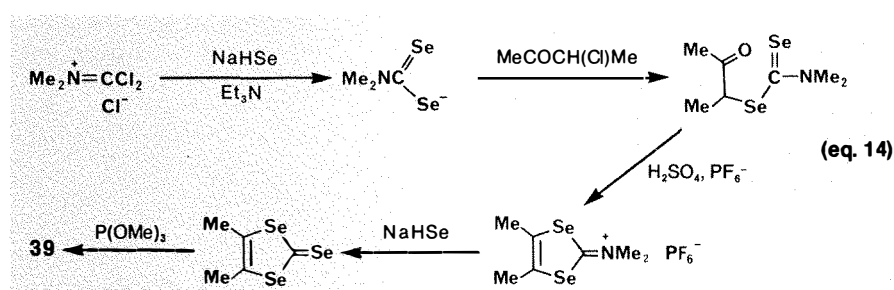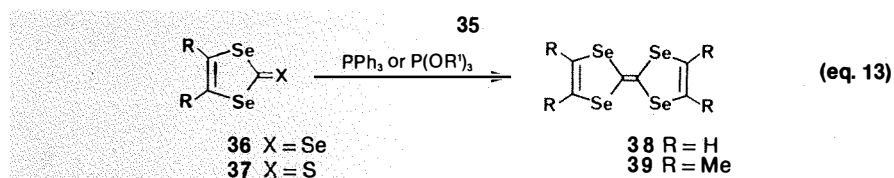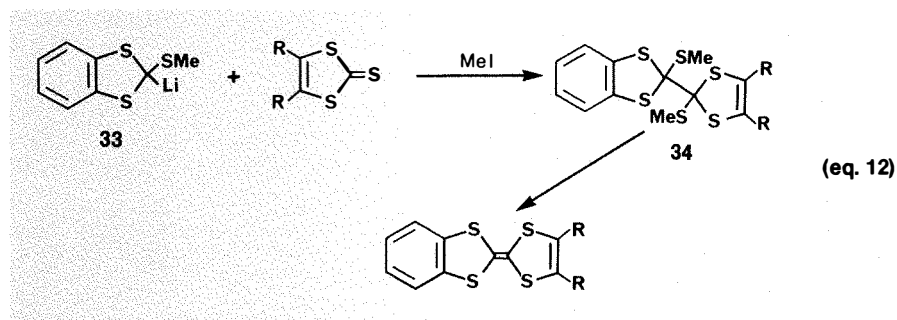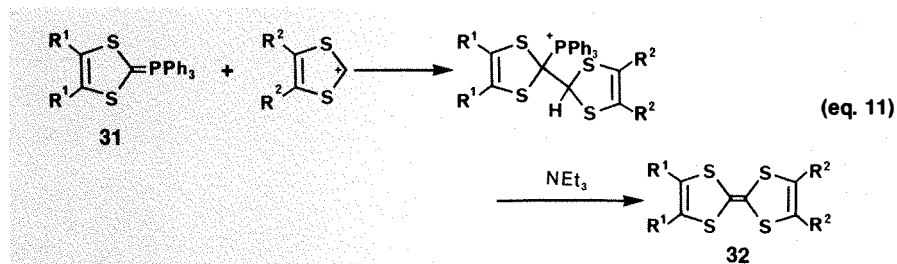
15),[24] were prepared independently in 1982, and in 1984 the thiophene-fused derivative **46** was obtained.[64] The methodology in each case was reaction of a 1,2-ditellurate with 0.5 mol. equiv. of tetrachloroethene. Compound **46** is nonplanar with an asymmetric boat conformation, as shown by X-ray crystallography. The oxidation potential of DBTTeF (**43**), as determined by cyclic voltametry, is less than that of DBTSF

(**42**) and the same as that of DBTTF (**7**). Cowan[23] suggests that ionization is influenced by two factors which have the op-

(eq. 11)

(eq. 12)

(eq. 13)

36 X = Se
37 X = S

38 R = H
39 R = Me

(eq. 14)

40

41

42 X = Se
43 X = Te

44

(eq. 15)

45

46

posite effects in the series S, Se and Te: these are the valence-state ionization potentials of the heteroatoms and the differences in their orbital interactions with carbon. The complex of **45** with TCNQ has a conductivity comparable to that of TTF-TCNQ.[24]

Summary

This article has highlighted the major advances in synthetic methodology towards TTF and analogous systems with special attention on recent developments. Numerous fulvalenoid donors are now available by efficient procedures; these structures offer an impressive range of steric and electronic variations on the parent molecule, TTF, *e.g.*, substitution of sulfur for selenium and tellurium, the presence of alkyl, aryl or electron-withdrawing substituents, derivatives with fused heterocyclic rings and extended π-orbital frameworks, and symmetrical and unsymmetrical derivatives. However, TTF derivatives substituted with strongly electron-donating groups are still absent. With the preparation of TTeF derivatives a formidable challenge was overcome, but TTeF and TMTTeF, the prime tetratellurafulvalene targets, are still unknown. Extensive studies by physicists on salts and complexes of TTF-based donors have greatly enhanced our understanding of the organic solid state, and it now appears that the old donor, TTF, born in 1970, has had its day. Current attention is focused sharply on new salts of TMTSF **(39)** and BEDT-TTF **(28)** which are the only organic superconductors known. Synthetic work in this area seems certain to continue, since organic metals, to a degree unrivalled by other intrinsic conductors, allow chemical manipulation of the structure and properties of conducting materials.

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About the Author

After undergraduate studies at Wolverhampton Polytechnic, Dr. Bryce received the Ph.D. degree from York University in 1979 for work on sulfur and selenium heterocycles under the supervision of Dr. J.M. Vernon and Dr. P. Hanson. This was followed by post-doctoral work at University of British Columbia, Vancouver, with Professor L. Weiler and at Bristol University with Dr. R.W. Alder. Dr. Bryce moved to Durham in 1981 where he is now lecturer in organic chemistry. His research includes the synthesis and solid-state properties of organic metals and electroactive materials, heterocyclic synthesis and organic reactive intermediates.

Aldrichimica Acta

Lanthanides in Organic Synthesis

4-Acetoxy-2-azetidinone: A Useful Heterocyclic Synthon

The Aldrich *FIRST* System of Information Retrieval — An Update

About Our Cover:

Our chemist-collector recently bought this small winter landscape (oil on canvas, 14 x 12¼ inches) by Jacob van Ruisdael in a London auction. Rather than describe it, he asked us to read what the late Wolfgang Stechow wrote about Ruisdael's winter landscapes in his treatise on *Dutch Landscape Painting of the Seventeenth Century* (Phaidon, London, 1966). Professor Stechow did not know this painting, yet his description appears so applicable:

"...there is no trace of the traditional gaiety... It would be altogether absurd to think of skaters when looking at this picture; the real topic is the forlorn mood of a winter day... the mood is without any grandiloquence...profound, and wonderfully intimate... The 'dejected day' is now silenced by a deep, desolate grey from which some patches of sharply lit snow stand out threateningly rather than soothingly... There is nothing comparable with this in Dutch seventeenth-century landscapes; and outside of landscapes, only the deep gloom that spreads over a religious tragedy through the magic of Rembrandt's chiaroscuro comes to mind. I do not doubt that in spite of all technical and colouristic discrepancies, Rembrandt's 'synthesis of the visible and the invisible' here inspired Ruisdael: the very fact that all outward, imitative features of such an 'influence' are missing, is eloquent, for this can be expected of the fruitful relationship between two very great artists.

"It is as though greatness in the interpretation of winter as a drama had been preserved for one single artist: Jacob van Ruisdael."

Pictures from the Age of Rembrandt

Twenty-five paintings that have been reproduced on our *Acta* covers, and six that have been on our catalog covers are among thirty-six paintings in an exhibition of Dutch paintings at Queen's University in Kingston, Ontario. The fully illustrated catalog written by Professor David McTavish contains a wealth of art-historical information — enough for several evenings of relaxed enjoyment — probably the best value in art-history anywhere.

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Eight beautiful 14 x 11 inches, full-color reproductions of paintings on our catalog covers are available, ready for framing, to add beauty to your laboratory.

Selections from the Aldrichimica Acta, 1968-1982

Because of the ever-increasing demand for earlier issues of the *Acta*, we now offer a collection of articles from volumes 1-15. We chose those articles which we believe are still of interest to our readers — 354 pages of great review articles, in one beautiful hardbound volume.

I have found a rather simple method for heating reaction mixtures at constant temperature, which your readers may find useful.
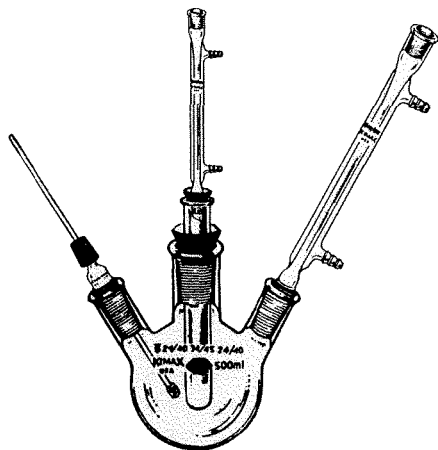
The 25 x 200-mm test tube which contains the reaction mixture is fitted into the center neck (ℑ 34/45) of the round-bottom flask using a No. 4 rubber filter adapter, as shown in the diagram. The test tube is then fitted with a condenser (ℑ 19/22) using a No. 2 rubber filter adapter. The side arms of the round-bottom flask are fitted with a reflux condenser and a thermometer. A solvent having a boiling point equal to the constant temperature required is placed in the round-bottom flask and heated to reflux with a heating mantle. The refluxing solvent vapors will then maintain a constant temperature around the test tube reactor. A wide variety of solvents or solvent mixtures may be used to maintain different temperatures.

Howard L. Murray
Associate Professor of Chemistry
Northeastern Illinois University
5500 N. St. Louis Avenue
Chicago, IL 60625

Atmospheric moisture can sometimes ruin an organic or inorganic reaction. Some people go to great pains to flame glassware, dry solvents and otherwise prepare for anhydrous reaction conditions, then connect dry nitrogen or argon tanks to their flasks with tubing which might well have been used previously for condenser water. A simple solution is to maintain two sets of tubing labeled "wet" and "dry", respectively. Dry tubing can be stored closed into a loop using quick connectors, and hung over a convenient hook labeled "DRY TUBING ONLY".

Charles E. Gragg
Department of Chemistry
North Carolina State University
Box 5247
Raleigh, NC 27650

Editor's note: Aldrich carries various sizes of polyethylene tubing quick disconnects.

Cleaning a 10-microliter syringe can be time-consuming if the methodology necessitates prolonged rinsing with solvent. A disposable pipette tip (200-microliter capacity) serves as a "quick-disconnect" joint between the syringe and the water aspirator. With the syringe removed, the needle is dipped into the rinse solvent while the pipette tip is held over the barrel. (The broad end of the pipette tip is attached to the aspirator through a pressure tubing.) The syringe can be easily cleaned with a number of solvents in sequence. Thus, tedious rinsing as well as contamination due to rubber/glass connections can be avoided. An intermediate trap prevents the solvent from getting into the aspirator.

Ashok D. Deshpande
The College of William and Mary
Virginia Institute of Marine Science
School of Marine Science
Gloucester Point, VA 23062

I would like to report a simple solution to a problem that has been a constant annoyance to us and, I'm sure, many other NMR users.

The problem involves the sticking of caps to NMR tubes. Often the amount of force required to remove a cap results in a broken or chipped tube. Previously, we have cut off the offending cap with a razor blade – saving the tube and sample, but ruining the cap.

However, if the cap is warmed *gently* with a heat gun, it will soon soften and can be easily removed without being destroyed.

Rick M. Ede
Wood Technology Division
Forest Research Institute
Private Bag, Rotorua
New Zealand

Editor's note: For your convenience, Aldrich offers NMR caps and NMR tubes in various grades.

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 Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt**. *We reserve the right to retain all entries for consideration for future publication.*
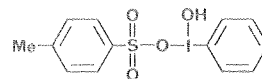
Professor G. F. Koser at the University of Akron suggested that we offer hydroxy-(tosyloxy)iodobenzene, a useful reagent for the *cis*-ditosyloxylation of alkenes,[1] the α-tosyloxylation of ketones[2] and the phenyl-iodination of alkynes[3] and (trimethylsilyl)-arenes.[4] This is a very versatile reagent which we would like to call "Koser's Reagent".

Naturally we made it.

1) Rebrovic, L.; Koser, G.F. *J. Org. Chem.* **1984**, *49*, 2462.
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It was no bother at all, just a pleasure to be able to help.

Lanthanides in Organic Synthesis*

John R. Long
Aldrich Chemical Company, Inc.

1. Introduction

Judging by the chemical literature of the 1970's, one might be tempted to assume that there are relatively few ways in which the lanthanides can be applied to organic transformations; indeed, the most comprehensive and definitive compilation of data on reagents useful to the synthetic chemist, the Fiesers' "Reagents for Organic Synthesis,"[1] made infrequent mention of lanthanides other than ceric ammonium nitrate (CAN) before 1977. In one case, it was to recommend cerous hydroxide for the destruction of peroxides.[2]

In contrast to the scant attention given during most of the 1970's to the role of lanthanides in organic synthesis, aspects of f-element organometallic chemistry (featuring σ- and π-bonded derivatives) have been thoroughly reviewed by Marks[3-5] as well as Schumann and Genthe.[6] While the chemistry of complexes having lanthanide-carbon bonds is only briefly considered in this article, the background information provided by these reviews is extremely instructive.

Most lanthanide ions are paramagnetic, a property first exploited in the mid-1950's when it was found that the dysprosium(III) ion accelerated the rate of decarboxylation of phenylmalonic acid.[7] This "magnetic catalysis" was considered a minor effect,[8] and not until 1960 was this phenomenon applied to the resolution of the inadvertent overlap of NMR spectral resonances.[9]

Within 10 years, a variety of lanthanide-dionate complexes were being specifically designed to induce sizeable, clean proton NMR shifts.[10] However, within the framework of this rapidly developing field, the unique coordinating ability of the lanthanide shift reagents was essentially ignored as far as applications in organic synthesis were concerned, and until recently, the application of the entire spectrum of rare earth elements (lanthanides plus scandium and yttrium) and compounds to organic processes has suffered from the lack of an investigative effort such as that generated in the development of the NMR shift reagents.
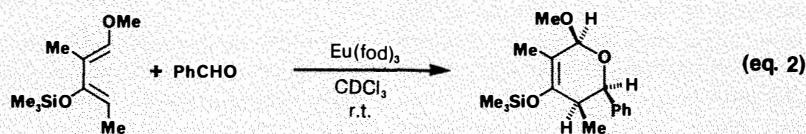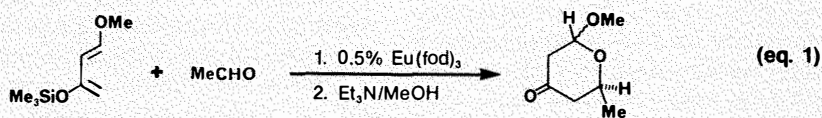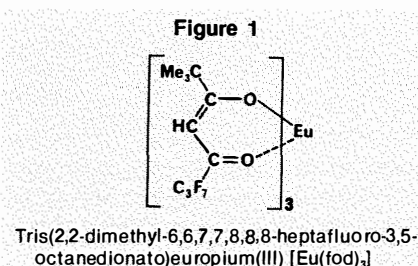
Recently, however, the chemical literature has witnessed at least two major reviews[11,12] as well as a cascade of research articles that described new and surprising uses for lanthanides in organic synthesis. A review article on organolanthanoid complexes by Schumann[13] speculated on the potential of such complexes in catalysis and organic synthesis.

The purpose of this article is to put into focus the diverse chemistry reflected in this rapidly growing field.

2. Interactions of shift reagents with organic substrates

Modest synthetic utility has been shown for certain shift reagents, initially attributed to their ability to induce conformational changes or to selectively stabilize complexes in a desirable coordination scheme.

In one of the first examples of a specific synthetic application of a lanthanide shift reagent, Eu(fod)₃ (Fig. 1) acted as a mild Lewis acid catalyst in hetero-Diels-Alder reactions (eq. 1).[14]

Figure 1

Tris(2,2-dimethyl-6,6,7,7,8,8-heptafluoro-3,5-octanedionato)europium(III) [Eu(fod)₃]

In this scheme, the character of the aldehyde is altered by the lanthanide cation so that it can act as a potent hetero-dienophile. This promotion can be attributed to the oxophilicity of the europium species, which, appropriately complexed, can exploit favorable solubility properties.

The resulting cyclocondensations represent a method for the stereospecific synthesis of carbon-branched pyranose derivatives (eq. 2) where endoselectivity is maintained through a wide range of aromatic and aliphatic aldehydes.

Extension of this chemistry to chiral europium(III) ligands shows promise for asymmetric induction and enantioselectivity in organic synthesis. The latter feature is possible through the use of a chiral catalyst such as Eu(hfc)₃, tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III) (Fig. 2).

Figure 2

Tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III) [Eu(hfc)₃]
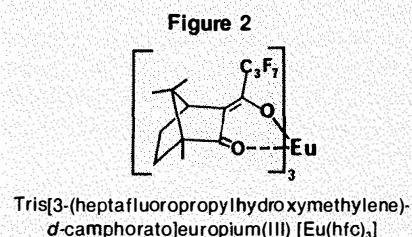
Described as "interactivity of chiral auxiliaries with chiral catalysts,"[15] this technique can be applied to the synthesis of optically pure saccharides, including L-glycosides, while avoiding formal resolution or glycosylation. The Eu(hfc)₃ complex

(eq. 1)

(eq. 2)

also promotes the cyclocondensation of aldehydes with siloxydienes with considerable asymmetric induction (eq. 3).[16]

Ytterbium shift reagents also can promote cycloaddition reactions, in some cases more efficiently than the europium analogs.[17] In chemistry applicable to the synthesis of milbemycin/avermectin targets, ≤5% Yb(fod)₃ catalyzed the diene-acetaldehyde cyclocondensation (eq. 4), whereas one equivalent of zinc chloride was required to effect similar conversions in like yields.

The lone isomer **A** was produced in 48% yield following desilylation and alumina-induced spirocyclization.

This mode of catalysis is especially attractive for dienes having sensitive functionalities. Cycloaddition of substrates bearing acid-labile components has been effected using Yb(fod)₃ at only 5 mole % levels (eq. 5).[18]

Immediately following Danishefsky's pioneering work, several reports of cyclocondensations promoted by lanthanide shift reagents appeared in the literature. The Eu(fod)₃/hetero-Diels-Alder methodology offers a novel approach to highly functionalized δ-lactones.[19] Such a scheme provides access to natural products *via* synthetically useful intermediates.

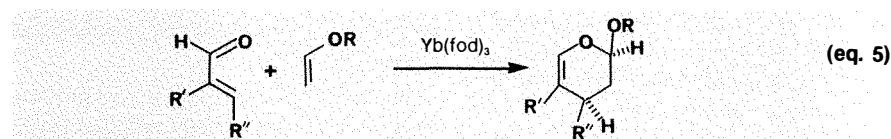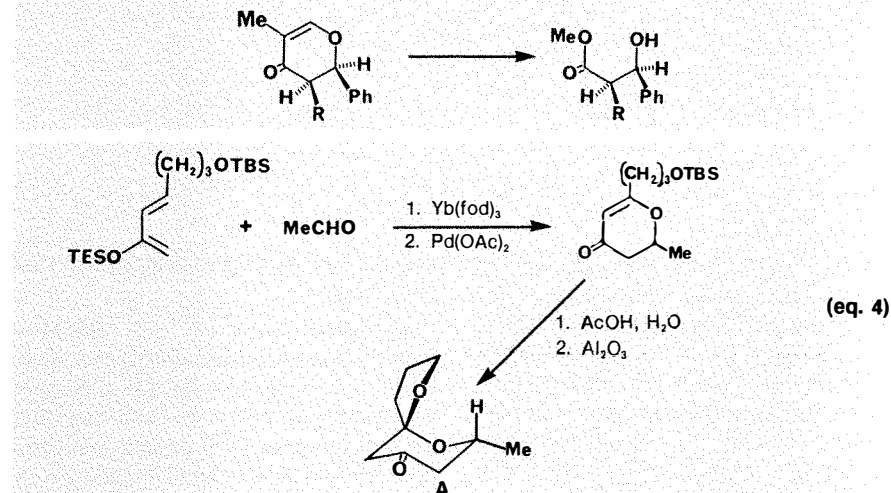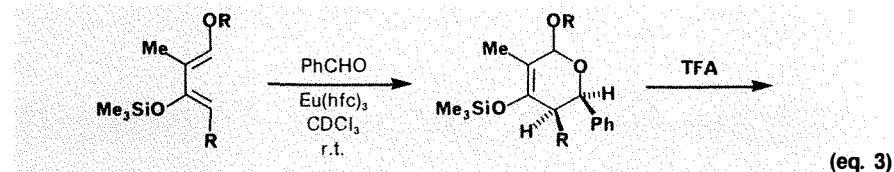### 3. Catalytic effects of lanthanide(III) salts

An early report of a catalytic oxidation of an organic substrate by a simple lanthanide salt focused on the oxidizing ability of the nitrate anion, which was promoted by various Ln³⁺ ions.[20] Of the lanthanides studied (La, Sm, Eu, Tm, Yb), ytterbium nitrate gave the highest yield of benzils from benzoins (eq. 6).

Extension of this chemistry eventually led to the development of a new method for the high-yield nitration of phenols using one equivalent of sodium nitrate as nitrating agent in excess HCl;[21] lanthanide catalysis was effective under mild conditions which leave many other aromatic systems unaltered. Three particular aspects of this study should be emphasized:

(i) An acid medium is required (in 1:3 water/ethyl ether), but the method is potentially suitable for acid-sensitive compounds since reasonable reactivity is observed in a medium as weak as 0.5 mol. equiv. HCl.

(ii) The ortho:para ratio of products is a function of the acidity: greater acidity favors ortho-nitration (para-substituted phenols undergo 80-90% nitration at the ortho position).

(iii) Small quantities of lanthanide catalyst are required (0.01 mol. equiv.) and other lanthanum salts work as well as the nitrate; also effective are nitrates of Nd, Sm, Eu, Tb, Yb, and Tm.
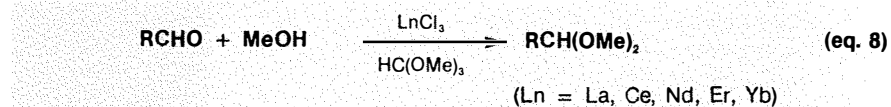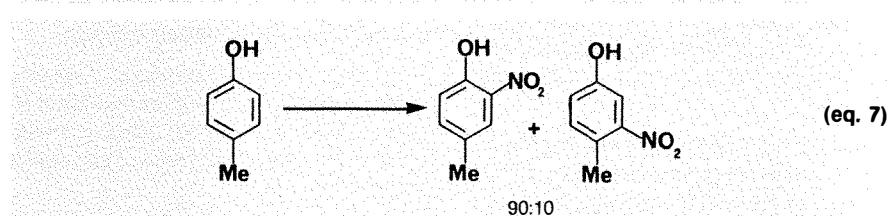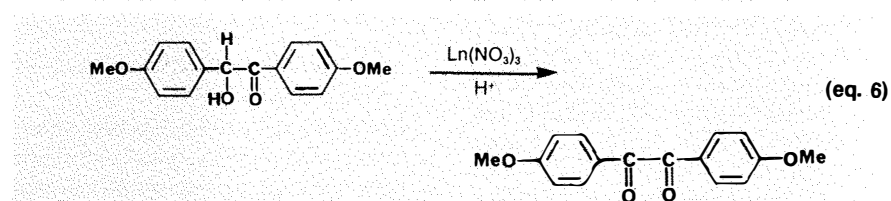
Equation 7 shows a typical product distribution. This procedure is selective for the nitration of phenol rings in the presence of those having substituents other than OH, a property not observed under HNO₃/H₂SO₄ nitration conditions.[22]

A variety of lanthanide chloride salts effect aldehyde acetalization rapidly and under mild conditions.[23] With trimethyl orthoformate as a water scavenger, the reaction proceeds in minutes at room temperature with no side-products (eq. 8).

Yields greater than 90% are typical, with lanthanum, cerium and neodymium chlorides being effective for aliphatic linear aldehydes while erbium and ytterbium chlorides are superior for aromatic and cyclic aldehydes. Under the given experimental conditions, zinc chloride was ineffective.

4. Cerium compounds in organic synthesis

The first indication of the strength of the interaction between the ceric ion (Ce⁴⁺) and

(eq. 3)

(eq. 4)

(eq. 5)

(eq. 6)

(eq. 7)

90:10

RCHO + MeOH $\xrightarrow[HC(OMe)_3]{LnCl_3}$ RCH(OMe)₂   **(eq. 8)**

(Ln = La, Ce, Nd, Er, Yb)

alcohols was described in 1901,[24] and for decades the ceric ammonium nitrate (CAN) salt has held a premier position among lanthanide oxidants useful in organic synthesis.[25]

While a thorough treatment of cerium(IV) chemistry is clearly beyond the scope of this article, presentation of selected and recent reports of its use is appropriate because of the background it provides for the subsequent examination of the cerous (Ce^{3+}) ion as a catalyst in organic reductions.

One of the few disadvantages of CAN lies in the quantity of material sometimes required to oxidize alcohols; in addition, such processes may not be as systematic or consistent as other methods. However, both ceric ammonium sulfate and CAN (eq. 9) have been used as catalysts in the sodium bromate oxidation of secondary alcohols to ketones.[26] The preference for secondary alcohols is quite pronounced (eq. 10).

Cerium(IV) sulfate exhibits similar selectivity: 4-dodecanol is converted to 4-dodecanone in 98% yield, but 1-dodecanol undergoes only 3% conversion.

A novel cerium(IV) reagent, cerium pyridinium chloride (CPC), promoted side-chain methoxylation of higher polymethylbenzenes.[27] However, such reactions using CPC are extremely slow when run in alcohols other than methanol; this and other considerations led to the development of a more convenient and general procedure for benzylic alkoxylation of methylarenes.[28]

Another new cerium(IV) reagent, ceric triethylammonium nitrate, has been prepared for use in the mild high-yield oxidation of benzylic alcohols and α-hydroxy ketones to the corresponding carbonyl compounds.[29] This CAN analog is stable, soluble in methylene chloride, acetonitrile, acetone, alcohols and water; it gives high yields in simple, nonacidic solvents and produces minimal secondary products from carbon-carbon bond cleavage.

Further adjustments to the environment about the cerium(IV) ion allow the formulation of additional reagents having mild oxidizing capacities.[30-32]

The scope of the catalytic potential of the cerium(III) ion was intimated by Pratt[33] in an investigation of the addition of aromatic amines to quinones. Use of hydrated cerous chloride in place of cupric acetate as an oxygen carrier in the oxidation of byproduct hydroquinone resulted in improved yields and easier product separation from metal complexes.

(eq. 9)

(eq. 10)

(eq. 11)

(eq. 12)

(Ln = Eu, Ce, Sm) (eq. 13)
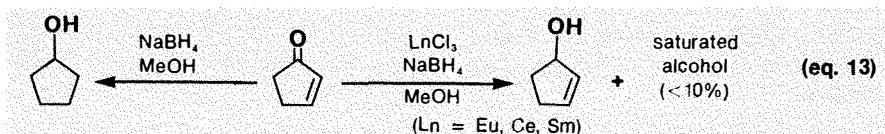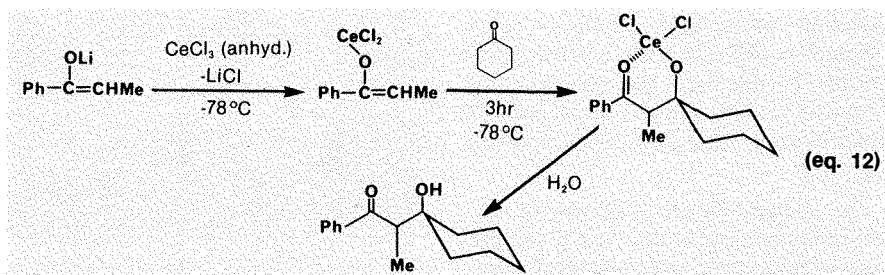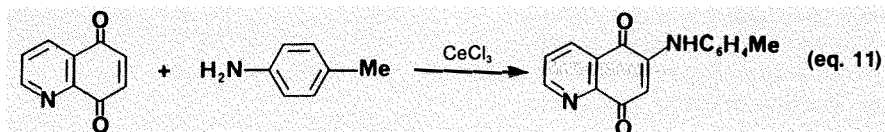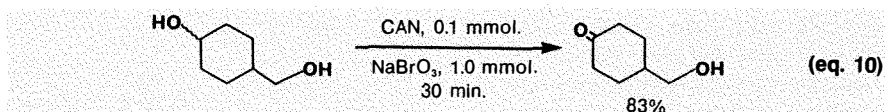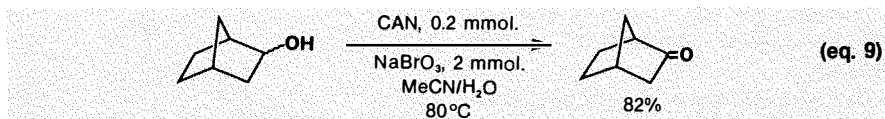
In addition to improving product yields and shortening reaction times, cerous chloride promoted the regioselective addition of p-toluidine to the 6-position of 5,8-quinolinequinone (eq. 11).

To more fully elucidate the role of the cerium(III) ion in these additions, Pratt suggested that the influence of the Lewis acid catalyst in reactions of 6-chloro-5,8-quinolinequinone was exerted primarily through the heterocyclic nitrogen atom; the resulting N-Ce interaction also allows the cerium ion to assume a position in close proximity to the 8-carbonyl oxygen with concomitant 6-position activation.

In the case of the addition of p-nitroaniline to 1,4-naphthoquinone, or the replacement of the methoxy group in 2-methoxy-1,4-naphthoquinone, the catalytic effect was ascribed to coordination of cerium to a carbonyl group.

Lithium bis(trimethylsilyl)amide or (more frequently) lithium diisopropylamide, upon reaction with ketones, produces an enolate that reacts with *anhydrous* cerium(III) chloride at -78°C to afford a cerium enolate.[34]

This transmetallation product, when applied to aldol couplings as shown in eq. 12, exploits the stronger chelation of the cerium ion (relative to lithium) in the six-membered intermediate. This suppresses retro-aldol and/or cross-enolization and gives higher

yields than reaction with corresponding lithium enolates. Generally, no differences in stereoselectivities were observed between the two enolate systems.

Cerium enolates also provide favorable routes to α-bromo β-hydroxy ketones, important intermediates to α,β-epoxy ketones.

5. Application of lanthanide(III) salts to selective reductions

In the late 1970's, Jean-Louis Luche and co-workers began to evaluate the role of lanthanide salts in selective organic reductions. Even with the extensive arsenal of available reagents, including sodium cyanoborohydride, diisobutylaluminum hydride and 9-borabicyclononane (9-BBN), there has remained room for improvement in yield, selectivity and reaction conditions in reductions of carbonyl groups in complex organic molecules.

In his first publication in this area, Luche found samarium trichloride and cerium trichloride (hydrated forms) to be especially effective in the selective conversion of α,β-unsaturated ketones to allylic alcohols,[35] even in the case of 2-cyclopentenone, which tends to undergo 1,4-addition (eq. 13). (Essentially 100% reduction was observed with all reagent systems.)

Advantages to the lanthanide chloride/sodium borohydride tandem include:

(i) Almost exclusive 1,2-reduction occurs under mild conditions that do not affect carboxylic acids, esters, amides, halides, as well as cyanide and nitro groups.

(ii) The reactions require no special atmospheric conditions and may be run at room temperature in a few minutes.

(iii) The amount of water present in the commercially available hydrated lanthanide salts has little effect on selectivity.

This method was also applied to the reduction of natural products, using cerium(III) chloride with sodium borohydride to minimize the formation of saturated alcohols and give good yields of allylic alcohols with good stereoselectivity (eq. 14).[36]

The sodium borohydride/cerium trichloride system can be used in a broad pH range without significant loss of regioselectivity; it is also efficient in the presence of pyridine, which is known to induce 1,4-reductions under a variety of conditions.[37]

Reactions using erbium trichloride also exhibited the same regioselectivity in diethyl ether solution.
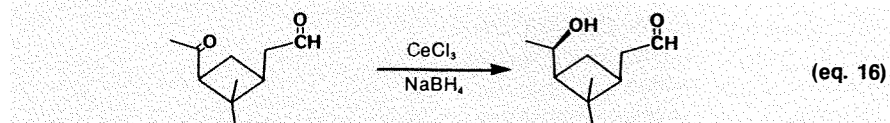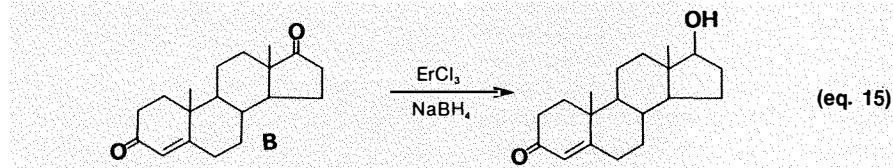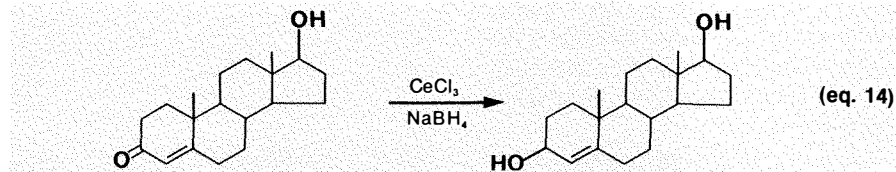
Extending this technique to the reduction of the dione, **B**, demonstrated an intramolecular selectivity attributable to conversion of the more reactive C-3 carbonyl to a monoketal intermediate (eq. 15).[38] This allows the preferential reduction at C-17, and also demonstrates the sharp contrast between aldehyde and ketone ketalization using lanthanide chlorides as catalysts.

This system typically allows the convenient, one-pot selective reduction of a less reactive carbonyl group in the presence of a more reactive one.

Also noteworthy was the dependence of the ketal yield upon the choice of lanthanide salt. Lighter lanthanide ions (Ce^{3+}, Nd^{3+} - softer Lewis acids) having larger ionic radii were preferred in cases where the aldehyde-ketone discrimination became more difficult.

Further study of the role of lanthanides in the reduction of carbonyl groups demonstrated the potential for selectively reducing ketones in the presence of aldehydes.[39] This reverse selectivity has resulted in the development of the first direct process than can be used in place of multistep procedures that gave low yields and/or separation problems caused by insufficiently selective catalysts.

In a typical reaction, two carbonyl compounds, or a dicarbonyl compound (two equivalents), are dissolved with cerium trichloride in water/ethanol; sodium borohydride is added at -15 °C to give the selective reduction of the ketone, leaving the aldehyde group intact (eq. 16).
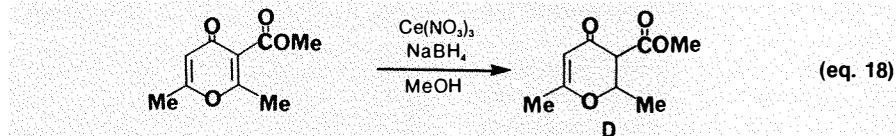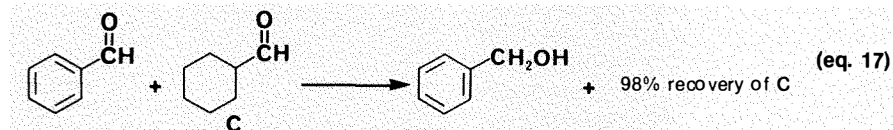
In general, selectivity is excellent for nonconjugated aliphatic and alicyclic carbonyl compounds, but diminishes for conjugated aldehydes. This preference can be exploited in the reduction of mixtures of aldehydes, however (eq. 17).

Given the hypothesis that the formation of a geminal diol is critical to nonconjugated aldehyde function protection, it was subsequently shown by NMR study that cerium(III) enhances diol stability better than any other cation tested. This implies that the cerium ion is large enough to provide protection during reduction, but still allows ready recovery of the aldehyde during workup. The utility of the cerium ion is also fortuitous in that it is one of the least expensive of the lanthanides.

The application of a sodium borohydride/cerium(III) nitrate reagent to a pyrone reduction produced results that departed somewhat from the 1,2-additions observed by Luche. Catalytic reductions of γ-pyrones can lead to complex mixtures of products via nonselective processes; however, the lanthanide/borohydride system provided a good yield of the specifically reduced dihydropyrone, **D**, from the unsaturated precursor, while preserving the carbonyl function adjacent to the double bond (eq. 18).[40]

Figure 3

Structural representation of α-enones

While many metal salts have been shown to be effective in modifying sodium borohydride reductions, the use of lanthanides in the selective 1,2-reduction of α-enones (Fig. 3) is potentially a very widely applicable synthetic tool. For this reason, an extensive and systematic study of the mechanistic and stereochemical aspects of this procedure was undertaken.[41] The following were considered to be the salient points:

(i) Cerium(III) remains the recommended lanthanide species, best used as $0.4M$ methanolic $CeCl_3 \cdot 6H_2O$ with 1 mol. equiv. of sodium borohydride, usually at room temperature.

(ii) Reaction rate and selectivity were sensitive to changes in solvent as well as metal ion; methanol was by far the best solvent, and nonlanthanide metal ions were not effective.

(iii) A specific catalytic effect was demonstrated, with the lanthanide-catalyzed decomposition of the borohydride anion by the solvent appearing to be the rate-determining step; this implies

(eq. 14)

(eq. 15)

(eq. 16)

(eq. 17) + 98% recovery of C

(eq. 18)

that BH_4^- is not the actual reducing species, rather one or more alkoxyborohydrides (eqs. 19-21).

This is consistent with the observation that alkoxyborohydrides are more reactive than the borohydride ion; this is also borne out by the observation that reactions run in isopropyl alcohol give poor results because the respective alkoxy-borane species are more slowly formed, *viz.*, $[H_{4-n}B(O\text{-}i\text{-Pr})_n]^-$.

The role of the lanthanide cation appears to be to modify electron density and hence the reactivity of the environment of the carbonyl group. Subsequent attack at the adjacent carbon atom is enhanced.

The utility of the selective reduction techniques described in these sections is so pronounced that the term 'Luche reduction' is essentially generic. Natale's review[12] is recommended for a more extensive examination of the types of synthetic methodology that have evolved from this base.
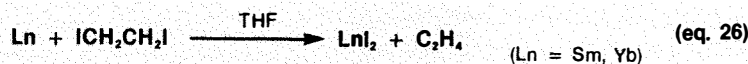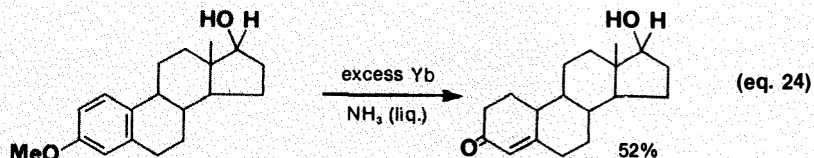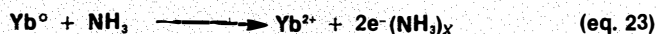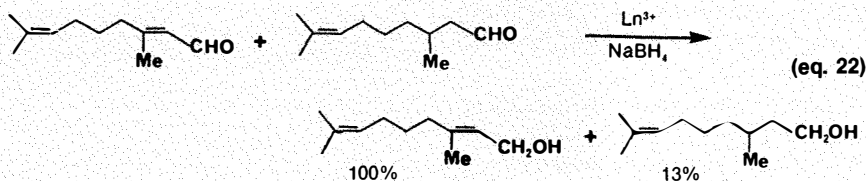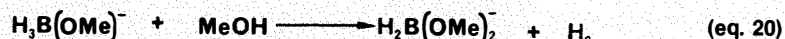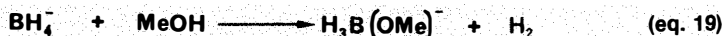
In systems using lanthanides other than cerium (which is too insoluble in THF to be effective), samarium triiodide or erbium trichloride demonstrated similar lanthanide ion control of selective reductions;[41] this was in particular contrast to reductions carried out in the presence of lithium or sodium ions.[42,43] The utility of SmI_3 is also interesting in view of the extensive chemistry developed for SmI_2 reductions (section 6).

In a subsequent study of reaction parameters, lanthanide ions were found to promote the selective reduction of conjugated aldehydes in the presence of nonconjugated aldehydes in aqueous ethanol (eq. 22). Erbium trichloride was the preferred catalyst, usually where the solubility of cerium trichloride in solvents such as isopropyl alcohol was unfavorable.[44] The authors described the interaction between the lanthanide and the intermediate substrate as a "chelating effect."

Chromium(III) was also effective in several selective reductions, although with lesser yields. The chromium ion is also undesirable from the standpoint of spent catalyst disposal.

6. Zero-valent and low-valent reductions

Reduction of a variety of organic functional groups has long been carried out using ammonia solutions of alkali metals.[45] Given the strongly electropositive character of lanthanides such as ytterbium (which features a $4f^{14}6s^2$ electron configuration), it follows that ytterbium/ammonia solutions should convert α,β-unsaturated

$$BH_4^- + MeOH \longrightarrow H_3B(OMe)^- + H_2 \qquad \text{(eq. 19)}$$

$$H_3B(OMe)^- + MeOH \longrightarrow H_2B(OMe)_2^- + H_2 \qquad \text{(eq. 20)}$$

$$H_2B(OMe)_2^- + MeOH \longrightarrow HB(OMe)_3^- + H_2 \qquad \text{(eq. 21)}$$

(eq. 22) [reaction scheme: two aldehyde structures + $\xrightarrow[NaBH_4]{Ln^{3+}}$ giving alcohol products, 100% and 13%]

$$Yb^0 + NH_3 \longrightarrow Yb^{2+} + 2e^-(NH_3)_x \qquad \text{(eq. 23)}$$

(eq. 24) [steroid structure with MeO, $\xrightarrow[NH_3 (liq.)]{\text{excess Yb}}$, product 52%]

(eq. 25) [norbornadiene $\xrightarrow[t\text{-BuOH}]{Yb/NH_3\text{-THF}}$ norbornene, 65%]

$$Ln + ICH_2CH_2I \xrightarrow{THF} LnI_2 + C_2H_4 \qquad (Ln = Sm, Yb) \qquad \text{(eq. 26)}$$

(eq. 27) [isoxazole with CO_2Et $\xrightarrow[MeOH]{SmI_2}$ enamino ketone with NH_2, CO_2Et, 96%]

(eq. 28) [cyclopentanone =O + $ClCH_2OCH_2Ph$ $\xrightarrow{2\ SmI_2}$ $\xrightarrow[Pd/C]{H_2}$ product with OH, CH_2OH]

ketones to saturated ketones, alkynes to *trans*-alkenes and aromatics to 1,4-dihydroaromatics.[46]

The ammonia-solvated electron is stable for several hours at -33 °C, and is a powerful reducing agent (eq. 23).[47]

Careful manipulation of reaction conditions is required to effect the high-yield conversion in eq. 24.

In addition, the Yb/NH_3 system is able to selectively reduce certain double bonds (eq. 25).

Advantages of the ytterbium/ammonia system include the inertness of ytterbium to water and air relative to alkali metal reagents, and the fact that strongly basic hydroxides can be avoided.

Since the initial report in 1977 of the preparation of stable solutions of diiodides of samarium and ytterbium[48] according to eq. 26, an extensive and systematic chemistry has been developed for these systems;[49] this includes deoxygenation (epoxides and sulfoxides), dimerizations (benzyl halides), and reductions (imines and nitro groups to amines; aldehydes to

alcohols; alkyl halides and sulfonate esters to hydrocarbons; α,β-unsaturated esters to saturated esters *via* conjugate reduction). The conversion of aldehydes and ketones to pinacols is rapid and clean.[50]

The fact that this seemingly limited topic merits its own chapter in the sixth volume of the *Handbook on the Physics and Chemistry of Rare Earths* attests to its significance and synthetic potential. In light of Kagan and Namy's treatment of this subject,[49] this discussion will be limited to recent and novel uses typified by the reductive cleavage of isoxazoles[51] shown in eq. 27.

Advantages of the diiodosamarium method included the lack of competing olefin reductions, and the suitability of aprotic media for the reactions. The effectiveness of the diiodide as a one-electron-transfer reagent can be attributed to a high reduction potential $[E_0(aq)\ Sm^{2+}/Sm^{3+}$ equal to 1.55V] that is unusual for species soluble in organic solvents. Other applications include a new method for the hydroxymethylation of carbonyl compounds (eq. 28).[52]

The addition of tetraethylene glycol to a THF solution of SmI_2 changes the characteristic green color to purple. The reducing power of the probable SmI_2/glycol complex was tempered in its affinity for the carbonyl oxygen, thereby suppressing pinacol coupling and allowing the eventual isolation of the desired diol in good yield.

In contrast to ytterbium and samarium, activation of the metal is required in the case of cerium, which is less reactive toward alkyl or aryl halides. The *in situ* generation of an allylcerium iodide in the presence of a ketone produces a homoallylic alcohol in good yield (eq. 29).[53]

Reactions with benzyl iodide proceeded similarly in a chemoselective, one-step procedure. Other functional groups such as ester, nitrile, and aryl bromide were unaffected.

Additionally, several low-valent cerium reagents, *e.g.*, Ce/I_2, transform aldehydes and ketones into pinacols *via* reductive dimerization.[54] The failure of either cerium metal alone or cerium(III) iodide to effect the desired coupling implies that a divalent cerium species is responsible for driving the reaction. Some (but not all) aliphatic carbonyls undergo similar conversions.

One particular advantage of this method, as seen previously, is the efficiency and selectivity in the presence of functional groups such as ester, nitrile, and vinyl halide.

Imamoto *et al.*[55] reported a detailed investigation of carbon-carbon bond formation promoted by cerium amalgam and by organocerium(III) reagents generated from organolithiums and cerium(III) halides. Study of over 100 reactions demonstrated the utility of these reagent systems in a variety of addition reactions including Reformatsky-type and Barbier-type reactions.

Another method of producing useful organocerium reagents involved the treatment of organolithium compounds with cerium(III) iodide[56] (eq. 30).

Samarium(III) iodide was also effective. Reaction temperature of -65 °C appeared to give the cleanest conversions for all organocerium reagents used (*i.e.*, with *n*-BuLi, *sec*-BuLi, MeLi and PhLi in combination with CeI_3). At temperatures above 0°C, reagents having β-hydrogens converted acetophenone to 2,3-dihydroxy-2,3-diphenylbutane and/or phenethyl alcohol; use of methyllithium (having no β-hydrogen) resulted in nucleophilic addition to the carbonyl group.
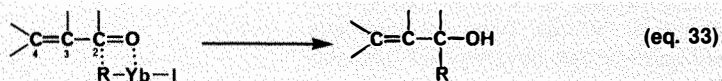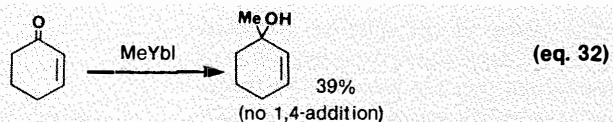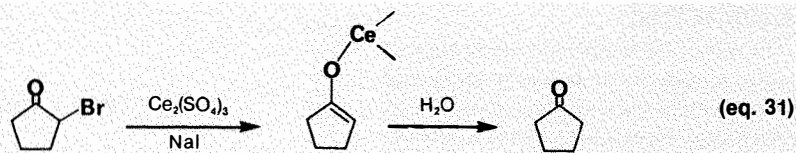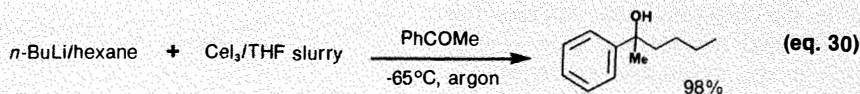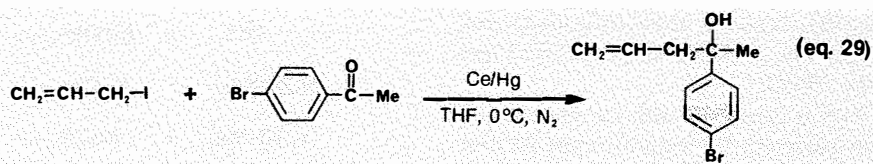
The synthetic potential of these particular lanthanide reagents lies in their distinctive reactivities relative to organolithium reagents: there is very little competing enolization that would result in unreacted ketone.

Ho attacked the problem of hydrodehalogenating α-haloketones by identifying CeI_3 as an appropriate combination of hard acid and soft base moieties for the attack on the carbonyl and halide groups, respectively (eq. 31).[57]

Reaction conditions called for mixing a THF solution of the α-haloketone with an aqueous mixture of cerium(III) sulfate and sodium iodide to produce the cerium iodide intermediate.

The first definitive descriptions of organometallic divalent lanthanide complexes also alluded to applications similar to Grignard methodology.[58,59]

More recently, it was shown that ytterbium metal reacts with alkyl or aryl iodides to give solutions of R-Yb-I species that react smoothly with ketones.[60] Similar reactions could be carried out with europium and samarium, which also have well-defined divalent forms.[5,61]

Diorganomercurials, upon reaction with ytterbium metal, form R_2Yb complexes that convert carbonyl compounds to alcohols *via* reductive coupling.[62]

Reaction of RYbI complexes with α,β-unsaturated carbonyl compounds selectively produces 1,2-addition products[63] in spite of the large ytterbium(II) ionic radius (eq. 32).

A similar Grignard reaction gives product ratios of 2.57:1 with respect to 1,2-addition *vs.* 1,4-addition.

The reaction of PhYbI with chalcone encounters some steric effects that reverse the product ratio for the respective R-M-I reactions: 1,2-addition is 50% for M = Yb, 6% for M = Mg; 1,4-addition is 10% for M = Yb, 94% for M = Mg. This regioselectivity was explained by the preferred attraction of the C-2 "hard site" to the harder lanthanide complex (eq. 33).

More recent studies included the low-temperature phenylytterbium iodide-induced cross-coupling with organic halides in the presence of transition-metal catalysts[64] and the use of methylytterbium iodide to convert active hydrogen compounds such as phenylacetylene or fluorene to corresponding acids or alcohols.[65]

The reactivity of methylytterbium iodide was markedly better than that of methylmagnesium iodide in similar reactions.

In their chapter on organometallic compounds of rare earths, Schumann and Genthe[6] provide a detailed examination of a variety of techniques and products that may develop into reagent systems for organic synthesis; a condensed report of these studies has also been published.[13]

The study of catalytic processes involving rare earths has been advanced by the synthesis and characterization of alkyl and hydride complexes of yttrium,[66] which, in part, were investigated because they provided NMR information *via* Y-H and Y-C

coupling. Although yttrium is not considered a lanthanide, that row of elements exhibits reactivities similar to yttrium, and subsequent comparisons are reasonably valid.

Similar divalent metallocene complexes of ytterbium, *i.e.*, (Cp)$_x$Yb(base/ligand)$_y$, were also shown to act as mild, one-electron reducing agents toward transition-metal carbonyl compounds such as Co$_2$(CO)$_8$,[67] CpCo(CO)$_2$[68] and other organometallic derivatives of cobalt.

In closing, Schumann and Genthe's chapter is recommended for an overview of rapidly developing synthetic organo-metallic chemistry that promises to have implications in the areas of homogeneous as well as heterogeneous organic synthesis. This includes Watson's work on the use of lutetium-hydride and lutetium-methyl complexes to activate C-H bonds.[69–71]

7. Implications for future research

Well into the 1980's we have seen a dramatic increase in the number of articles dealing with many new aspects of lanthanide chemistry. For example, new systems of NMR shift reagents have recently been prepared specifically to allow the extension of this critically useful tool to aqueous solutions.[72] Europium and ytterbium complexes of *S*-carboxymethyloxy-succinate were of primary interest.

New synthetic techniques are also available for application to the unique properties of the rare earths. The development of ultrasound as a synthetic tool in the preparation of colloidal potassium and its subsequent reaction with organic substrates[73] is such an event that could be adapted to organic synthesis using rare earths.

Vacuum deposition techniques have already been extended to the synthesis of samarium and ytterbium hydrogenation catalysts in low-temperature matrices.[74] This method produced solvated metal particles, *e.g.*, Sm-THF, that were 15-20nm across, porous (no preferred orientation), and had a BET surface area of 5.6 m^2/g.

Other imaginative uses of rare earths include the reduction of alkenes, aldehydes and ketones with intermetallic compounds containing absorbed hydrogen, *viz.*, LaNi$_5$H$_6$.[75] The use of du Pont's Nafion® polymer as a support for Cr(III) and Ce(IV) reagents useful in the oxidation of alcohols has also been reported.[76] Such conversions also involved the use of *tert*-butyl hydro-peroxide or sodium bromate as cooxidant.

It is becoming increasingly apparent that the synthetic organic chemist will be able to draw from a broad spectrum of reagents and methodology attributable to the novel chemistry of the lanthanides.

*Abstracted from Long, J.R. "Rare Earths: Implications in Organic Synthesis", in *Handbook on the Physics and Chemistry of Rare Earths*, 1986; Chapter 57, with permission of North Holland Publishing Co: Amsterdam.

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About the Author

Dr. John Long received the B.S. degree from the University of Toledo in 1967 and the Ph.D. degree in 1973 from the Ohio State University where he worked with Professor Sheldon Shore in the area of boron hydride chemistry. Postdoctoral appointments at the Ames Laboratory (Iowa State University) and the National Bureau of Standards afforded him the opportunity to study the chemistry of rare-earth water-splitting cycles and the synthetic potential of laser-induced chemistry, respectively. Presently, Dr. Long is responsible for most aspects of Aldrich's line of inorganic products.

Handbook on the Physics and Chemistry of Rare Earths

The dramatic growth in the use of rare earths in diverse scientific fields has been catalogued by the **Handbook on the Physics and Chemistry of Rare Earths**, K.A. Gschneidner, Jr. and L. Eyring, eds. Beginning in the spring of 1986, Aldrich will offer the full collection of these volumes, which contain comprehensive and critical reviews of research that is invaluable in applications involving catalysts, permanent magnets, lasers, phosphors, polishing materials, chemical probes and reagents, and much more.

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Oxidizing Agent

$NaBrO_2 \cdot 3H_2O$

The recent availability of sodium bromite (as the trihydrate) has given the synthetic organic chemist a new, mild reagent for his arsenal of oxidizing agents.[1] Sodium bromite is the preferred oxidant in the oxidative lactonization of α,ω-diols,[2] and provides good yields of α-bromo ketones from a variety of olefins.[3]

$$RCH=CHR' \xrightarrow[\text{AcOH (aq.)} \; \text{r.t., 5h}]{NaBrO_2} R-\overset{O}{\underset{}{C}}-\underset{Br}{C}HR'$$
(cyclic and acyclic)
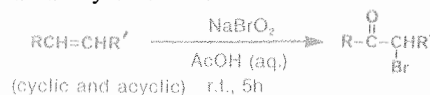
Hoffman degradation of selected amides can be simplified by replacing bromine or chlorine with sodium bromite promoted by sodium bromide.[4]

$$RCONH_2 \xrightarrow[\substack{NaBr \text{ (cat.)} \\ NaOH}]{NaBrO_2} RNH_2$$
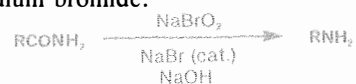
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4-Acetoxy-2-azetidinone:
A Useful Heterocyclic Synthon

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Chemistry Department
University of Bath
Claverton Down
Bath, England

Scheme 1
Nucleophilic displacement reactions of 4-acetoxy-2-azetidinone

(eq. 2)

Scheme 2
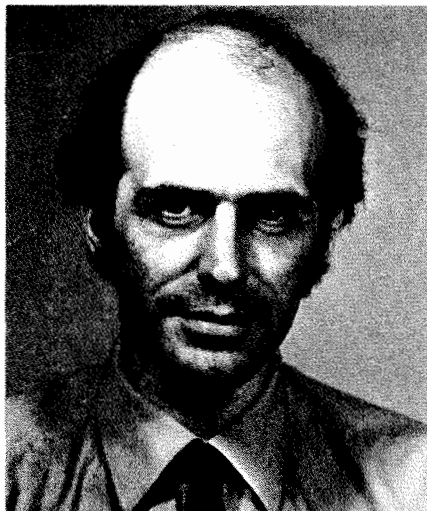
There is a constant demand for simple, stable, readily available, reactive intermediates in organic synthesis. Such compounds should be easily transformed in a minimum number of steps to highly functionalized organic molecules. 4-Acetoxy-2-azetidinone (**1**) meets the above criteria. It is easily prepared in *ca.* 60% yield by the [2 + 2] cycloaddition of chlorosulfonyl isocyanate (CSI) and vinyl acetate (eq. 1). (The reaction of chlorosulfonyl isocyanate with olefins is a general route to mono- and bicyclic β-lactams. This and other reactions of CSI have been reviewed.[5,6])

Reactions of 4-Acetoxy-2-azetidinone

Although there are four reactive sites in the ring of the β-lactam **1**, this overview will concern itself only with nucleophilic displacement reactions of the 4-acetoxy group. The acetate moiety is readily displaced by a wide range of nucleophiles under mild conditions (Scheme 1).

Nucleophilic displacement reactions of 4-acetoxy-2-azetidinone

Sulfur nucleophiles

The reaction of **1** with sulfur nucleophiles[2] is a high-yielding process in aqueous or alcoholic solution at room temperature. Sulfinic acids can also be used as nucleophiles in this displacement reaction affording 4-sulfonylazetidin-2-ones (**2**).
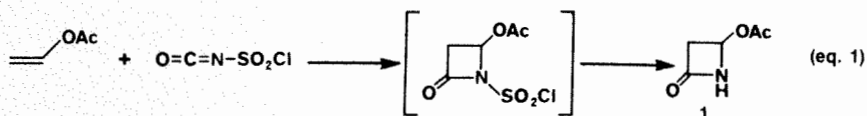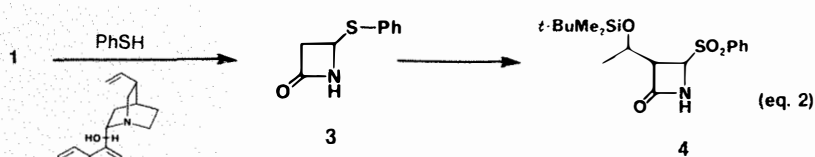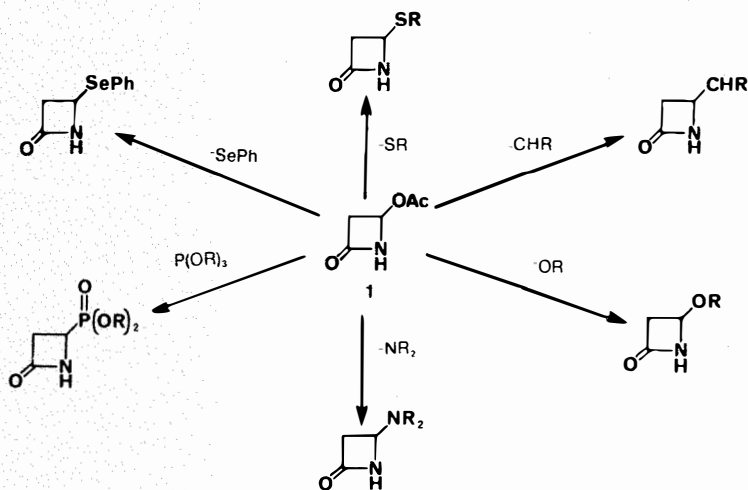
2
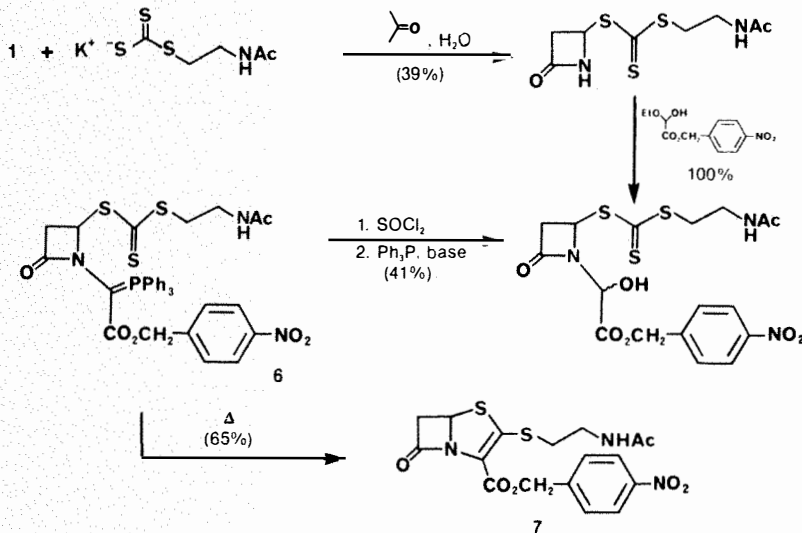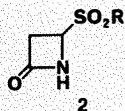
Asymmetric induction in this reaction has been described.[7] 1 was treated with thiophenol in the presence of cinchonidine[8] providing (+)-4-(phenylthio)azetidin-2-one (3) in 79% chemical and 38% optical yields (eq. 2). (Optically pure material was obtained by crystallization. Absolute configuration and optical purity were determined by converting 3 to the known sulfone 4.) This sequence was used in an asymmetric synthesis of (+)-thienamycin (5).

5
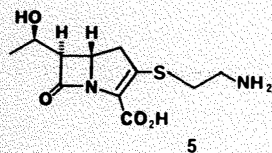
The reaction of 2 with thiols is of considerable importance as it allows rapid entry to penicillin and penem ring systems. Notable syntheses employing this approach have been described.[8-11] One example is shown in Scheme 2. The key reaction in this sequence was the trithiocarbonate 6 serving as a carbonyl-like component in a Wittig reaction providing the penem nucleus 7.

Sulfoxides are known to undergo a variety of interesting rearrangement reactions and this facet of sulfur chemistry has been employed in a novel synthesis of penems[12] (Scheme 3). The allylic sulfoxide 8 may be considered as both a masked thiol and a sulfonate ester which undergoes smooth rearrangement and cyclization to thiacephem 9. This interesting compound may be desulfurized with concomitant ring contraction to penem (10). It was noted that if water or ethanol was added to the thermolysis of 8, a higher yield of 9 was obtained.

The reaction of 1 with thiols has also been applied to the synthesis of novel β-lactam ring systems, e.g., 11[13] and 12.[14]

11   12
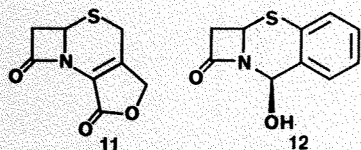
The articles cited in references 15-22 discuss further reactions involving thiols. Two further useful reactions[2] of 4-thioazetidin-2-ones are indicated in eqs. 3 and 4.

Azetidin-2-one (13, R = Me) is a stable distillable oil in contrast to the 4-bromo derivative which decomposes above -18 °C.[2] Chloroazetidin-2-ones (13) are also useful electrophiles in functionalization at C-4 of the β-lactam ring.


Scheme 3

(eq. 3)

R = Me or Me_2Si-t-Bu

(eq. 4)

(eq. 5)

14

R = n-butyl, allyl, vinyl, ethynyl, hexenyl
M = Li, Cl, Mg, Cu

(eq. 6)

14   20%   40%

Scheme 4

(eq. 7)
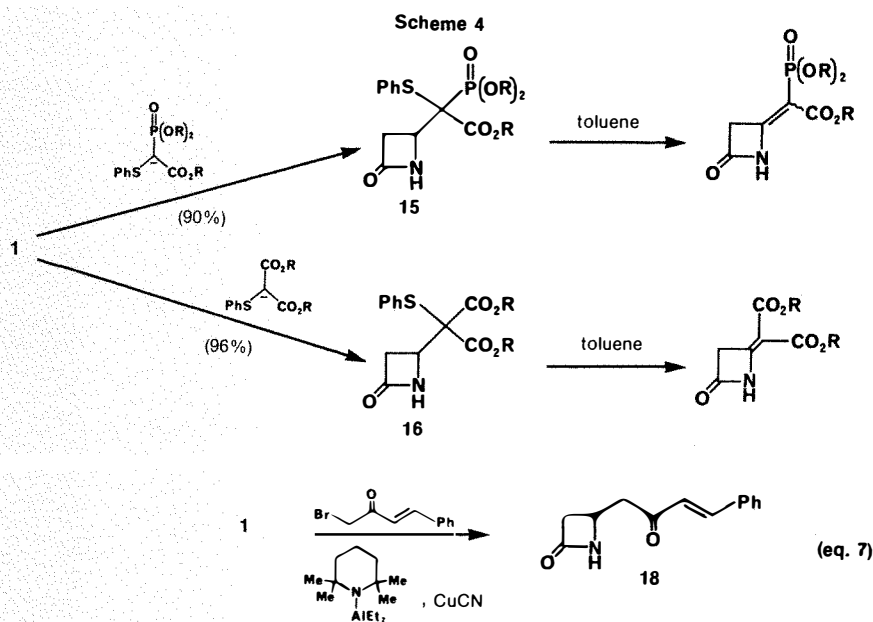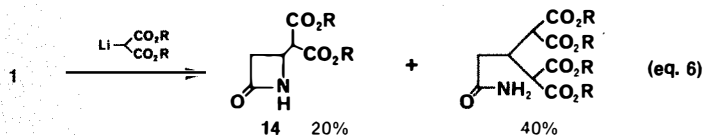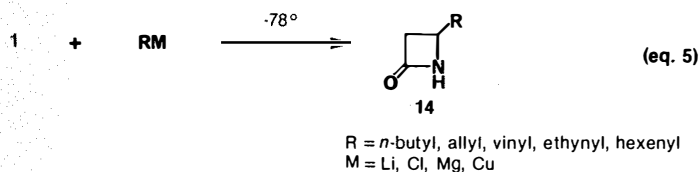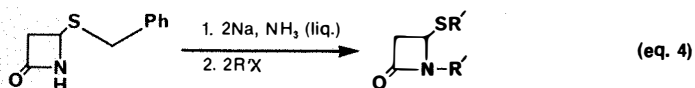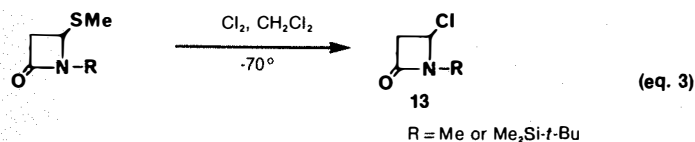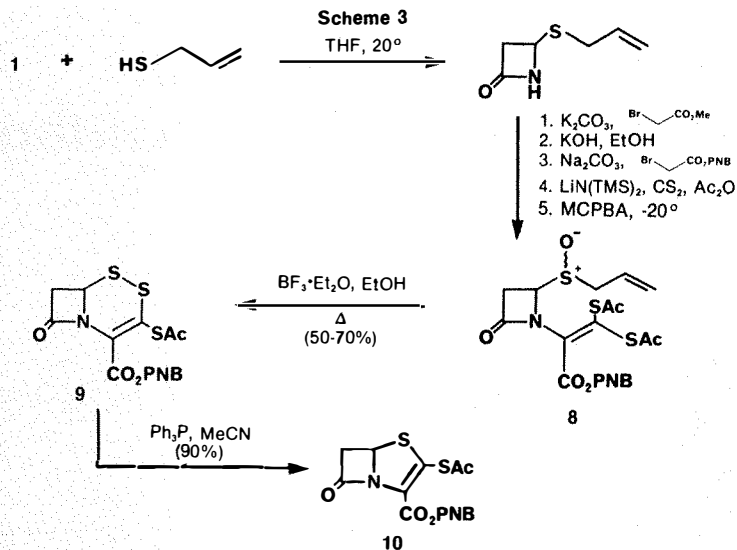
Carbon nucleophiles

Carbanions readily participate in a similar displacement reaction[7, 26-31] (eq. 5). It has been noted[24] that the reaction of **1** with Grignard reagents was inefficient and low yields of **14** were obtained; however, use of 4-(phenylsulfonyl)azetidin-2-one as the electrophile markedly improved the yields of **14**. If **14** has acidic hydrogen atoms in the 4-substituent, then significant ring cleavage occurs[23] (eq. 6).

It was observed[26-28] that if further deprotonation of **14** could be suppressed then yields should be maximized. This may be achieved by utilizing a tertiary stabilized carbanion[26,27] (Scheme 4).

This approach was successfully employed in a synthesis of novel 1-dethiacephems[27] **17**.
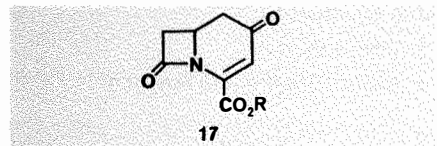
Aluminum enolates of α,β-unsaturated ketones also participate in C-4 carbon-carbon bond formation[29] (eq. 7). Inverse addition of the enolate and the presence of cuprous cyanide (10 mol %) result in moderate yields of **18**.

Lewis acid-catalyzed addition of silyl enol ethers to **1** results in efficient carbon-carbon bond formation[30] (eq. 8). Zinc iodide was found to be the most effective catalyst.

An analogous reaction has been employed[31] in an efficient synthesis of thienamycin from 6-aminopenicillanic acid (Scheme 5).

Boron trifluoride is an effective catalyst for the reaction of allyl silanes with **1** (eq. 9). The choice and amount of Lewis acid are important; *e.g.*, tin tetrachloride is ineffective.

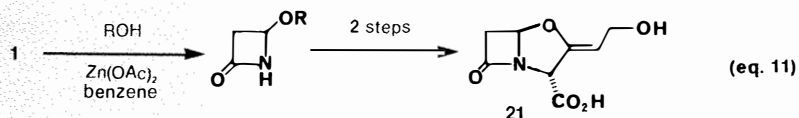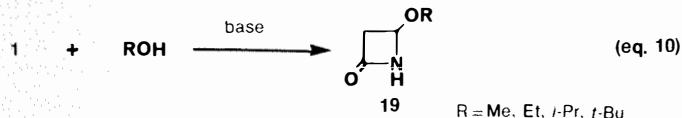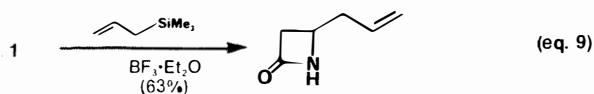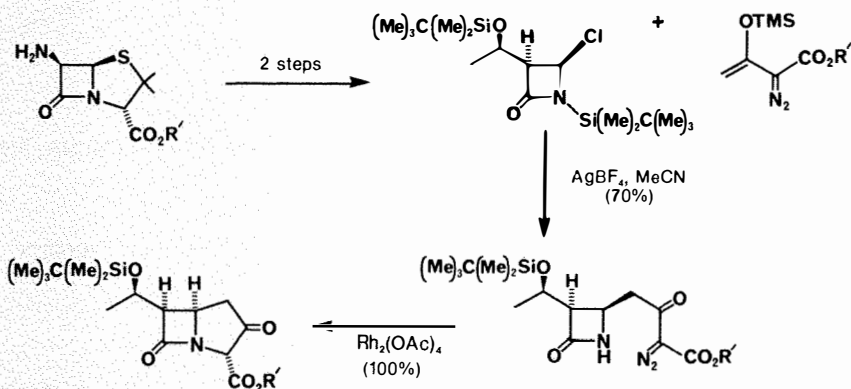Further examples are to be found in the articles cited in references 32-38.

Oxygen nucleophiles

Four examples of oxygen nucleophiles were reported initially by Clauss[2] (eq. 10).
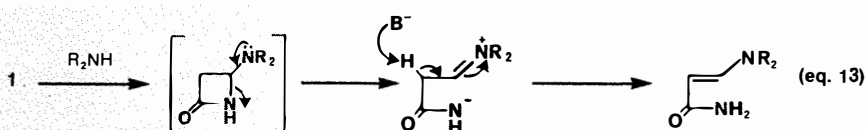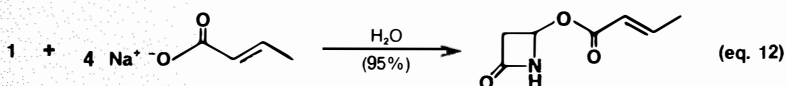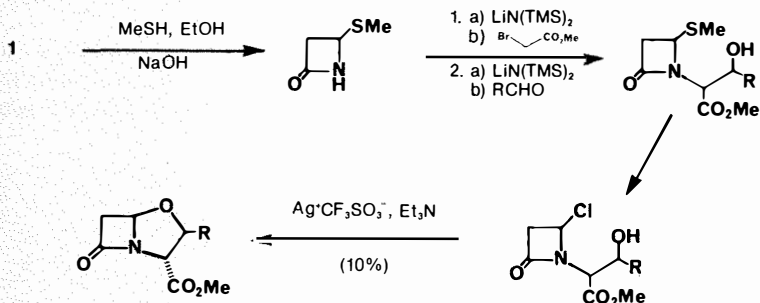
Yields of **19** varied from 18% (R = Me) to 15% (R = *t*-Bu). Phenoxide ions also react; however, the strongly basic reaction conditions lead to low yields of isolated β-lactams[39,40] (**20**).
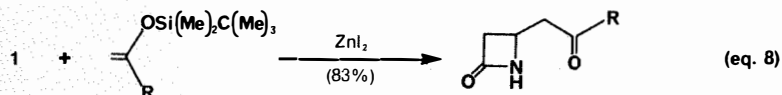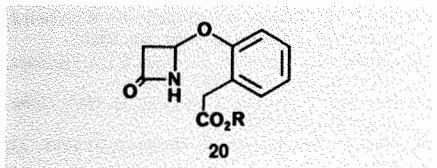
With the discovery of elavulanic acid[41,42] (21), a naturally occurring β-lactamase inhibitor, the reaction in eq. 10 became significant. Lewis acid-catalyzed displacement of acetate from 1 was employed[43,44] to produce key intermediates for the construction of the 7-oxo-4-oxabicyclo[3.2.0]heptane ring system 21 (eq. 11).

Silver is also effective in this type of reaction[45] (Scheme 6).

Carboxylate anions also undergo displacement reactions with 1[46] (eq. 12).

For further examples of oxygen nucleophiles, see references 47-52.

Nitrogen nucleophiles

Several nitrogen nucleophiles have been studied: azides, phthalimides and amines.[9] The first two afford the expected products 22 and 23 in good yields. Amines give ring-cleavage products, presumably via the process outlined in eq. 13.
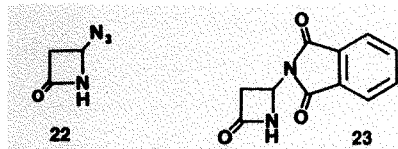

The 4-azidoazetidin-2-one 22 has been used as a key intermediate in the synthesis of a number of unnatural bicyclic β-lactams of the types 24 and 25. A further study of
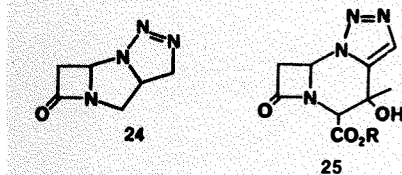
nitrogen nucleophile displacements was carried out leading to a variety of novel ring systems[54] (Scheme 7).

The base employed was potassium t-butoxide/18-crown-6, which gave reasonable yields of 26 and 27. It was noted that N-tosylethanolamine also produced small amounts of the 4-alkoxyazetidin-2-one 28. These β-lactams were further modified to produce novel bicyclic ring systems.
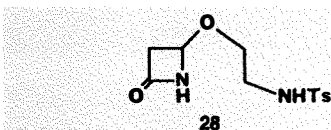
Phosphorus nucleophiles

Original work by Clauss et al.[2] reported only one example of phosphorus nucleophiles (eq. 14).

This reaction was subsequently investigated in detail[55-57] and extended to include a wide range of trivalent phosphorus esters (Tables 1 and 2).
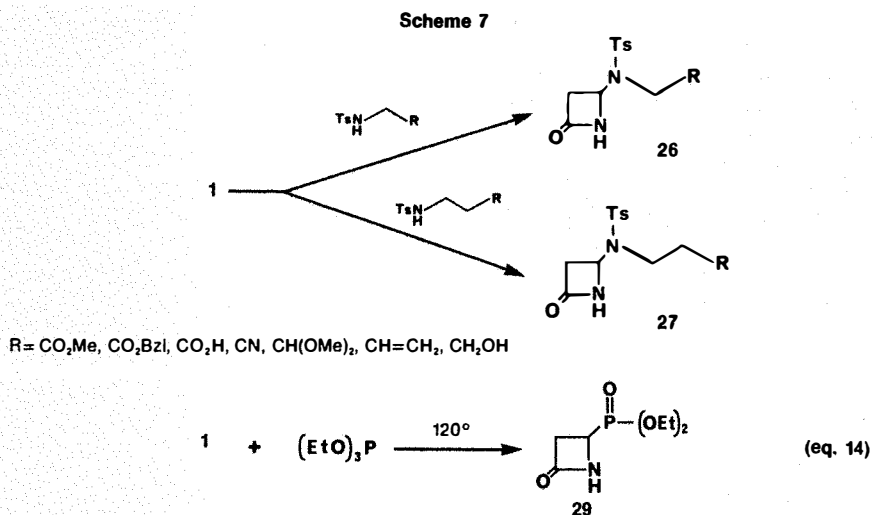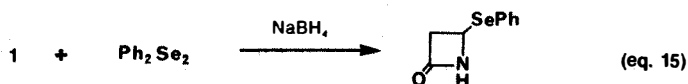
Scheme 7

R = CO₂Me, CO₂Bzl, CO₂H, CN, CH(OMe)₂, CH=CH₂, CH₂OH

$$1 \quad + \quad (EtO)_3P \quad \xrightarrow{120°} \quad \text{[structure 29]} \qquad (eq.\ 14)$$

Table 1
Phosphites employed in equation 14

1. $(MeO)_3P$	3. $(PhCH_2O)_3P$
2. $(EtO)_3P$	4. $(CCl_3CH_2O)_3P$ — no reaction

Table 2
Phosphonites employed in equation 14

1. $MeP(OEt)_2$
2. $MeP(OCH_2Ph)_2$
3. $MeP(OCH_2CCl_3)_2$

$$1 \quad + \quad Ph_2Se_2 \quad \xrightarrow{NaBH_4} \quad \text{[structure with SePh]} \qquad (eq.\ 15)$$

These organophosphorus compounds have been utilized to synthesize novel phosphorus-containing bicyclic β-lactams 30,[56] 31,[58] and 32.[59]
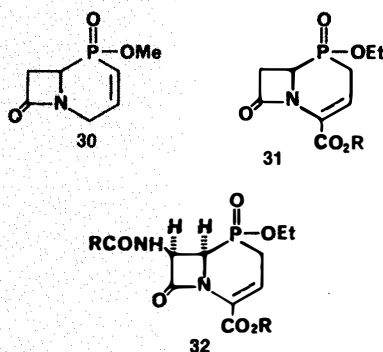
Furthermore, cleavage of the β-lactam bond in 29 leads directly to novel aminophosphonic and aminophosphinic acids[55,57] which exhibit interesting biological activity.

Selenium nucleophiles

One example has been reported[28] (eq. 15).

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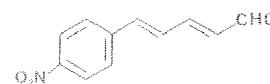59) Idem *ibid.* **1984**, *25*, 1737.

About the Author

Dr. Stuart J. Mickel received the B.Sc. degree in 1979 from Heriot-Watt University, Edinburgh, and the Ph.D. degree from the University of Bath in 1982, under the supervision of Professor Malcolm M. Campbell. His doctoral research concentrated on the synthesis of novel organophosphorus derivatives of β-lactams. In 1982 he studied at Harvard University as a Fulbright Scholar, where he worked with Professor E.J. Corey. He then returned to the University of Bath as a Research Officer. He is presently a Senior Research Chemist within the Central Research Group of CIBA-GEIGY PLC, Manchester. His current research interests lie in organophosphorus chemistry and natural product synthesis.

"Spy Dust" Ingredient?

As a result of the recent news reports (cited below) regarding the use of tracer chemicals by the Soviet KGB to track the activities of United States citizens in the Soviet Union, we have had several inquiries for **5-(4-nitrophenyl)-2,4-pentadienal**, thought to be an ingredient in the tracer powder.

Chem. Eng. News **1985**, August 26, p 6. *Science* **1985**, *229*, 952, 1071.

Since 1977, the chemical literature has reflected a dramatic increase in research on lanthanides in organic synthesis. Several recent reviews[1-5] treat the following areas:

Hetero-Diels-Alder Catalysis

Lanthanide shift reagents mediate an exciting variety of condensation reactions.

(ref. 6)
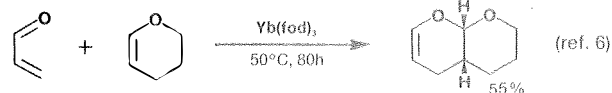
Special features of these systems include distinct chiral-shift-reagent interactions with chiral auxiliaries in hetero-Diels-Alder reactions, as well as compatibility with dienes having sensitive functionalities.

Aldol Coupling

Cerium enolates (e.g., 1), generated from lithium enolates with anhydrous cerium(III) chloride, give less retro-aldol and cross-enolization products in the aldol reaction; the reaction conditions are quite mild.[7]
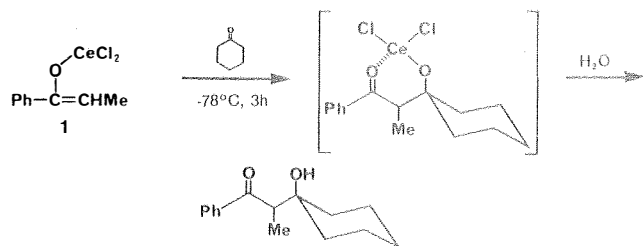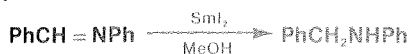

Low-Valent Reductions

The high-yield preparation of samarium(II) and ytterbium(II) species in THF[8] according to the reaction

$$Sm + ICH_2CH_2I \longrightarrow SmI_2 + C_2H_4$$

has provided new routes to carbon-carbon bond formation via reductive coupling,[9] and a variety of functional-group transformations.[10]

$$PhCH = NPh \xrightarrow[MeOH]{SmI_2} PhCH_2NHPh$$

The SmI_2 reagent is also useful as a one-electron transfer reagent,[9] and promotes the reductive ring opening of isoxazoles to enamino ketones.[11]

Low-valent reductions involving cerium reaction systems[12] and organoytterbium reagents[13] have also been developed and compared with Grignard methodology.[14]

Selective Reductions with NaBH₄

The cerium(III) chloride/sodium borohydride tandem is well established in the area of selective reductions.[15] The mild conditions have little effect on other functionalities, and the reaction proceeds rapidly under routine atmospheric conditions, with any of several commercially available hydrated lanthanide chloride salts. The selectivity can be inter- or intramolecular, and ketones are reduced preferentially over aldehydes.

The selective reduction of a less reactive carbonyl group in the presence of a more reactive one exploits the catalyst's ability to promote the protection of the more reactive carbonyl as a monoketal intermediate.[16] In this case erbium trichloride was effective.
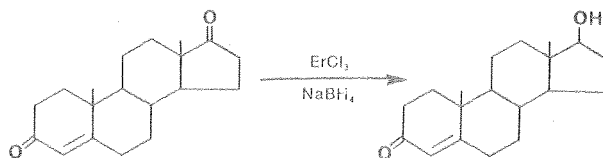
Other Applications

Ho[17] used an aqueous mixture of cerium(III) sulfate and NaI to produce a CeI_3 species capable of hydrodehalogenating α-halo ketones in THF.
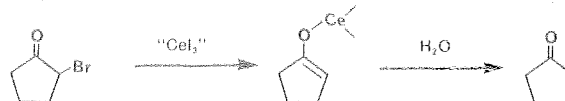
Aldehydes, ketones and alkenes can be reduced by reaction with intermetallic compounds containing absorbed hydrogen, e.g., $LaNi_5H_6$.[18]

In addition to offering a full line of lanthanide metals and salts for synthesis, the 1986-1987 Aldrich Catalog/Handbook includes a variety of hydrogen-storage alloys featuring rare-earth components. Anhydrous halides and standard solutions are also available.

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The Aldrich *FIRST* System of Information Retrieval – An Update

David W. Griffiths
Aldrich Chemical Co., Inc.

The Aldrich *FIRST* (*F*ragment *I*nformation *R*etrieval of *S*tructures) system was introduced more than fifteen years ago[1] both as a service to our customers and as a sales-generating tool. Over the years, we have processed many thousands of requests and have mailed many computer printouts of structurally related compounds to our customers as part of our free *Computer Search Service*. Since these computer-generated listings contain items offered through the Alfred Bader Library of Rare Chemicals as well as those products added to the Aldrich inventory between catalogs, our customers will always have access to those compounds in our complete inventory which meet their requirements in various categories of specific interest to them.

From the inception of the *FIRST* system, it was possible to retrieve certain specifically oriented benzene derivatives.[2] At that time, the system was most successful for nitrogen-containing benzene derivatives

Table II
Benzene Ring Substitution Patterns
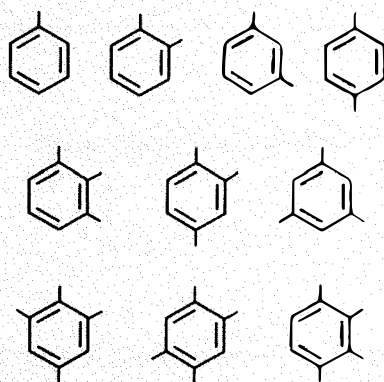
Note: In an unsymmetrical multi-substituted benzene derivative such as

any computer-generated listing containing this pattern will include 2,4- as well as 3,4- and 2,5-derivatives since the position of the "parent" functional group is not specified.

Table I
Retrieval of Specifically Oriented Benzene Derivatives

Class of Compound	Structure Fragments Required (other than benzene ring)
1,2-phenylenediamines	$-NH_2$, N–C–C–N
1,3-phenylenediamines	$-NH_2$, N–C–C–C–N
1,4-phenylenediamines	$-NH_2$, N–C–C–C–C–N
2-aminophenols	$-NH_2$, –OH, N–C–C–O
2-aminobenzenethiols	$-NH_2$, –SH, N–C–C–S
2-nitroanilines	$-NH_2$, $-NO_2$, N–C–C–N
3-nitroanilines	$-NH_2$, $-NO_2$, N–C–C–C–N
4-nitroanilines	$-NH_2$, $-NO_2$, N–C–C–C–C–N
picrylamines (2,4,6-trinitro-anilines)	$-NH_2$, $-NO_2$, N–C–C–N, N–C–C–C–N, N–C–C–C–C–N

Table III
Benzene Derivatives

A. 5-Substituted salicylic acids

Technique — request [structure] , –OH and $-\overset{\overset{\text{O}}{\|}}{\text{C}}$–OH

S37987-5	5-(Aminomethyl)salicylic acid
S44938-5	5-(Methylthio)salicylic acid
S63768-8	5-(Hydrazinosulfonyl)salicylic acid
14,618-8	5-Methoxysalicylic acid, 98%
15,270-6	5-Fluorosalicylic acid, 99%
F1,760-1	5-Formylsalicylic acid, 97%

B. 3,5-Disubstituted phenols

Technique — request [structure] and –OH.

|	
S59979-4	3,5-Diethoxyphenol
S65909-6	3-*tert*-Butyl-5-methylphenol
S70658-2	3,5-Diethylphenol
13,263-2	3,5-Dimethoxyphenol, 99%
24,708-1	3,5-Bis(trifluoromethyl)phenol, 96%
D7,060-0	3,5-Dichlorophenol, 99%

C. 2,4,5-Trisubstituted phenyl ethers

Technique — request [structure] and C–O–C.

|	
S36019-8	2,4-Dibromo-5-methylanisole
S41232-5	4-(2,4,5-Trichlorophenoxy)butyric acid
S67828-7	2-(2,4,5-Trichlorophenoxy)acetyl chloride
15,205-6	2,5-Dimethyl-*p*-anisaldehyde, 99%
16,186-1	2-(2,4,5-Trichlorophenoxy)propionic acid, 97%
19,712-2	2,4,5-Trichlorophenoxyacetic acid, 98%

Table IV
Pyridine Derivatives

A. 2,6-Disubstituted pyridines

Technique — request [structure] and disubstitution

while excluding [structure] and [structure]

S44633-5	2-Chloro-6-ethoxypyridine
S65920-7	2-Cyano-6-methylpyridine
15,436-9	2,6-Pyridinedimethanol, 98%
19,892-7	2,6-Diphenylpyridine, 97 + %
25,600-5	2,6-Pyridinedicarboxaldehyde, 98%
P6,380-8	2,6-Pyridinedicarboxylic acid, 99%

B. 3-Monosubstituted pyridines

Technique — request [structure] and monosubstitution.

S59655-8	3-Iodopyridine
S66833-8	2-(3-Pyridyl)-2-propanol
19,666-5	3-Fluoropyridine, 99%
28,113-1	Methyl 3-pyridylcarbamate, 99%
H5,700-9	3-Hydroxypyridine, 98%
P6,480-4	3-Pyridinesulfonic acid, 97%

C. Pentasubstituted pyridines

Technique — request [structure] , [structure] and [structure]

while excluding mono- and disubstitution.

S44350-6	Diethyl 2,4,6-trimethyl-3,5-pyridinedicarboxylate
S59731-7	3,4,5,6-Tetrachloropicolinonitrile
13,800-2	Pentachloropyridine, 98%
15,879-8	Pentafluoropyridine, 99 + %, GOLD LABEL
22,562-2	4-Amino-3,5,6-trichloropicolinic acid, tech.
24,801-0	3,5-Dichloro-2,4,6-trifluoropyridine, 99%

Table V
Naphthalene Derivatives

A. 2-Monosubstituted naphthalenes

Technique — request [structure] and monosubstitution.

S56197-5	2-Ethoxynaphthalene
S64805-1	2-Naphthyl propyl ether
S73146-3	2-Iodonaphthalene
18,024-6	2-Naphthoic acid, 99%
27,084-9	2-Naphthalenethiol, 99 + %
A6,640-5	2-Aminonaphthalene

B. 1,4-Disubstituted naphthalenes

Technique — request [structure] and disubstitution

while excluding [structure]

S39133-6	N-(4-Cyano-1-naphthyl)acetamide
S67703-5	4-Methoxy-1-methylnaphthalene
10,324-1	4-Methoxy-1-naphthaldehyde, 99%
22,627-0	4-Dimethylamino-1-naphthyl isothiocyanate, 98%
25,061-9	4-Amino-1-naphthalenesulfonic acid, 97%
A4,340-5	1-Amino-4-bromonaphthalene, 97%

C. 1,2,4-Trisubstituted naphthalenes

Technique — request [structure] and [structure]

while excluding mono- and disubstitution.

S59591-8	2,4-Dibromo-1-methoxynaphthalene
S62969-3	4-Bromo-1-hydroxy-2-naphthoic acid
14,354-5	4-Fluorosulfonyl-1-hydroxy-2-naphthoic acid, 99%
22,416-2	4-Chloro-1-hydroxy-2-naphthoic acid, 95%
22,728-5	1-Diazo-2-naphthol-4-sulfonic acid
25,197-6	2,4-Dichloro-1-naphthol, 98%

because a large number of nitrogen-containing structural fragments had been coded into it (see Table I).

Thus, this type of retrieval could account for only a small percentage of the total number of benzene derivatives offered by Aldrich. Moreover, it was not possible to retrieve benzene derivatives having a specific substituent orientation without taking into account the actual types of substituents, as were being requested more frequently. Therefore, the need for additional structure fragment codes was clearly apparent.

By assigning a separate fragment code to each of ten benzene ring substitution patterns (Table II), a greater degree of flexibility was introduced into the Aldrich *FIRST* system. It is now possible to produce listings of such diverse benzene derivatives as 5-substituted salicylic acids, 3,5-disubstituted phenols and 2,4,5-trisubstituted phenyl ethers, as exemplified in Table III.
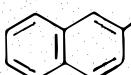
A similar line of reasoning proved useful in the areas of pyridine and naphthalene derivatives. Separate fragment codes were assigned to pyridines substituted in the 2-, 3- and 4- positions, respectively, and to pyridines which are either mono- or disubstituted. Thus, it is possible to produce listings of 2,6-disubstituted pyridines, 3-monosubstituted pyridines and pentasubstituted pyridines (see Table IV).

Separate fragment codes were also assigned to naphthalenes substituted in the 1- and 2- positions (since all of the main substitution points in naphthalene are either the 1- or the 2- position) and to those naphthalenes which are either mono- or disubstituted. Thus, it is possible to generate listings of 2-monosubstituted naphthalenes, 1,4-disubstituted naphthalenes and 1,2,4-trisubstituted naphthalenes (see Table V).

These improvements in coding of substitution patterns in benzene, pyridine and naphthalene derivatives have greatly increased the utility of the Aldrich *FIRST* system.
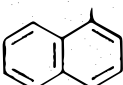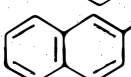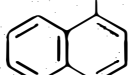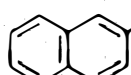
By using our free computer search service as described in our Catalog/Handbook, we hope our customers will find this system to be to their advantage.

References.
1) Buth, W.F. *Aldrichim. Acta*, 1968, *1*(1), 3.
2) Griffiths, D.W. *ibid.* 1974, *7*(2), 35.

*Trifluoroacetic Acid
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