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Chiral Oxazolidinones in Asymmetric Synthesis

Preparation and Reactivity of Acyclic (Pentadienyl)iron(1+) Cations: Applications to Organic Synthesis

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About our Cover

The painting on our cover, *Attachment* (oil on canvas, 99 x 79.5cm), was painted by Sir Edwin Henry Landseer (1802-1873) in 1829. Landseer, considered in his day England's greatest painter, was known for his engaging animal images and portraits of pets, including those of Queen Victoria. Dogs are particularly prominent in his work, and none of his canine heroes so well captures the spirit of Victorian sentiment as the terrier depicted in *Attachment*. The painting is an illustration of Sir Walter Scott's short poem "Helvellyn", the story of a young man's tragic death in 1805 and his faithful terrier's long vigil beside the lifeless body. The young man suffered an accidental fall while on a climbing expedition to the Helvellyn mountain in Scotland's Lake District, and his remains lay undiscovered for three months. Scott's poem is the only account of the incident; no additional verification has ever appeared.

As depicted by Landseer, the story's setting is a dramatic backdrop of stormy sky and large imposing faces of bare rock that suggest dizzying heights. The body lies close to the edge of a high cliff, and the juxtaposition of strong light and looming shadow heightens the drama. The brightly colored areas direct the viewer's gaze to the attentive canine, who gingerly paws at her master's windswept cloak in hopes of some response.

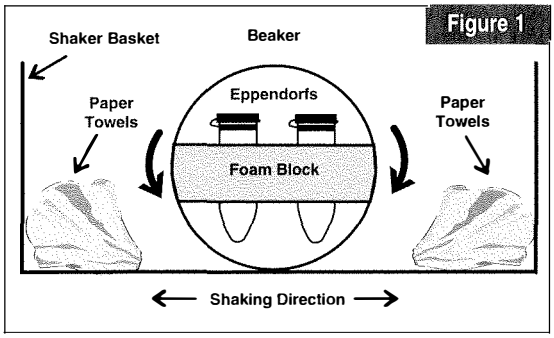
This painting is in the collection of The Saint Louis Art Museum, gift of Mrs. Eugene A. Perry in memory of her mother, Mrs. Claude Kirkpatrick.

Lab Notes

Inversion Mixing on a Reciprocating Shaker

When small volumes are incubated with an affinity resin, the resin must be maintained in suspension, yet violent agitation will spread the resin on the walls of the tube. If a hematology mixer is not available, a reciprocating shaker can be used for the gentle inversion of Eppendorf tubes. A block of foam is cut to fit inside a beaker and the Eppendorf tubes are pushed into slots cut through the block (**Figure 1**). The beaker is laid on its side in the carrier basket of the shaker with its axis perpendicular to the direction of shaking. To prevent jarring impacts of the beaker with the basket walls, the sides are cushioned with crumpled-up paper towels. When the speed is set to give a rolling of the beaker, the resin continuously drops through the solution and surface tension maintains the solution at the bottom of the Eppendorf tube. This mixing device should also work with platform mixers (if a box is used to restrain the beaker!) and with the incubator baths (at a lower water level) found in biochemistry laboratories.

Figure 1

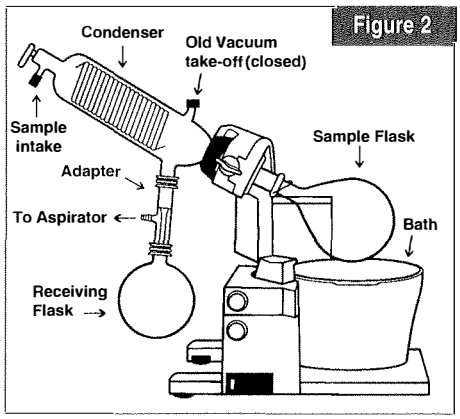


Vasek A. Mezl, Associate Professor
Department of Biochemistry, University of Ottawa
451 Smyth Road
Ottawa, Ontario K1H 8M5, Canada

Glass Adapter for Increasing Rotorvaping Efficiency

Submitted is an adapter that increases the efficiency of solvent evaporation under reduced pressure. Please note that this is a *general* design and may be modified to fit individual requirements dictated by the type of apparatus employed. I have used a rotary type apparatus that had the vacuum take-off exit directly opposite to the opening leading to collection of the distillate. I observed that there was competition between the two paths the distillate could take. The distillate could go to the vacuum take-off opening, as well as to the opening of the distillate-collection lead, resulting in a diminished efficiency of the distillation process. This latter is a function of the vapor pressure of the distillate at these two exits. The addition of the adapter to the apparatus altered the path of the vacuum take-off lead in such a fashion that now the distillate was collected in a flask cooled to about -35 °C. Thus, the vapor pressure of the distillate was not contributing negatively to the reduced pressure of the vacuum source, and was leading to an increased efficiency of the process. Naturally, the *old* vacuum take-off lead was closed during the distillation. **Figure 2** shows the apparatus with the adapter. It is an inexpensive addition that saves time and materials. May all your existing reduced-pressure problems evaporate with this adapter.

Figure 2



Respectfully submitted,
Harry E. Hadd, Ph.D., Associate Professor Emeritus
Indiana University Medical School
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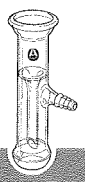
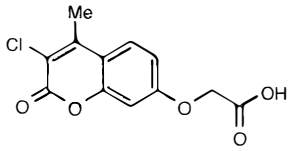


"Please Bother Us."

by

Jai Nagarkatti, President

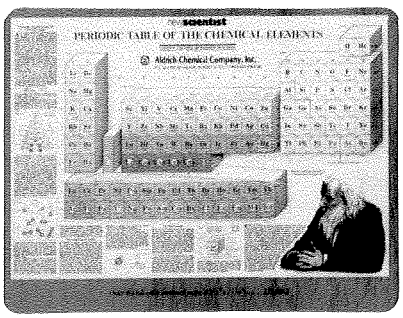


Dr. Lawrence Phillips of the National Cancer Institute kindly suggested that we make this coumarin derivative. The acid chloride is used as a fluorescent, precolumn derivatizing reagent for liquid chromatographic analysis of hydroxylated natural products. The postcolumn detection sensitivity is much higher for the 3-chloro-substituted compound than for the unsubstituted analog.

Phillips, L.R. et al. *Synth. Commun.* **1996**, *26*, 1805.

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, *Aldrichimica Acta*). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. **Z15,000-2**). If we publish your *Lab Note*, you will also receive an Aldrich periodic table turbo mouse pad (Cat. No. **Z24,409-0**). It is Teflon®-coated, 8½ x 11in., with a full-color periodic table on the front. We reserve the right to retain all entries for future consideration.



Chiral Oxazolidinones in Asymmetric Synthesis[1]

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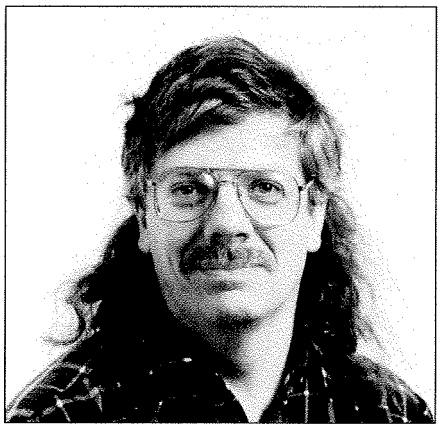
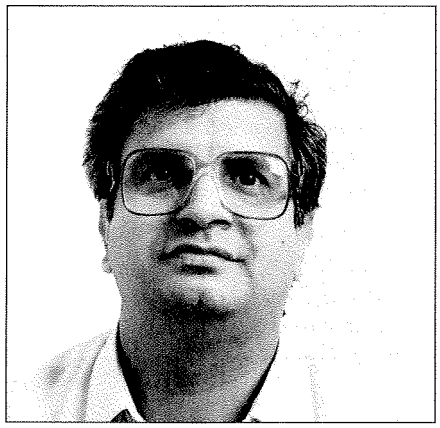
Abstract

Chiral oxazolidinones (Evans' chiral auxiliaries) have been utilized as auxiliaries for a wide range of asymmetric transformations. The methodology has been highly successful in the stereoselective construction of a number of natural products, antibiotics, and other medicinally important compounds. The present review is focused on the utility of oxazolidinones in synthesis.





1. Chiral Auxiliaries

The use of a chiral auxiliary in a chemical reaction parallels, in many regards, that of a protecting group: The moiety must be attached to the substrate molecule, it must be stable to the reaction conditions, and it must be removed at the end of the reaction. However, unlike a protecting group that is a passive partner in the reaction, a chiral auxiliary must provide the vehicle for asymmetric induction. This asymmetric induction can also be accomplished through non-interactive means, such as by sterically blocking reaction at one face of the substrate. A chiral auxiliary doubles as a protecting group in some instances; this will be illustrated with *N*-acyl oxazolidinones where the parent carboxylic acid would react under identical reaction conditions.

Unlike chiral catalysts, auxiliaries are used stoichiometrically since they allow for asymmetric induction by modifying the structure of the substrate molecule. A low yield or inefficient process for the attachment of the moiety may be tolerated if this step is at the beginning of a synthetic sequence and the starting materials are readily available. However, the procedure needs to be applicable to a wide variety of compounds. Ideally, the successful auxiliary would be introduced in high yield; be available in a very high optical purity; and, for use on a large scale, be available at a reasonable cost. Historically, molecular units that require a large number of steps for their preparation from readily available materials will not find widespread acceptance.[2] In addition, derivatives of the chiral auxiliary should preferably be crystalline. This permits removal of diastereomeric impurities by crystallization and leads to an increase in the apparent selectivity.

As already mentioned, the moiety should be stable to the desired reaction conditions and provide high degrees of asymmetric induction. If further reactions are required, the unit should not be destroyed by them, nor interfere with subsequent asymmetric inductions. Double asymmetric induction can be a great benefit, but mismatched pairs usually cause problems. The auxiliary should not hinder reactions at the desired site and, preferably, should promote the needed reaction.

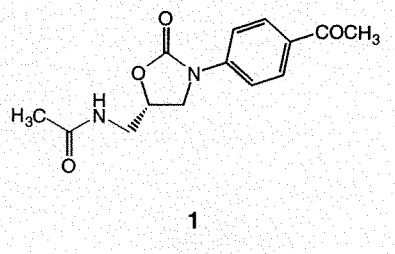
The chiral auxiliary should be removable under mild conditions. This allows for delicate functionality elsewhere in the molecule to be present without the need for protection. In addition, the removal procedure should be general, proceed in high yield, and should not destroy the chiral auxiliary unit, as the latter may be expensive. This would permit recycling of the chiral unit. Many chiral auxiliaries fail to fulfill this last requirement. Once removed, the chiral auxiliary should be easily separable from the desired product. If a reaction has to be scaled up, the need for a chromatographic separation could create problems.

2. Oxazolidinones and *N*-Acyl Oxazolidinone Derivatives

2-Oxazolidinones are widely used as chiral auxiliaries, and the resulting degree of asymmetric induction can be high in transformations ranging from alkylations to aldol reactions and to Diels-Alder reactions. Rather than list these reactions, this review will illustrate how oxazolidinones work using the syntheses of complex molecules as examples. Only the key steps involving the chiral auxiliary will be considered.

Some oxazolidinones are biologically active in their own right. Such an example is DuP 721 (**1**), an orally active synthetic antibacterial agent.[3-6]

Chiral oxazolidinone auxiliaries provide access to chiral enolates, and those described



1

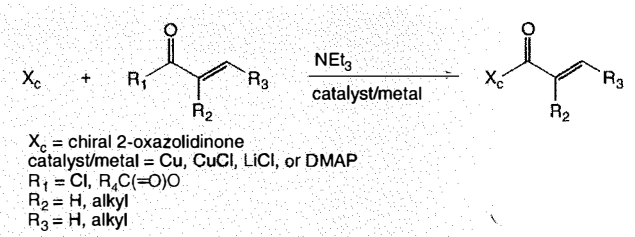
in this review have been used in the synthesis of several natural products, macrolides, and antibiotics.[7-16]

The numerous routes to oxazolidinones have been reviewed elsewhere.[1] Many of the common oxazolidinones are now commercially available, even at scale. The *N*-functionalization of the heterocyclic system is, therefore, the first key step in a synthetic sequence.

N-Acyl oxazolidinones are readily accessible by reaction of *n*-butyllithium with the auxiliary, followed by addition of acid chlorides.[17-19] Lithiated oxazolidinones also react with mixed anhydrides to form *N*-acyl imides.[10,13]

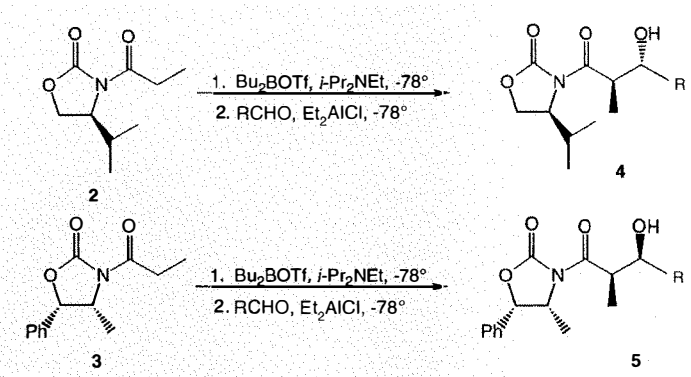
Recently, several new procedures for the *N*-acylation of chiral oxazolidinones have been put forward (**Scheme 1**). These avoid the use of *n*-BuLi and circumvent the problems associated with the polymerization of acroyl chlorides under the reaction conditions. In one procedure, a large variety of oxazolidinones was acylated at room temperature with triethylamine and catalytic quantities of *N,N*-dimethyl-4-aminopyridine (DMAP).[20] The acylating agent was either an anhydride (mixed or symmetrical) or an acid chloride. In an alternate procedure, the oxazolidinone was efficiently acylated with anhydrides using triethylamine and a slight molar excess of lithium chloride.[21]

Two other procedures result in *N*-acryloylation of oxazolidinones. Of these two, the first is a two-step procedure wherein the oxazolidinone is first converted to the *N*-trimethylsilyl derivative and is then heated under reflux with acryloyl chloride in toluene for extended periods of time.[22] The second employs copper(I) chloride, copper powder, triethylamine, and 10% DMAP in the presence of the oxazolidinone and acryloyl chloride.[23]



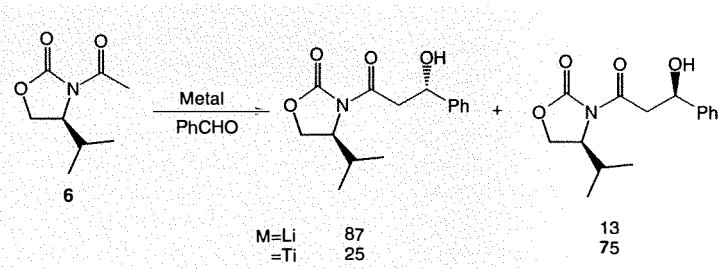
X_c = chiral 2-oxazolidinone
catalyst/metal = Cu, CuCl, LiCl, or DMAP
R_1 = Cl, $R_4C(=O)O$
R_2 = H, alkyl
R_3 = H, alkyl

Scheme 1



2 **4** **3** **5**

Scheme 2



6

M=Li 87
=Ti 25

13
75

Scheme 3

3. Reactions of Oxazolidinones

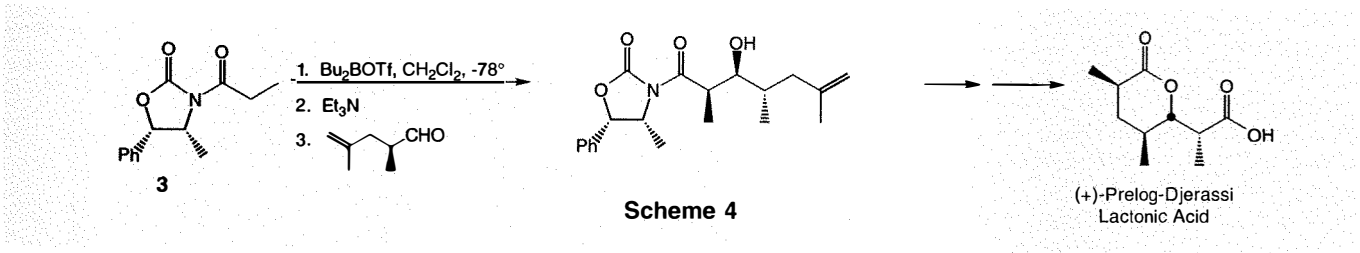
3.1. Aldol Reaction

The development of chiral enolates that participate in highly stereoregulated aldol condensations has been a challenging undertaking, since the control of both reaction diastereoselection and enantioselection must be addressed. The *Z*-enolates of chiral *N*-acyl imides **2** and **3** undergo the aldol condensation reaction with aldehydes in a highly stereoregulated fashion, providing α-substituted-β-hydroxy imides in high yields (**Scheme 2**). A variety of aldehyde structural forms are tolerated in this reaction (**Table 1**).[17]

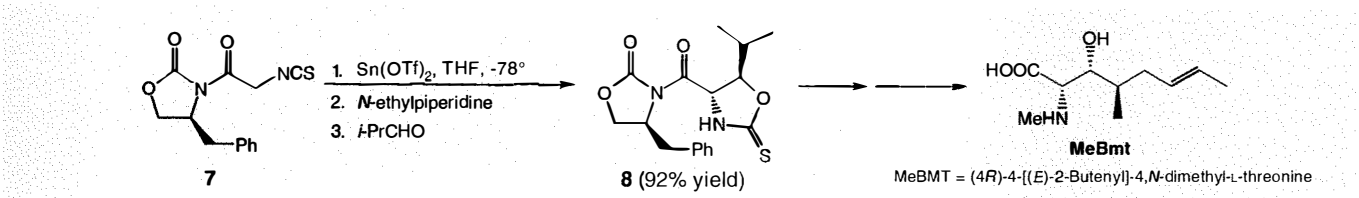
For dialkylboryl enolates, the stereochemistry of the kinetic aldol product has been shown to be strongly coupled to enolate geometry, while for dicyclopentadienylchlorozirconium enolates, kinetic *erythro*-selective condensations have been observed from either enolate geometry.[24] In aldol reactions under chelation control, high selectivities are observed for titanium enolates but rarely so for other metals such as lithium, zinc, and tin. The most efficient aldol processes utilize boron enolates, which provide a well-ordered transition state that leads to predictably high levels of stereoselection.[25] The solvent also plays an important role in aldol reactions of an

Table 1. Diastereoselection in the Aldol Reaction.

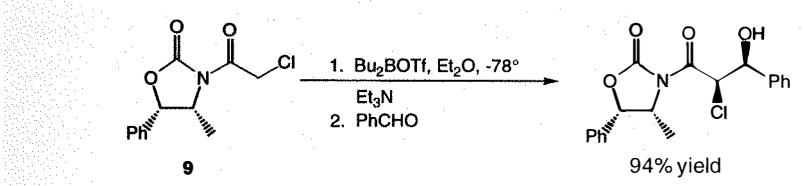
Imide	Aldehyde RCHO	Erythro Selection	%Yield of **4** or **5**
2	*t*-BuCHO	497:1	78
2	*n*-BuCHO	141:1	75
2	PhCHO	500:1	88
3	*t*-BuCHO	1:500	91
3	*n*-BuCHO	1:500	95
3	PhCHO	1:500	89



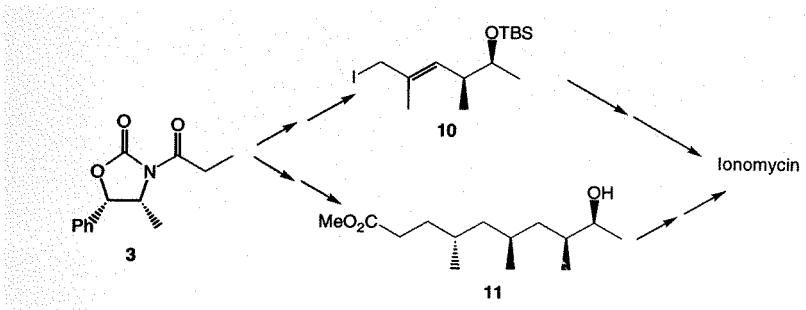
Scheme 4



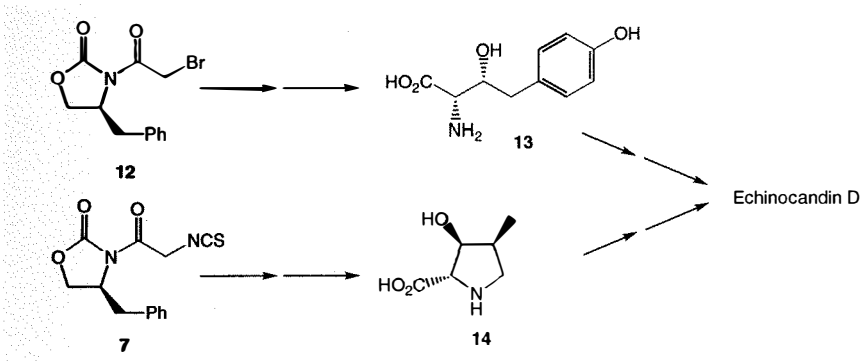
Scheme 5



Scheme 6



Scheme 7



Scheme 8

acyloxazolidinone-derived titanium enolate. Thornton and co-workers have reported that diethyl ether produces nearly a fivefold higher diastereofacial selectivity than THF with titanium enolates. This strong solvent effect most likely arises from stoichiometric binding of THF to the metal in the transition structure, whereas ether is not bound.[26-28] Thornton et al. have also demonstrated that aldol reactions of the titanium enolate of **6** with aldehydes give high diastereofacial selectivities for the *syn* aldol adducts derived from chelation control (**Scheme 3**). This reversal in reactivity, as compared with that of the boron enolate, permits the production of either enantiomeric aldol product from a single oxazolidinone.

An aldol condensation of oxazolidinone **3** has been utilized in the synthesis of (+)-Prelog-Djerassi lactonic acid (**Scheme 4**).[29]

The chiral glycine synthon **7**, as its derived stannous enolate, undergoes a highly *syn*-diastereoselective aldol addition reaction with aldehydes to give aldol adduct **8**. This adduct was then converted to the unusual C_9 amino acid, MeBmt, found in the immunosuppressive peptide cyclosporine (**Scheme 5**).[30]

The diastereoselective aldol reaction of **7,** an isothiocyano derivative, with aldehydes gives *syn*-β-hydroxy-α-amino acids; whereas, the corresponding chloro derivative **9** gives *anti*-β-hydroxy-α-amino acids with different aldehydes (**Scheme 6**).[31]

3.2. Macrolide Synthesis

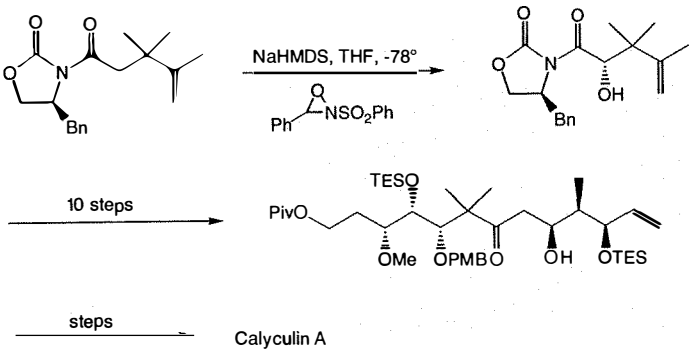
The total synthesis of the ionophore antibiotic ionomycin has been achieved using synthons **10** (C_1-C_{10}) and **11** (C_{11}-C_{16}) generated through asymmetric aldol reactions of the chiral enolate derived from **3** (**Scheme 7**).

Derivatives of two unusual β-hydroxy-α-amino acids in echinocandin D, a member of a family of lipopeptides that possesses high antifungal activity, have been synthesized by the asymmetric glycine aldol methodology. The *N*-Boc, *O*-benzyl derivative of (*2S,3R*)-3-hydroxyhomotyrosine (**13**), and the methyl ester of (*2S,3S,4S*)-3-hydroxy-4-methyl proline (**14**) have been synthesized in four steps starting from oxazolidinones **12** and **7**, respectively (**Scheme 8**).[9]

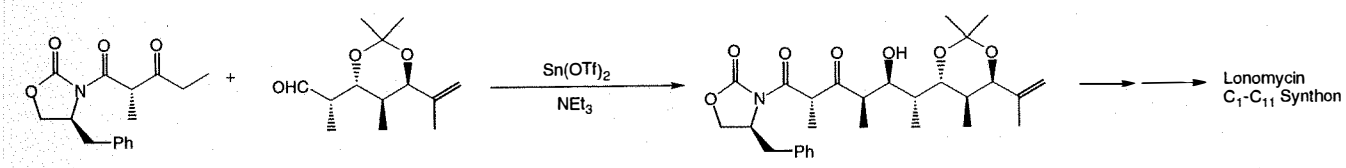
A convergent asymmetric synthesis of the marine natural product calyculin A, a

tumor promoter and potent inhibitor of protein phosphatases, has been accomplished by Evans et al. through the union of two subunits comprising the C_1-C_{25} and C_{26}-C_{37} portions of the molecule. These fragments were constructed utilizing auxiliary-based asymmetric aldol, alkylation, hydroxylation, and Michael reactions to establish 10 of the 15 stereogenic centers (**Scheme 9**). The remaining chirality was incorporated through internal asymmetric induction.[10,12,13]

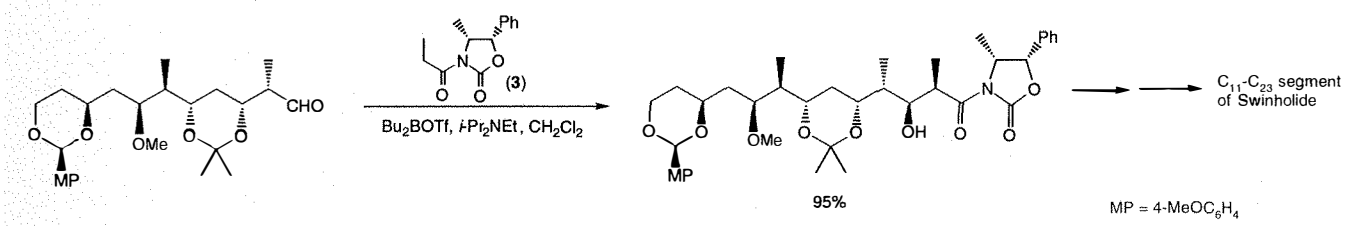
The asymmetric aldol methodology has also been used in the construction of the lonomycin C_1-C_{11} synthon (**Scheme 10**),[11] and the C_{11}-C_{23} segment of the marine macrolide swinholide A (**Scheme 11**).[32]



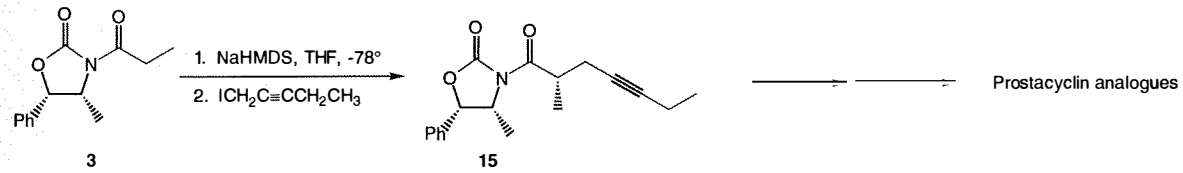
Scheme 9



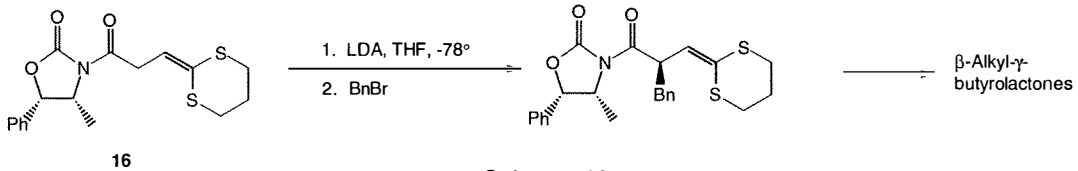
Scheme 10



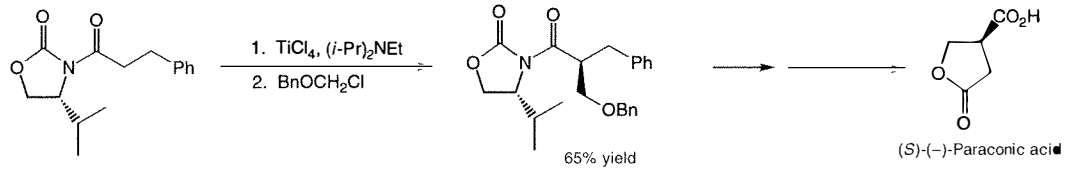
Scheme 11



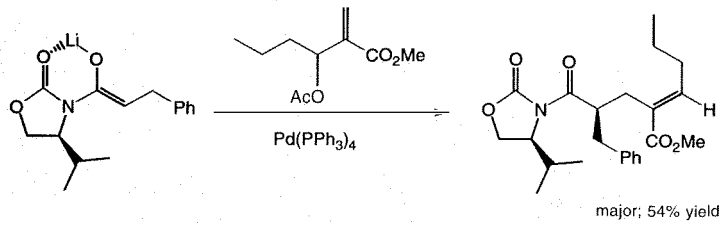
Scheme 12



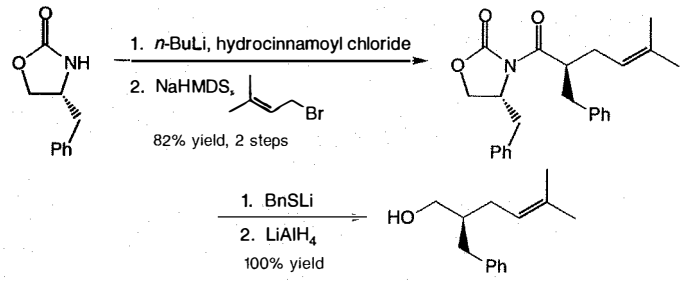
Scheme 13



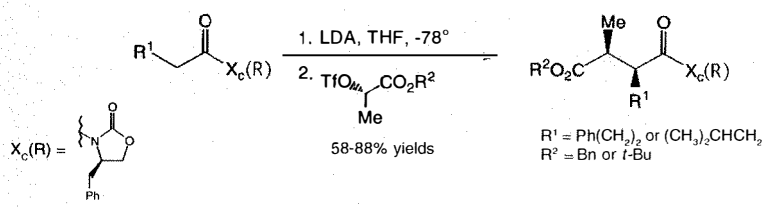
Scheme 14



Scheme 15



Scheme 16



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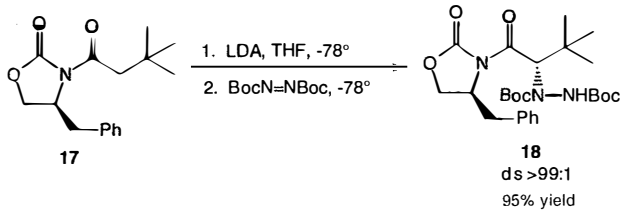
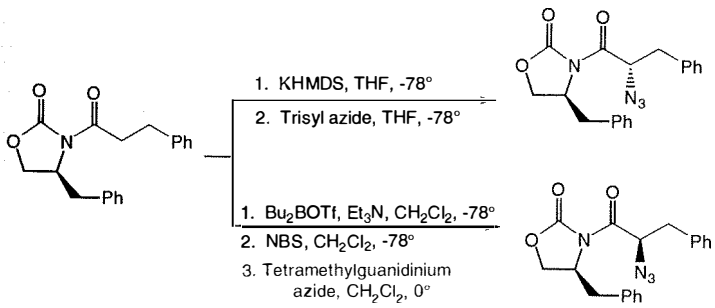


Scheme 18



Scheme 19

3.3. C-Alkylation

With the development of chiral enolate systems, Evans and co-workers found that the enolates of **2** and **3** exhibit excellent levels of asymmetric induction in alkylation reactions.[30,33-35] The diastereoselective alkylation of **3** with 1-iodo-2-pentyne gives the alkylated product **15** — an intermediate in the synthesis of prostacyclin analogs (**Scheme 12**).[36]

Canan Koch and Chamberlin used this methodology in the enantioselective preparation of β-alkyl-γ-butyrolactones. The key step in their approach was an oxazolidinone face-directed alkylation of a lithiated ketene dithioacetal **16** that proceeded with excellent regiochemical and high diastereofacial selectivity (**Scheme 13**).[18]

The alkylation approach has been utilized in the synthesis of unusual amino acids: β-methyltryptophan,[37,38] β-methyl tyrosine,[39] and phenylalanine homologs.[40] Crawforth and Rawlings have used an alkylation approach to prepare (*S*)-(−)-paraconic acid, which is a key intermediate in the synthesis of A-factor, an inducer of cytodifferentiation in many streptomycetes (**Scheme 14**).[41] The key step was the stereospecific benzyloxymethylation of a titanium oxazolidinone enolate.

The 2-substituted (*E*)-4-alkylidenepentanedioates can be synthesized asymmetrically by Pd-catalyzed coupling of oxazolidinone lithium enolates with 3-acetoxy-2-methylenealkanoates (**Scheme 15**).[42] The products are intermediates in metallo peptidase inhibitor synthesis.

A chiral oxazolidinone was used to synthesize an intermediate needed for the production of pyrrolinone-based HIV protease inhibitors (**Scheme 16**).[43]

The addition of chiral secondary triflates to chiral imides produced 2,3-disubstituted succinates with excellent diastereoselectivity (>98:2) (**Scheme 17**).[44]

3.4. α-Amination

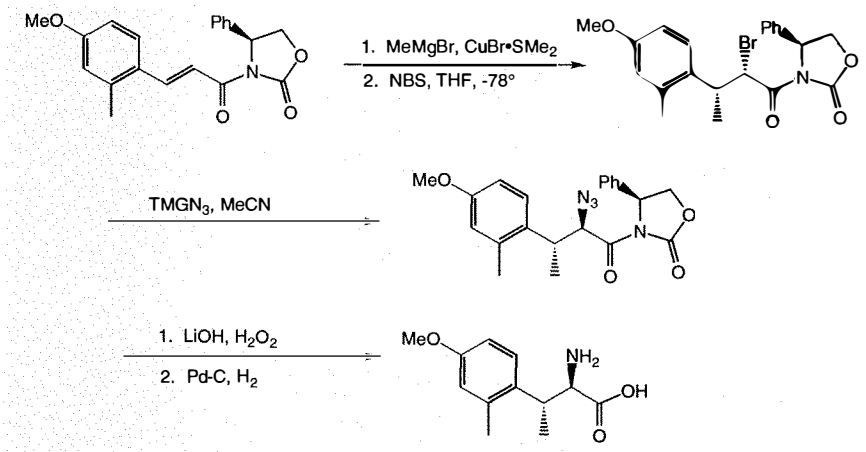
Evans has applied chiral oxazolidinone enolates to stereoselective amination reactions in order to synthesize nonproteinogenic and unusual α-amino acids. Di-*tert*-butyl azodicarboxylate (DBAD) reacts with the lithium enolates of **17** to provide hydrazide adducts **18** in excellent yield and high diastereoselectivity (**Scheme 18**). Adducts **18** can be converted to amino acids.[45,46]

Azidation of chiral imide enolates has also been used to prepare (*R*) and (*S*) α-amino acids, either directly in an electrophilic sense,[47,48] or through a halogen intermediate in a nucleophilic manner (**Scheme 19**).[49] Examples of unusual amino acids prepared by this methodology include:

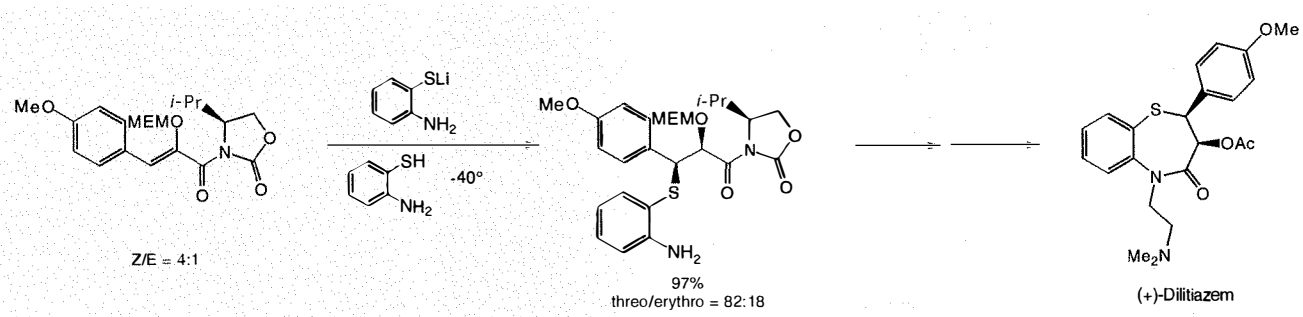
all four isomers of β-methylphenylalanine,[50] tetrahydrofuranylglycine,[51] derivatives of phenylalanine, and tyrosine (**Scheme 20**),[52,53] as well as unusual analogs of cyclic aliphatic, aromatic, and adamantyl amino acids.[54]

3.5. Michael Additions

The last example (**Scheme 20**) used a Michael addition to provide an enolate for amination. Conjugate addition of organocuprates to α,β-unsaturated *N*-acyl oxazolidinone provides good diastereoselectivity and also allows access to β-branched carboxylic acids[55] or β-substituted GABA analogs.[56] The face selectivity of this reaction has been exploited by Naito and co-workers in a synthesis of the important cardiac drug (+)-dilitiazem (**Scheme 21**).[57]



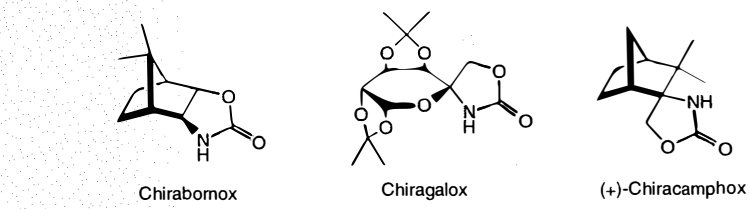
Scheme 20

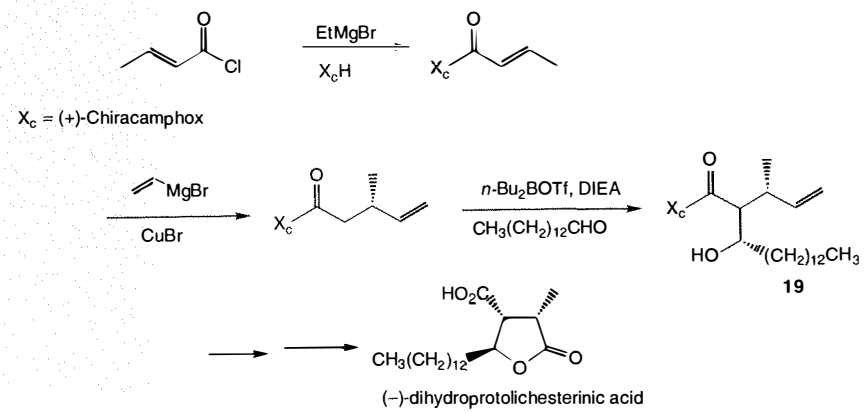


Scheme 21

New chiral oxazolidinones derived from tryptophan,[58,59] (–)-borneol,[60] D-(+)-galactose,[61] and (–)-camphene[62] serve as potentially powerful additions to the existing pool of chiral auxiliaries in asymmetric synthesis.

Chiracamphox has been used to induce asymmetry in the synthesis of (–)-dihydroprotolichesterinic acid, a potential antibacterial agent (**Scheme 22**).[63] After protection of compound **19** as the acetate, oxidative cleavage to the acid was carried out with $KMnO_4$. Last, the chiral auxiliary was cleaved with $LiOH/H_2O_2$ to give the desired acid.





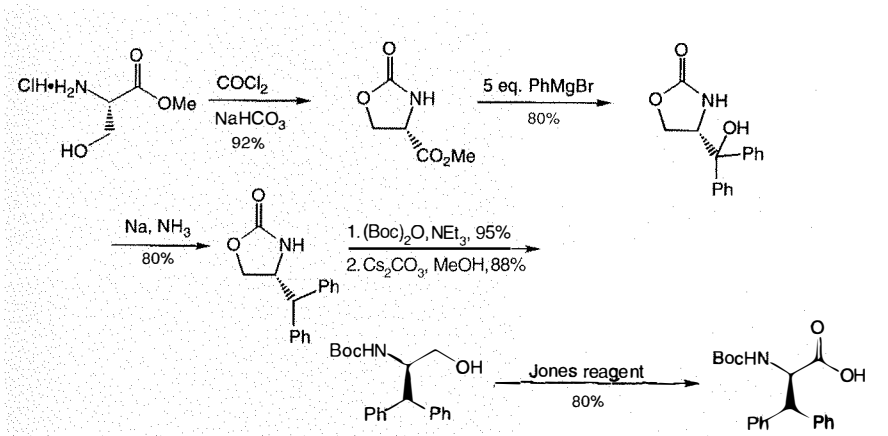
Scheme 22

3.6. Remote Reactions

Sibi et al. have employed the oxazolidinone derived from L-serine methyl ester hydrochloride in the synthesis of unnatural amino acids such as diphenylalanine (**Scheme 23**).[64-68] Cane et al. have used the auxiliary approach in the chain elongation of Nargenicin, a polyketide antibiotic (**Scheme 24**).[14]

3.7. Pericyclic Reactions

Evans has utilized this methodology in the synthesis of carbacephem-related antibiotics, especially the carbacephalosporins.

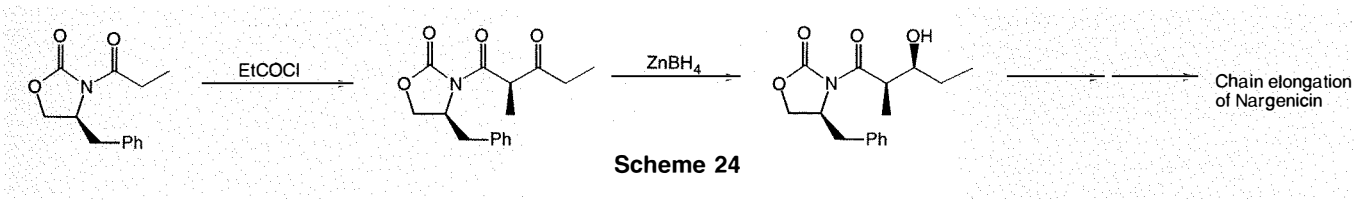


Scheme 23

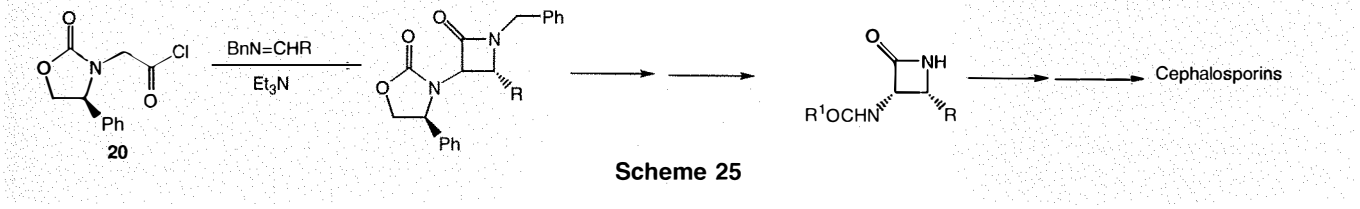
The azetidinones are obtained by the cycloaddition of a 4(*S*)-phenyloxazolidin-2-one-3-ylacetyl halide (**20**) and an imine formed from a benzylamine and a 3-arylacrolein. The acid halide is converted in situ by reaction with a trialkylamine to the corresponding ketene that provides the azetidinone intermediate by cycloaddition with the imine (**Scheme 25**). The cycloaddition is also the key step in the asymmetric synthesis of β-lactams and cephalosporins.[69,70]

4. Cleavage of the Oxazolidinone Auxiliary

After the stereospecific reaction with the chiral auxiliary, the oxazolidinone needs to



Scheme 24



Scheme 25

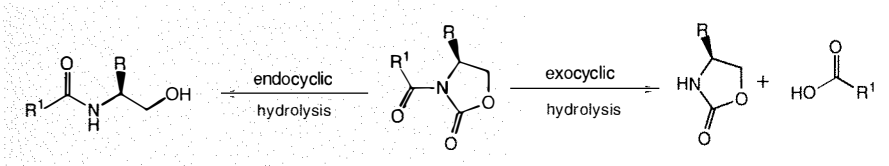


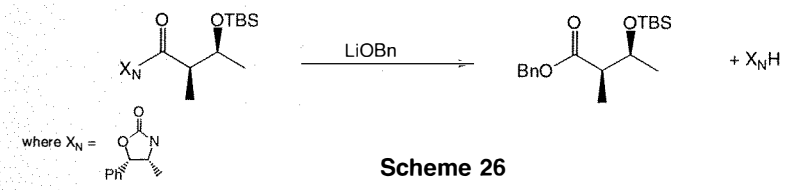
Figure 1. Cleavage of Oxazolidinones.

be separated from the product and preferably recycled. Cleavage of the auxiliary can be either exo- or endocyclic (**Figure 1**).[71] The larger the R^1 group, the more likely the endocyclic cleavage will occur with basic reagents.

The undesired endocyclic oxazolidinone cleavage can be circumvented by use of lithium hydroperoxide in place of the hydroxide.[72,73] Thus, regioselective exocyclic cleavage is observed for all classes of oxazolidinone-derived carboximides, even those with bulky R^1 groups, when the peroxide reagent is employed. Numerous reagents have been used to cleave *N*-acyloxazolidinones (**Table 2**).[1]

Table 2. Reagents for Cleaving *N*-Acyloxazolidinone Auxiliaries.

Reagent	Product	References
KOH, LiOH, $LiOH/H_2O_2$	Carboxylic acids	72,73
$LiBH_4$, $LiAlBH_4$	Alcohols	13,33,74-77
LiOR, NaOR, BrMgOR, $Ti(OR)_4$	Esters	8,9,17,33,36,47,78
LiSR, $BnSAlMe_3Li$	Thioesters	79-82
N_2H_4/*n*-amylONO/NH_4Cl, Cp_2TiCl_2, CP_2ZrCl_2	Amides	13,57,83-84
MeONHMe•HCl/$AlMe_3$	Weinreb amide	85-90



Scheme 26

Cleavage with lithium alkoxides yields esters (**Scheme 26**)[8,33] while thioesters can be accessed using lithium thioalkoxides. In addition to lithium, other metal counterions, such as sodium, magnesium, and titanium have been employed successfully.[9,17,36,47,78]

Thioesters are also obtained when the oxazolidinone is cleaved using an aluminum benzylthiol "ate" complex that is formed in situ from trimethylaluminum and lithium benzylthiolate (**Scheme 27**).[82] The attack of

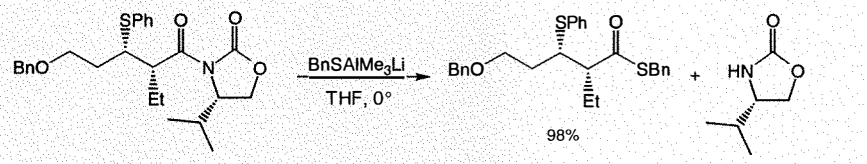
the sulfur nucleophile is *exo* even in sterically demanding systems.[79-81]

Aldehydes and ketones are not readily accessible from chiral *N*-acyl oxazolidinones, but the aluminum amide derived from trimethylaluminum and *N,O*-dimethylhydroxylamine hydrochloride yields the *N*-methoxy *N*-methyl amide (**Scheme 28**).[86,87] These amides may then serve as precursors to aldehydes and ketones.[87-90]

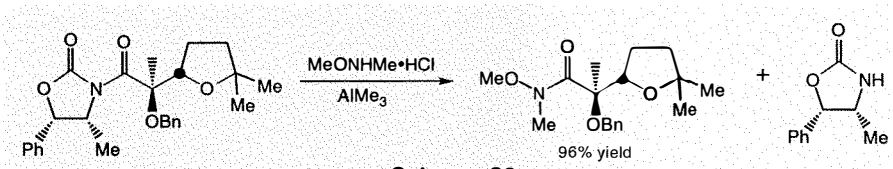
Aldehydes are also available by a two-step process that involves reduction to the alcohol, followed by oxidation.[91] Other methods used to prepare aldehydes are reduction of *N*-methoxy-*N*-methylamides with DIBAL[87] and treatment of thioesters with triethylsilane-Pd/C.[92]

Amides may be obtained by group IV metal-catalyzed aminolysis,[84] or transamination in the presence of an aluminum catalyst.[13,57,85] Hydrazide nucleophiles can also be used to effect the transformation (**Scheme 29**).[83]

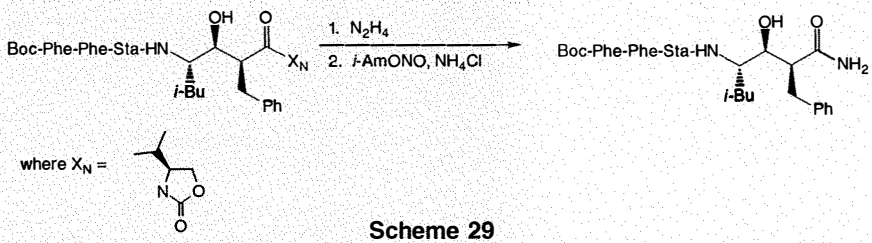
Valine-derived oxazolidinones have a propensity to undergo lactonization; this was exploited in a total synthesis of the polyether antibiotic ionomycin (**Scheme 30**).[78]



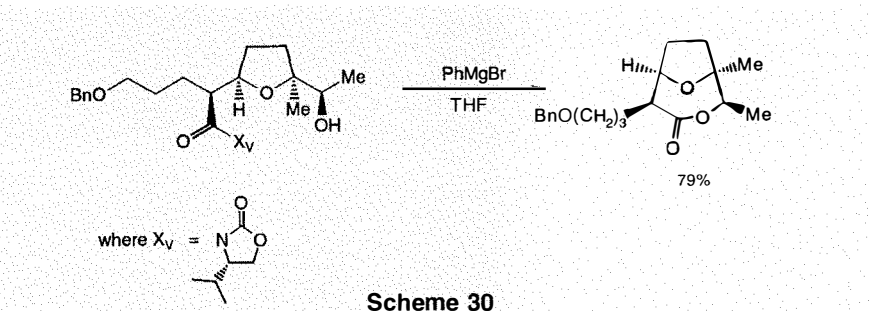
Scheme 27



Scheme 28



Scheme 29



Scheme 30

5. Conclusions

Oxazolidinones have been used as chiral auxiliaries in a wide range of reactions. The degree of asymmetric induction at the new stereogenic center can be high. Applications of the chiral oxazolidinone methodology to the synthesis of complex molecules illustrate the power of the approach. The ability of *N*-acyloxazolidinones to form rigid chelates with metal ions, as well as the masking of one face of the system by the sterically encumbering 4-substituent, makes this chiral auxiliary system one of the most versatile available. General methods exist for the attachment of the auxiliary moiety to the substrate molecule in high yield. A wide variety of reactions are then available where the oxazolidinone not only provides the required asymmetric induction but is also stable to the reaction conditions. Finally, the auxiliary unit can be detached intact to provide a variety of motifs in the desired unit. Thus, oxazolidinones fulfill all the requirements of a useful chiral auxiliary unit.

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About the Authors

David Ager was born in Northampton, England in 1953. He received a B.Sc. from Imperial College, London, and a Ph.D. from the University of Cambridge, working with Dr. Ian Fleming (Jeopardy) on organosilicon chemistry. In 1977 he was awarded a Science Research Council Postdoctoral Fellowship that allowed him to collaborate with Professor Richard Cookson FRS at the University of Southampton. In 1979 he joined the faculty of the University of Liverpool as a Senior Demonstrator. This was followed by an assistant professor position at the University of Toledo in Ohio. In 1986, he joined the NutraSweet Company's Research and Development group that has now become NSC Technologies, part of Monsanto Growth Enterprises. Dr. Ager is responsible for the chemical development of new products for the fine chemical intermediate business.

David Schaad was born in Fond du Lac, Wisconsin in 1964. He obtained his B.S. degree from the University of Wisconsin, Madison and Ph.D. from the University of Colorado at Boulder in 1992 under the direction of Professor Clark Landis. He continued at this institute as a postdoctoral associate with Professor Tarek Sammakia.

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Indra Prakash was born in Muzaffarnagar, India in 1956. He received an M.Sc. degree in 1977 from the University of Roorkee, India, and was awarded the Gold Medal for academic distinction. In 1982, he received a Ph.D. from Kurukshetra University, India under the direction of Professor S.P. Singh. He also worked at Union Carbide in Bhopal, India. After coming to the United States, he joined Professor Kagan at the University of Illinois at Chicago and worked on the preparation of phototoxic, photoantibiotic agents. He later collaborated with Professor Moriarty to study the utility of hypervalent iodine reagents in organic synthesis, and then with Professor Sosnovsky at the University of Wisconsin-Milwaukee on the synthesis of anticancer and NMR contrast agents. After joining Aldrich Chemical Company in 1987 as a Senior Chemist, he became a Principal Investigator for a National Cancer Institute contract at Aldrich. In addition to his administrative and technical responsibilities with the NCI contract, he developed several new product lines (preparing chiral products using enzymes, NMR contrast agents, compounds used in PET and radiation tomography) and wrote technical bulletins. Currently, Dr. Prakash is a project leader developing processes for new sweetener candidates for The NutraSweet Kelco Company, a business unit of Monsanto.

Preparation and Reactivity of Acyclic (Pentadienyl)iron(1+) Cations: Applications to Organic Synthesis

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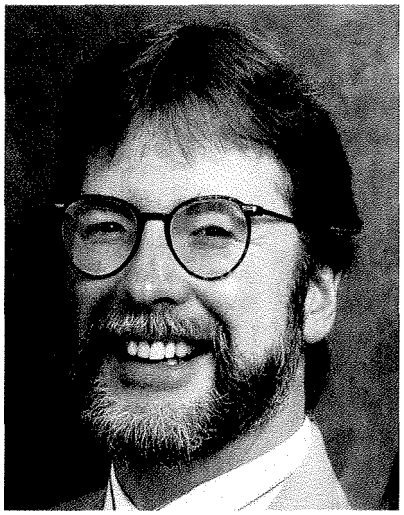


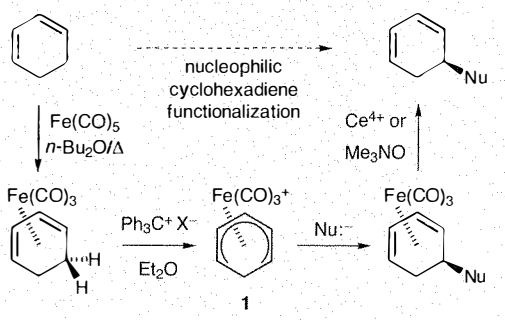
Nucleophilic attack on coordinated polyenes is one of the paradigms of π-organometallic chemistry.[1] Where reactions of this type occur with predictable regioselectivity they can be of synthetic utility. For example, the tricarbonyl(cyclohexadienyl)-iron(1+) cation (**1**, **Scheme 1**)[2] is known to undergo nucleophilic attack at the dienyl terminus to afford substituted (cyclohexadiene)$Fe(CO)_3$ complexes. Cation **1** may be prepared via hydride abstraction from the parent (cyclohexadiene)$Fe(CO)_3$ complex, which is in turn prepared by complexation of cyclohexadiene with $Fe(CO)_5$. Liberation of the substituted cyclohexadiene ligand can be effected by oxidation with $Ce(NH_4)_2(NO_3)_6$ or Me_3NO, and this sequence of steps serves as a regio- and stereoselective method for the functionalization of cyclohexadiene (**Scheme 1**).[2] The application of this methodology to natural product synthesis has been used in the preparation of carbazole,[3] limaspermine,[4] and *O*-methyljoubertiamine[5] alkaloids and trichothecenes.[6] The preparation and reactivity of the corresponding *acyclic* (pentadienyl)-iron(1+) cations (**2**) have been the subject of intense recent investigations in a number of laboratories (**Figure 1**).[7]

A. Preparation

The hydride abstraction method for the preparation of cationic organometallic complexes has been applied to the preparation of *acyclic* (pentadienyl)$Fe(CO)_3^+$ cations. However, in spite of what is indicated in a popular organometallic chemistry text, there are only a few examples since the success of this reaction requires the presence of a *cis*-alkyl substituent on the diene (Method A, **Scheme 2**).[8,9] The most common method for the preparation of cations **2** is the protonation of (pentadienol)- or (pentadienyl ether)$Fe(CO)_3$ complexes (Method B, **Scheme 2**).[8] Lillya and co-workers have demonstrated that ionization of the hydroxyl substituent occurs with anchimeric assistance from iron, and that isomerization of the initially generated transoid pentadienyl cation (**3**) to the more stable cisoid cation occurs with retention of configuration about the C1-C2 bond.[10] A third method of preparation involves protonation of (triene)-$Fe(CO)_3$ complexes with HBF_4 or HPF_6 (Method C, **Scheme 2**).[11] To date, a wide variety of (pentadienyl)iron(1+) cations have been prepared and *isolated* (**Figure 1**), including stereoselectively labeled cations **2ii** and **2jj**. Cations **2b**, **2l**, **2q**, **2r**, **2s**, **2z**, **2ee**, **2gg**, and **2ii** have been prepared in both optically enriched and optically pure form.

B. Structure, Spectral Characterization, and Electronic Distribution

The *first* crystal structure of a (pentadienyl)$Fe(CO)_3^+$ cation, **2x**, has recently been reported.[12] This structure indicates that the distance between the terminal pentadienyl carbons (C1/C5) and Fe (ca. 2.177 Å) is longer than that between Fe and C2/C4 (ca. 2.145 Å) or between Fe and C3 (2.109 Å). In addition, the angle about the C3 carbon in the ligand (ca. 129°) is greater than that about the C2/C4 carbons (ca. 122°), and the methyl substituents at C2/C4 are tilted *toward* the iron atom (ca. 8.7• below the plane of the pentadienyl ligand). Extensive NMR spectral analysis indicates that all of the *isolated* cations **2** (**Figure 1**) exhibit the "U" or cisoid structure in solution. In the parent cation **2a**, the signals due to protons attached to the ligand appear at δ 7.22 (C_3-H), δ 6.26 ($C_{2/4}$-H), δ 3.75 ($C_{1/5}$-H_{exo}), and δ 2.17 ($C_{1/5}$-H_{endo}), with couplings $J_{1exo\text{-}1endo}$ 3.5 Hz, $J_{1exo\text{-}2}$ 9.8 Hz, $J_{1\text{-}endo\text{-}2}$ 13 Hz, $J_{2\text{-}3}$ 6.8 Hz.[8a] The signals for these protons in the substituted cations appear in the same general order with variations due to substituent effects. The spectroscopic detection of an "S"



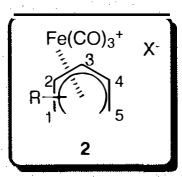
Scheme 1

or transoid (pentadienyl)iron cation has only been reported for a single sterically biased case (**eq 1**).[13] While NMR spectra for most cations **2** reveal only the cisoid conformer, it is generally believed that the cisoid (pentadienyl)Fe^+ cations **2** exist, in solution, in equilibrium with the less stable transoid form.

Extended Hückel molecular orbital calculations have indicated that the greatest portion of the positive charge in **2a** is located at C2/C4, followed by C3, and that C1/C5 bear the least partial positive charge.[10b] While it is not always valid to correlate ^{13}C NMR chemical shifts with the charge on coordinated atoms, it is instructive to note that the signals for C2/C4 of a variety of cations **2** appear farthest downfield.[10b,14-20] An empirical set of substituent effects on chemical shifts has been reported.[10b] The ^{57}Fe NMR spectrum of **2b** exhibits a signal at δ 1017.9.[21] On the basis of ^1H, ^{13}C, and variable temperature ^{31}P NMR spectroscopy, it has been proposed that phosphine-substituted (pentadienyl)$Fe(CO)_2PR_3^+$ cations, **2q-2w**, exist predominantly in the conformer which has the phosphine ligand in the basal position which is opposite to the CI substituent (B^1, **Figure 2**).[16,22,23]

C. Reactivity of Pentadienyl Cations

The acyclic (pentadienyl)iron(1+) cations **2** can act as excellent organometallic electrophiles toward a wide variety of nucleophiles. A priori, the reactivity of cations **2** might be anticipated to be similar to that of the corresponding (cyclohexadienyl)iron cation **1**. While this is true for a number of cases, *there exist significant differences between the reactivity of cyclic cation 1 and that of the acyclic cations 2*. Nucleophilic attack can take place on the cisoid form of the pentadienyl cation at either terminus to afford the *E,Z*-diene complexes **4** or **5**, or on the internal atoms of the ligand (C2/C3/C4) to afford complexes **6**, **7** or **8** (**Scheme 3**). Alternatively, since the transoid form exists in equilibrium with the cisoid form, nucleophilic attack on the transoid pentadienyl cation generates *E,E*-diene complexes **9** or **10**. Nucleophilic



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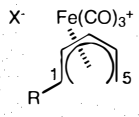
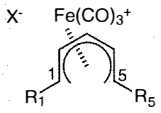
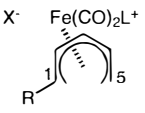
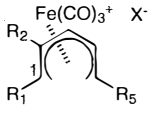




	R	Prep.	Ref.
2a	H	A,B	8a
2b	Me	B,C	8b,11
2c	Et	B	14,60
2d	*i*-Pr	B	60,61
2e	*n*-Pr	B	14
2f	*n*-Bu	B	14,62
2g	*t*-Bu	B	60
2h	*n*-Pent	B	14
2i	*n*-Hex	B	14
2j	*n*-Hept	B	14
2k	$(CH_2)_3CH=CH_2$	A	63
2l	CO_2Me	B	15,26
2m	$CH=CHCO_2Me$	B	27
2n	C_6H_5	B	60,64
2o	p-$C_6H_4OCH_3$	B	48

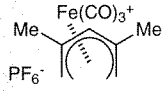
	R_1	R_5	Prep.	Ref.
2aa	Me	Me	B,C	8a,65
2bb	Me	Et	B	60
2cc	Me	*i*-Pr	B	31,60
2dd	Me	Ph	B	60,65
2ee	Me	CO_2Me	B	28a
2ff	Ph	CO_2Me	B	51
2gg	Me	SO_2Ph	B	29
2hh	Ph	Ph	B	67
2ii	D	Me	B	32a,68
2jj	D	CO_2Me	B	49b



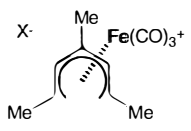


	R	L	Prep.	Ref.
2p	H	PPh_3	B	47
2q	Me	PPh_3	B	22,23
2r	Me	$P(OPh)_3$	B	22
2s	Me	PPh_2neomenthyl	B	22
2t	CO_2Me	PPh_3	B	48
2u	OMe	PPh_3	B	16
2v	OAc	PPh_3	B	16
2w	OBz	PPh_3	B	16

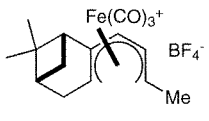
	R_1	R_2	R_5	Prep.	Ref.
2kk	H	Me	H	B	17
2ll	Me	Me	H	B	18
2mm	Ph	Me	H	B	18
2nn	Me	Me	Ph	B	17
2oo	Me	Me	*n*-Bu	B	24
2pp	Me	Me	*i*-Pr	C	32a
2qq	H	Me	Me	B	18
2rr	H	OMe	Me	B	19
2ss	H	$SiEt_3$	Me	B	20
2tt	H	Me	Ph	B	18



2x, Ref.9



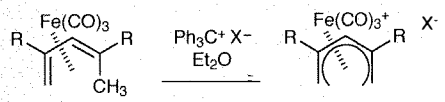
2y, Ref. 10b, 65



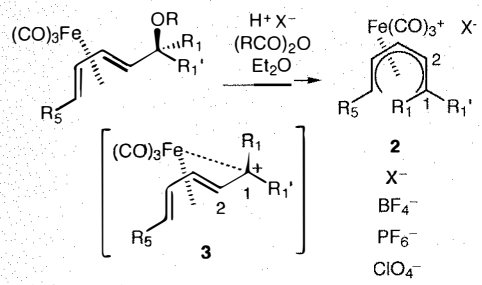
2z, Ref. 66

Figure 1

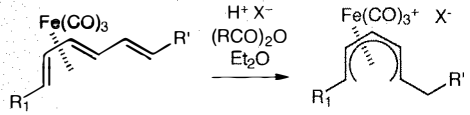
Method A:
Hydride abstraction from *cis*-diene complexes



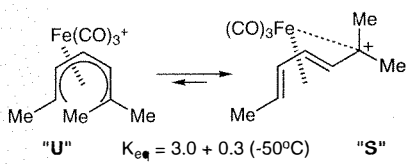
Method B:
Dehydration of dienol or dienyl ether complexes



Method C:
Protonation of triene complexes

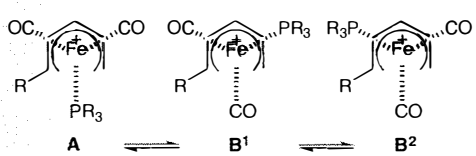


Scheme 2



"U" K_{eq} = 3.0 + 0.3 (-50°C) "S"

eq 1



A **B¹** **B²**

Figure 2

attack at the metal, with concomitant loss of a ligand, is a final possibility (**Scheme 3**). Except for attack at C3, all of these possibilities have been observed.

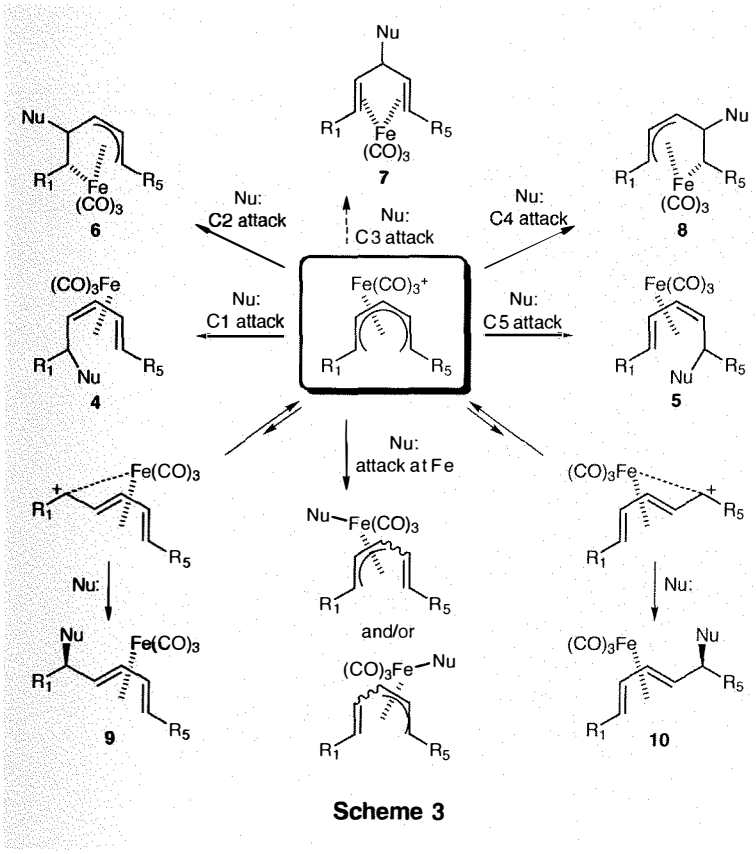
1. Reaction with Heteroatom Nucleophiles

In general, the reaction of cations **2** with water and alcohol nucleophiles leads to the formation of (*E,E*-dienol)- and (*E,E*-dienyl ether)$Fe(CO)_3$ complexes in excellent yields (**eq 2**).[8,10,11,17-20,24] The stereochemistry at the alcohol methine carbon, relative to the (diene)$Fe(CO)_3$ fragment, was established as "Ψ-exo" on the basis of X-ray diffraction analysis.[25] The formation of the Ψ-exo-*E,E*-dienol products is rationalized on the basis of reaction of the weak oxygen nucleophiles with the less stable, but more reactive, transoid pentadienyl form of the cations on the face opposite to $Fe(CO)_3$. In contrast, the reaction of water or alcohols with pentadienyl cations bearing an electron-withdrawing substituent (e.g., **2l**, **2m**, and **2ee**) gives the corresponding *Z,E*-diene complexes (e.g., **11**, **Figure 3**).[26-28] This may be due to the increased reactivity of these cations in the "U" form. Grée et al. have utilized the optically active *Z,E*-diene complex (2S)-**11** in the preparation of intermediates **12** and **13** (**Figure 3**) for the synthesis of AF/AK toxins.[28b]

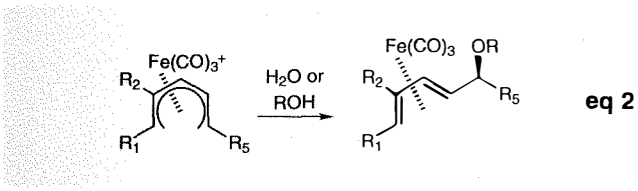
Reaction of cations **2** with Group 15 neutral nucleophiles (1°/2°amines,[29,30] phosphines,[31,32] and arsines[33]) affords the cationic complexes **14/15** (**Scheme 4**). Deprotonation of the ammonium salts generates the correspondingly substituted amine complexes. Reaction of cations **2** with phosphites proceeds via an Arbuzov-type reaction to give dienyl phosphonates.[34] It has recently been demonstrated that the addition of amines[35] and phosphines[18,32,36] is reversible in certain cases (**Scheme 4**). Thus, kinetic nucleophilic attack occurs on the more abundant cisoid form of the cation to generate *E,Z*-diene complexes **14**. Where there are significant steric interactions between the amine/phosphine and other substituents present on the pentadienyl ligand, nucleophilic attack may be reversible. At higher temperatures and longer reaction times, the thermodynamically more stable *E,E*-diene complex **15** is formed via nucleophilic attack on the much less abundant transoid form of the pentadienyl cation. It is worth noting that nucleophilic attack of phosphines on the (*cyclohexadienyl*)$Fe(CO)_3^+$ cations is not reversible.[37]

Deprotonation of either the *E,Z*- or the *E,E*-dienyltriphenylphosphonium salts **14** or **15** ($R_3A = PPh_3$) leads to the formation of the corresponding *E,E*-dienyl ylides. Uncomplexed dienyl ylides participate in Wittig olefination with low *E/Z*-selectivity (ca. 1:1). In contrast, the complexed ylide **16** undergoes olefination with greater *Z*-selectivity (1:4, *E:Z*, **Scheme 5**).[34a,38] The perfumery component 1,3*E*,5*Z*-undecatriene has been prepared by this methodology.[34a]

Reaction of pentadienyl cations **2** with halide ions proceeds via attack at the metal followed by loss of a ligand; in the case of **2x** loss



Scheme 3



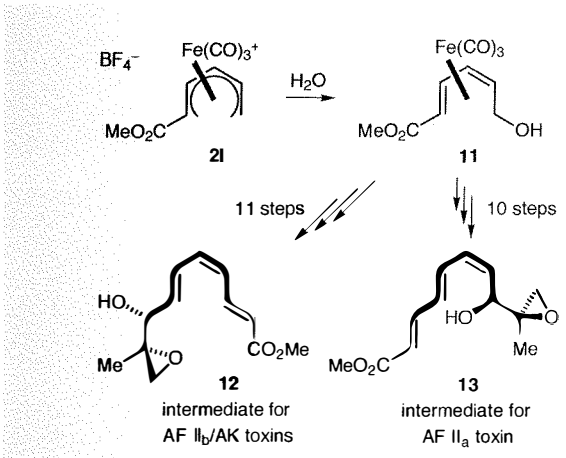
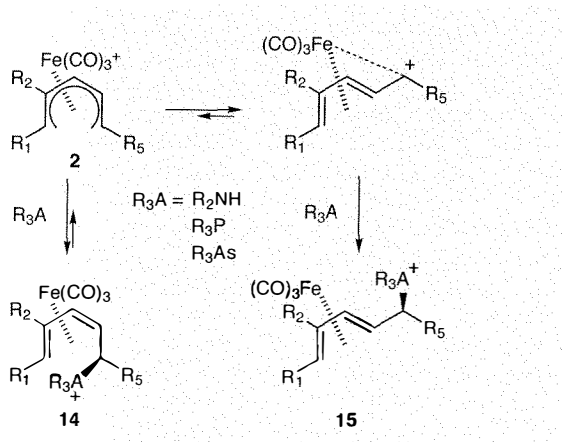


Figure 3



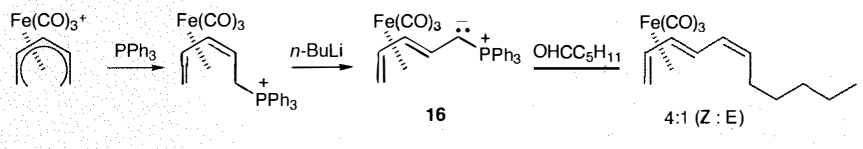
Scheme 4

of coordinated CO gives a (pentadienyl)-$Fe(CO)_2I$ complex **17**, while for **2aa** this entails decomplexation of two atoms of the pentadienyl ligand to afford the (allyl)-$Fe(CO)_3X$ complexes **18** (**eq 3**).[39] By comparison, reaction of **2ee** with tetrabutylammonium fluoride (TBAF) affords a "very complex mixture" of unidentified products.[40]

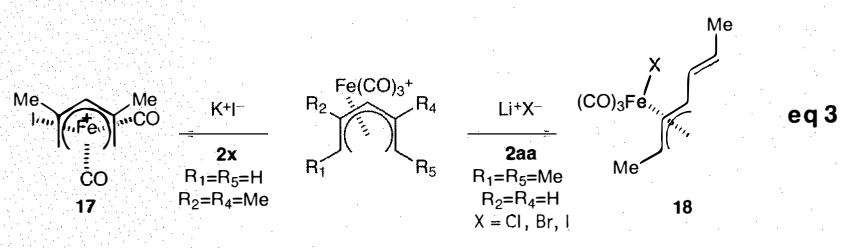
2. Reaction with Carbon Nucleophiles

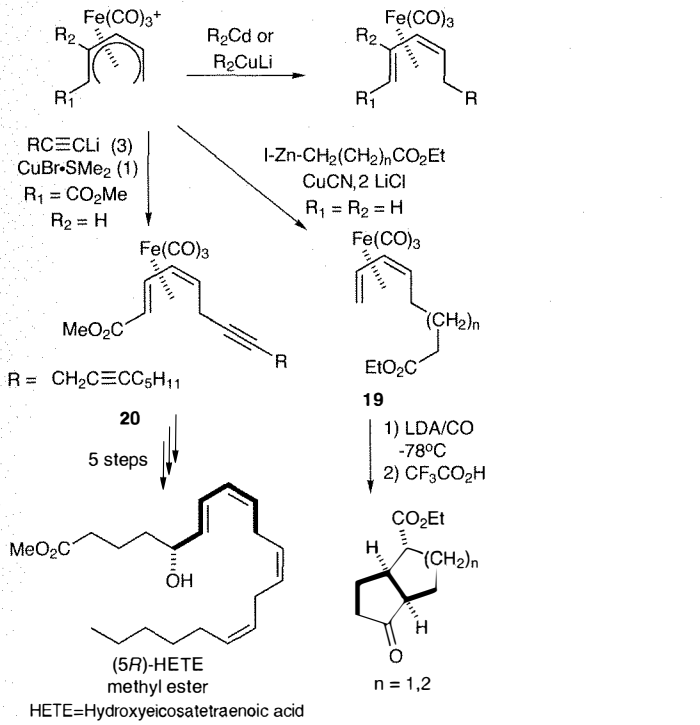
The reaction of cations **2** with simple organocadmium reagents[41] or organocuprates[17,20,42] gives *E,Z*-diene complexes (**Scheme 6**). Likewise, the reaction of functionalized organozinc reagents in the presence of CuCN ("Knochel reagents")[43] with cations **2** affords the diene complexes **19**.[44] Even alkynyl cuprates, usually considered to be the least reactive of organocuprate ligands,[45] react with cations **2** to give 1*E*,3*Z*,6-dienyne complexes **20**.[15,46] For 1- or 2-substituted or 1,2-disubstituted pentadienyl cations (e.g., **2b**, **2l**, **2n**, **2kk**, **2ll**, and **2mm**) nucleophilic attack occurs at the less sterically hindered terminus of the pentadienyl ligand with excellent regioselectivity; however, for 1,4-disubstituted pentadienyl cations (e.g., **2qq** and **2tt**), mixtures of regioisomeric products are formed. Yeh et al. have further utilized dienes **19** in intramolecular cyclocarbonylation reactions to produce [3.3.0]- and [3.4.0]bicycloalkanones.[44b] The optically active (methyl 2*E*,4*Z*-hexadecadiene-7,10-diynoate)-$Fe(CO)_3$ complex **20** (R = $CH_2C{\equiv}CC_5H_{11}$) prepared from (2*R*)-**2l** was utilized in the enantioselective synthesis of (5*R*)-HETE methyl ester (**Scheme 6**).[15]

The reaction of (pentadienyl)-$Fe(CO)_2PPh_3^+$ cations **2p**, **2v**, or **2w** with alkyl or aryl lithium compounds proceeds via attack at C2 to afford complexes **21** (**Scheme 7**).[16,47] For the parent system (R = H), the resulting σ,π-allyl complex **21** is unstable and decomposes in solution over a period of time in the presence of air via carbonyl insertion and reductive elimination to afford cyclohexenone products.[47] Similarly, malonate nucleophiles react with (methoxycarbonylpentadienyl)iron cation **2l** at C2 to afford predominantly **22** (**Scheme 8**).[48,49] The substituted σ,π-allyl complexes **21** (R = OAc, OBz)[16] and **22**[48] are considerably more stable than the parent system **21** (R = H), and after isolation may be structurally characterized by X-ray diffraction. In contrast to **21**, oxidation of **22** (R = H; Ce^{4+}) results in the formation of a vinylcyclopropanecarboxylate in good yields (**Scheme 8**).[49] The difference in stability of **21** and **22**, and their divergent paths for the loss of the iron atom, may be

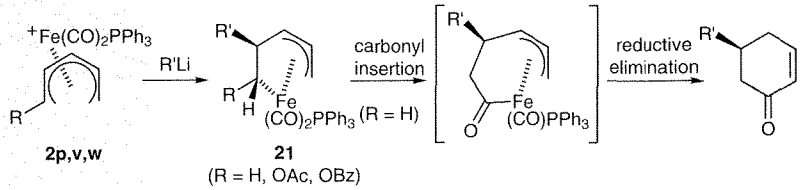


Scheme 5

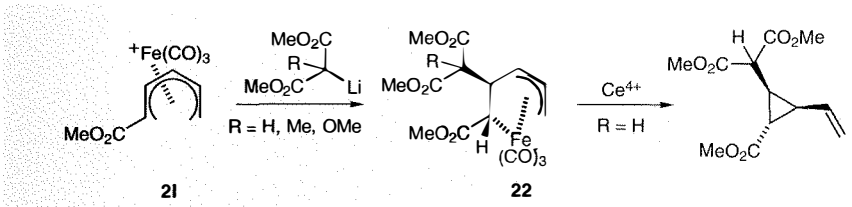




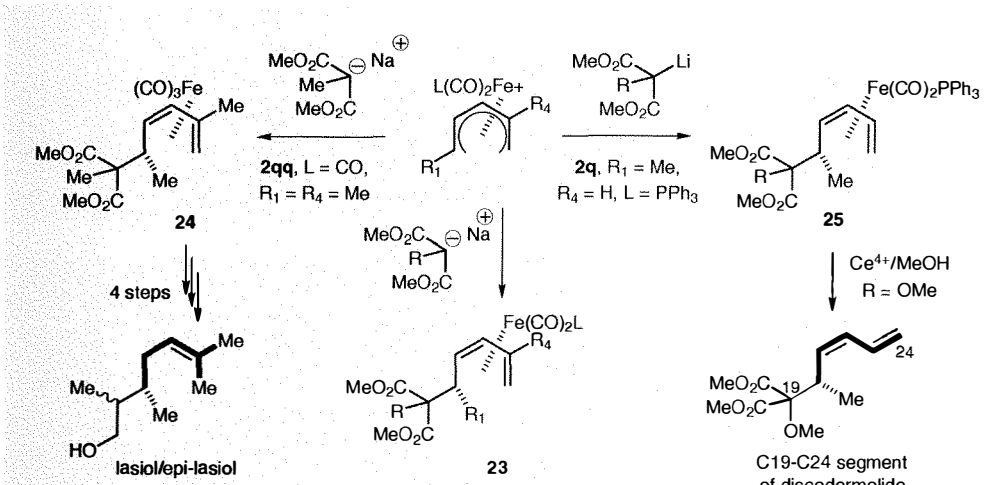
Scheme 6



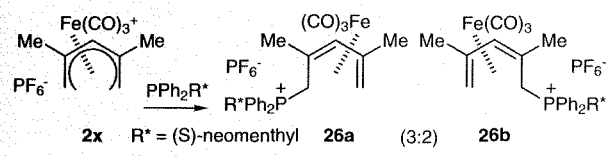
Scheme 7



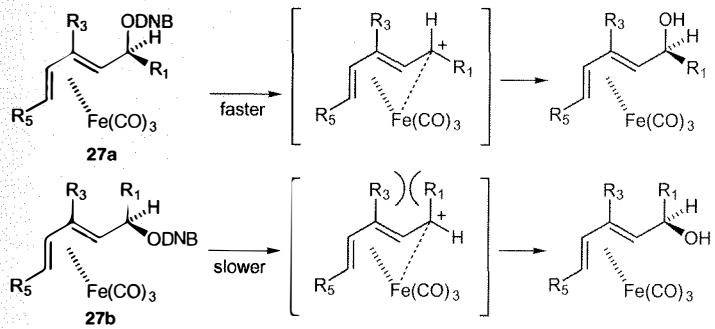
Scheme 8



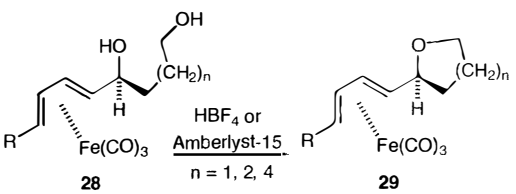
Scheme 9



eq 4



Scheme 10



eq 5

attributed to the retarding effect of an electron withdrawing substituent on the rate of carbonyl insertion.[50] The reaction of cations **2l**, **2ee**, or **2ff** with alkynyl cerium reagents,[51] or the reaction of cations **2b**, **2m**, or **2n** with dimethylmalonate anion,[27,48] gives mixtures of diene complexes resulting from attack at C5 and unstable σ,π-allyl complexes resulting from attack at C2. In comparison, the reactions of disubstituted (pentadienyl)$Fe(CO)_3^+$ cations **2x**,[9] **2qq**,[42] **2ss**,[20] and **2tt**[42] or $Fe(CO)_2PPh_3^+$ cation **2q**[23] with malonate anions proceeds via attack at C1 to afford *Z*-1,3-diene complexes **23** (**Scheme 9**). The synthesis of the rearranged terpenes lasiol/epi-lasiol from **24**,[42] and the preparation of the C19-C24 segment of the immune response suppressant discodermolide from **25**[23] have been reported (**Scheme 9**).

The regioselectivity of nucleophilic attack by carbon nucleophiles at the pentadienyl termini versus attack at an internal carbon appears to depend upon both the nucleophile and the substituents present on the pentadienyl ligand. The general trends can be summarized as follows: Nucleophilic attack by organocuprates occurs at the sterically less hindered terminus. Nucleophilic attack by malonate anions on $Fe(CO)_3$-complexed 1-*substituted* pentadienyl cations occurs with little regioselectivity unless there is either a strongly electron-withdrawing or strongly electron-donating substituent present at the terminal position of the ligand. The presence of a 2-*substituent* has a pronounced directing effect for malonate attack at C5. Regioselectivity of nucleophilic attack on $Fe(CO)_2PPh_3$-complexed pentadienyl cations is generally improved over that of the corresponding $Fe(CO)_3$ complexed cations due to the increased stability/decreased reactivity of the $Fe(CO)_2PPh_3$ cations. Finally, the steric bulk of the malonate nucleophile has only a minor effect on the regioselectivity of nucleophilic attack on the pentadienyl ligand.

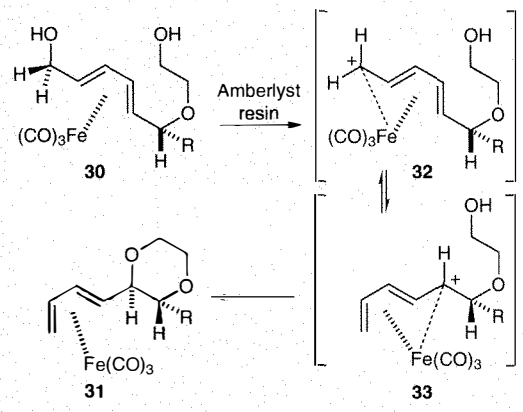
3. Resolution via Pentadienyl Cations

The desymmetrization of C_2-symmetrical (pentadienyl)$Fe(CO)_3$ cations has been reported. Thus the reaction of **2x** with (*S*)-neomenthyldiphenylphosphine gives a mixture of the two optically active diastereomeric phosphonium salts **26a** and **26b** (20% de). Slow recrystallization of this mixture gives a *single* diastereomer **26a** with >80% mass recovery via an asymmetric

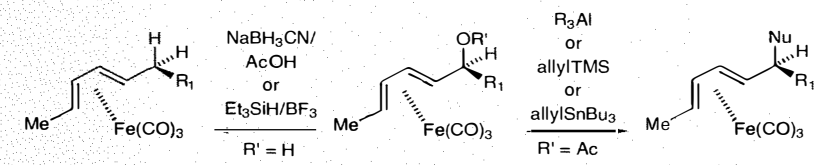
transformation of the second kind (**eq 4**).[32] The reaction of the symmetrical cation **2aa** with (–)-sparteine (-78 °C) led to the formation of (3,4,5,6-η⁴-1,3*E*,5*E*-heptatriene)-$Fe(CO)_3$ in an optically enriched fashion, albeit with low enantiomeric excess (ca. 6% ee).[52] Recently, Käser and Salzer reported the kinetic resolution of racemic α-methylbenzylamine by reaction with the optically pure cation **2z** (38% de).[35]

D. In Situ Generation and Reactivity of Transoid Pentadienyl Cations

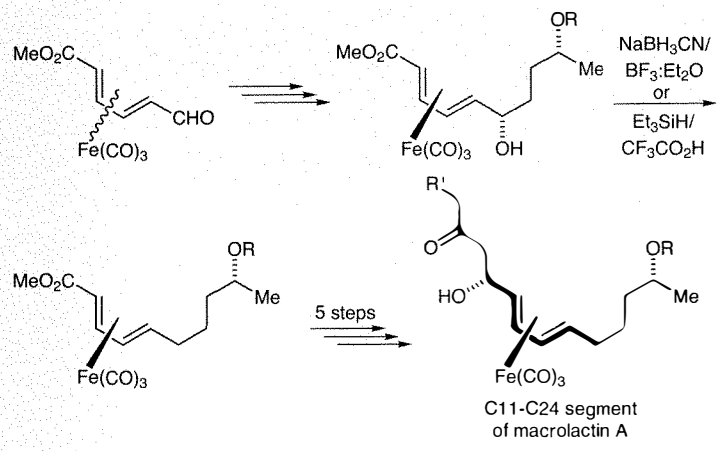
In the early 1970s, Lillya reported that Ψ-exo dienyl dinitrobenzoates **27a** undergo solvolysis (acetone/H_2O) at rates which were ca. 10-60 times faster than those of the free ligands while the corresponding Ψ-endo dienyl dinitrobenzoates **27b** undergo solvolysis slower than the free ligands.[53] These reactions take place with net retention of configuration at the center undergoing substitution (**Scheme 10**). These results are rationalized on the basis of ionization of the leaving group with anchimeric assistance from the iron atom, followed by attack of the external nucleophile on the face of the cation opposite to iron (i.e., double inversion). The Ψ-exo dinitrobenzoates have the leaving group oriented favorably for this ionization, while the Ψ-endo dinitrobenzoates must undergo rotation about the diene-to-Cα bond which would bring the remaining substituent at the α-carbon into steric congestion with the dienyl portion of the molecule. In a similar fashion, cyclodehydration of dienyldiols **28** under acidic conditions affords 5-, 6-, or 8-membered-ring ethers **29** (**eq 5**).[54] An unusual rearrangement of dienyldiol **30**, in the presence of Amberlyst® resin (acidic form), gave dienyl-1,4-dioxane **31** (**Scheme 11**).[55] This transformation is believed to involve the generation of the transoid pentadienyl cation **32** followed by rearrangement to the transoid pentadienyl cation **33** and eventual intramolecular nucleophilic capture. Good yields for cyclization (50-91%) are only observed for the Ψ-endo glycol ethers **30**. A similar 1,2-transposition of the $Fe(CO)_3$ group was observed in the reaction of cyanophosphonates with weak nucleophiles in the presence of Lewis acids.[56] The stereoselective substitution of dienol complexes using (diethylamino)-sulfur trifluoride (DAST) proceeds via the transoid pentadienyl cations.[40]



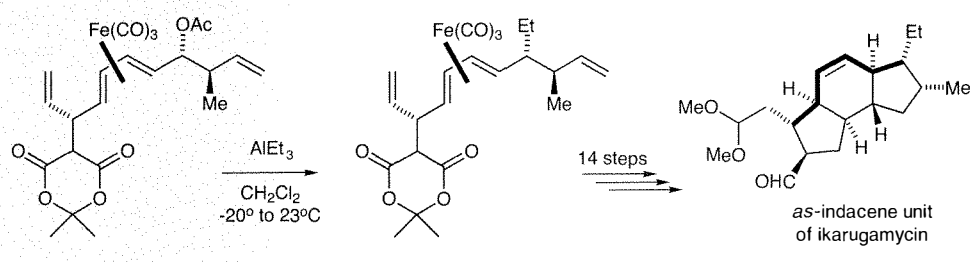
Scheme 11



Scheme 12



Scheme 13



Scheme 14

The in situ generated transoid pentadienyl cations may also undergo reaction with hydride and carbon nucleophiles. Under acidic conditions, the selective ionic reduction of hydroxyl functionalities adjacent to (diene)$Fe(CO)_3$ may be accomplished (**Scheme 12**).[57] This methodology has been utilized in syntheses of the $Fe(CO)_3$ complexed segments of the polyene macrolactin A (**Scheme 13**).[57a,b] Likewise, substitution of dienyl acetate complexes with weak carbon nucleophiles (allyltrimethylsilane, trialkylaluminums) occurs with retention of configuration.[58] This type of diastereoselective C-C bond formation has been utilized as a key step in the synthesis of the *as*-indacene unit (**34**) of ikarugamycin (**Scheme 14**).[59]

Acknowledgments

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About the Author

William Donaldson received his B.A. degree in Chemistry with Honors from Wesleyan University (1977), having done undergraduate research with Prof. Al Fry, and a Ph.D. degree in Organometallic Chemistry at Dartmouth College (1981) under the direction of Prof. Russell Hughes. After a postdoctoral fellowship with Prof. Myron Rosenblum at Brandeis University (1981-82), he returned to Wesleyan University as a Visiting Assistant Professor (1982-83), before coming to Marquette University as Assistant Professor in August 1983. He was promoted to Associate Professor in 1990 and Full Professor in 1996. Prof. Donaldson is the recipient of the Edward D. Simmons Award for Junior Faculty Excellence (1988) and the Rev. John P. Raynor Award for Teaching Excellence (1995) both from Marquette University, and held an Alexander von Humboldt Fellowship at Philipps Universitaet-Marburg (1990-91). His hobbies revolve around his family, particularly spending time with his wife, Pam, and his two sons, Scott and Jimmy.

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Thiazole-Based Routes to Amino Hydroxy Aldehydes, and Their Use for the Synthesis of Biologically Active Compounds

Esterifications, Transesterifications, and Deesterifications Mediated by Organotin Oxides, Hydroxides, and Alkoxides

Aldrichimica Acta

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About our Cover

The painting on our cover is *View in Suffolk* (oil on canvas, 37 x 49½ in.) by Thomas Gainsborough (1727-1788). When Gainsborough created this luminous view of the Suffolk countryside in the 1750s, landscape painting had only recently been established as an independent art form in Britain. It was still difficult for an English artist to sell enough landscapes to make a decent living, so Gainsborough, like most English painters, supported himself by doing portraits. Though landscape painting would remain for him an unprofitable sideline, Gainsborough was by far the most original and inventive English landscapist of the eighteenth century.

When he executed this early work, Gainsborough was under the spell of contemporary French painting, which he would have seen in London collections. Tied to French sensibilities is the treatment of the countryside as an elegant park, populated by carefree peasants like the handsome pair courting in the foreground. This modish artificiality, however, is tempered by Gainsborough's familiarity with the more naturalistic Dutch landscape tradition and, more importantly, by his own direct observations. Gainsborough's empathy with nature transcends conventional, imported formulas and looks ahead to the great achievements of English landscape painters of the nineteenth century.

Credit: The Saint Louis Art Museum. The John Fowler Memorial Collection, Bequest of Cora Liggett Fowler.

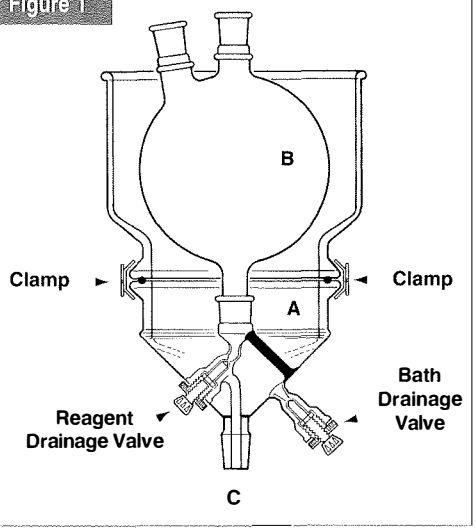
Lab Notes

A Practical Setup for the Transfer of Thermally Unstable and/or Insoluble Reagents

How often have you encountered the problem where cannulation of a reagent is impractical because of its thermal instability and/or insolubility?

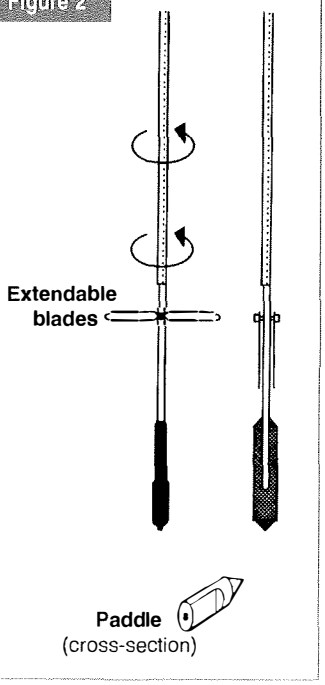
To alleviate the problem, we have found the following apparatus ideally suited for the transfer of thermally unstable and/or insoluble compounds (**Figure 1**). The design and use of this piece, to the best of our knowledge, is novel. The apparatus consists of a glass cooling bath **A** and a round bottom flask **B**. Attached to **A** is a valve, a female ground glass joint which is connected to **B**, and a male ground glass joint which can be connected to a 50–1000 mL angled two- or three-neck, round-bottom flask (**C**). The valve consists of a male joint with a threaded Teflon® nut and corresponding external glass screw threads. Flask **B** is constructed by attaching a male ground glass joint to the bottom of a 50- to 1000-mL angled two- or three-neck, round-bottom flask.

Figure 1



Cooling bath **A,** which has a slot in it to allow easy attachment, is connected to **B** containing the selected liquid. Teflon® sealing tape and a Delrin® plastic joint clip provide a tight seal. An electric motor clamped above **B** rotates a specially designed vertical rod equipped with a paddle and two extendable blades (**Figure 2**). It is essential to use a paddle that forms a good fit to the bottom of the female ground glass joint of **B**.

Figure 2



Agitation in flask **C** is achieved by placing an egg-shaped magnetic stirring bar large enough to stir the reaction mixture effectively. Flask **C** is clamped over the top of a magnetic stirrer whose flat top allows cooling or heating baths to be placed upon it. Temperatures inside **B** and **C** may be monitored by inserting a thermometer or a thermocouple probe through one of the necks. An inert atmosphere may be established through the use of rubber septa and syringe needles.

Flask **B** can be used for the preparation of lithium reagents at -78 to 25 °C; an addition funnel can be incorporated for large-scale work. Once the lithium reagent is prepared, the valve is opened and the organolithium reagent flows into flask **C** containing a solution of the appropriate electrophile.

Our laboratory has employed this apparatus extensively during the preparation of 1,1,2- and 1,2,2-trisubstituted 1,2-dihydronaphthalenes via the stereospecific 1,4-addition of organolithium reagents to unprotected 1- and 2-naphthalenecarboxylic acids at low temperature.

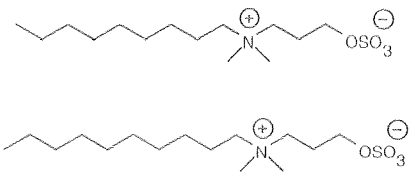
Plunian, B.; Mortier, J.; Vaultier, M.; Toupet, L. *J. Org. Chem.* **1996**, *61*, 5206.

Jacques Mortier*, Michel Vaultier, Richard Cantegril, and Philippe Dellis
Université Rennes-1, Synthèse et électrosynthèse organiques, UMR 6510 associée au CNRS campus de Beaulieu, 35042 Rennes Cedex, France

"Please Bother Us."

by

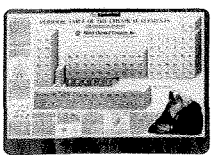
Jai Nagarkatti, President



Professor Hinze at Wake Forest University kindly suggested that we offer these zwitterionic surfactants. They have been utilized for the extractive separation of hydrophilic proteins, steroids, and vitamin E. Their lack of absorbance in the ultraviolet region and their inducement of phase separation at moderate temperatures are two of the advantages that allow them to be used for heat-sensitive compounds such as vitamin E.

Saitoh, T.; Hinze, W.L. *Anal. Chem.* **1991**, *63*, 2520. Idem *Talanta* **1995**, *42*, 119. Hinze, W.L.; Pramauro, E. *Crit. Rev. Anal. Chem.* **1993**, *24*, 133.

Naturally, we made these useful surfactants. It was no bother at all, just a pleasure to be able to help.



Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, *Aldrichimica Acta*). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. **Z15,000-2**). If we publish your *Lab Note*, you will also receive an Aldrich periodic table turbo mouse pad (Cat. No. **Z24,409-0**). It is Teflon®-coated, 8½ x 11 in., with a full-color periodic table on the front. We reserve the right to retain all entries for future consideration.

Thiazole-Based Routes to Amino Hydroxy Aldehydes, and Their Use for the Synthesis of Biologically Active Compounds

Alessandro Dondoni, Daniela Perrone*
Dipartimento di Chimica,
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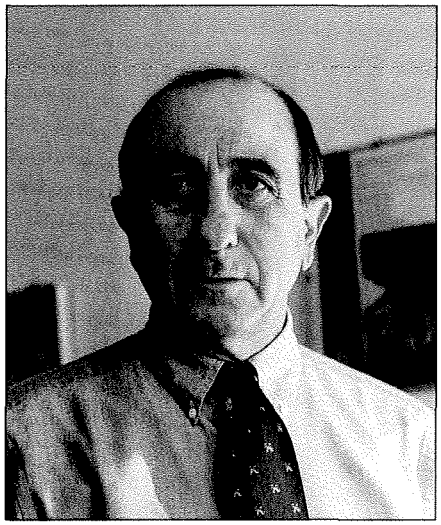
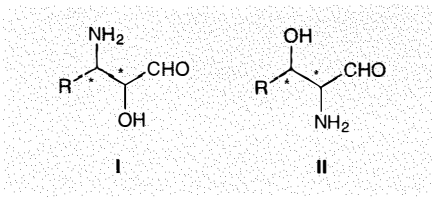
Università, 44100-Ferrara, Italy



While the total synthesis of intricate molecules of natural origin[1] is *per se* an admirable achievement and a stimulus for the invention of new chemistry,[2] the preparation of even modestly elaborated structures in a practical fashion and on a meaningful scale depends largely on the availability of relatively simple chiral building blocks. For instance, given the numerous options that are offered by the formyl group in stereoselective carbon-carbon bond forming reactions, synthetic methods leading to functionalized chiral aldehydes provide new opportunities for the construction of complex molecules. Hence, we describe in this account new routes to chiral aldehydes **I** and **II** bearing an amino and a hydroxyl group in the α and β positions, and provide examples



I **II**

of their use in the stereoselective synthesis of bioactive compounds or their precursors. While there are numerous syntheses of 1,2-amino alcohols,[3] methods that provide the concomitant installation of a manipulatable and synthetically useful functional group are quite rare.[4]

Our methods are part of a general synthesis of aldehydes that exploits the thiazole ring as a masked formyl group.[5] The synthetic equivalence is based on an operatively simple deblocking protocol that involves a one-pot, three-step reaction sequence, i.e., *N*-methylation, reduction, and hydrolysis (**Figure 1**). The essentially neutral conditions under which these reactions take place extend the range of applications of the method to the presence of various protective groups and stereocenters in the substrate. The facile cleavage of the thiazole ring; its high stability toward bases and acids, oxidants, and reductants;[6] and its tolerance of numerous types of synthetic transformations in the R side chain provide this heterocycle with considerable synthetic value as one of the most convenient formyl group equivalents.[7]

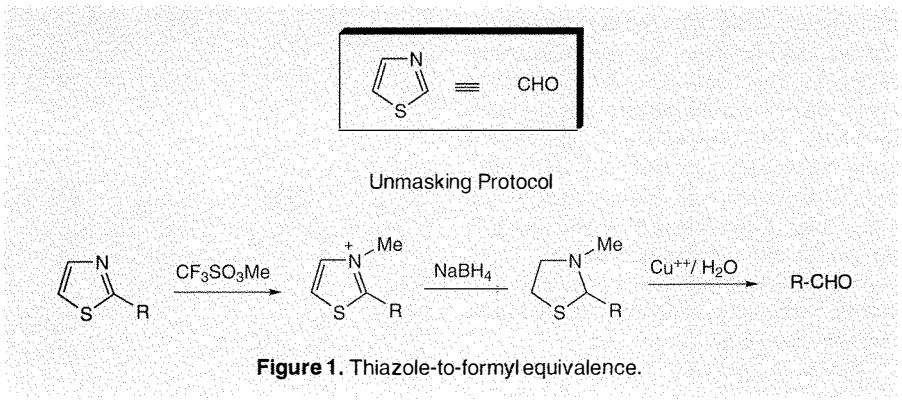


Figure 1. Thiazole-to-formyl equivalence.

Synthesis and Use of β-Amino-α-hydroxy Aldehydes I

A. Amino Aldehyde Route

The numerous proteinogenic α-amino acids that are available in both enantiomeric forms at relatively low prices constitute a convenient source of starting materials for the synthesis of aldehydes **I** (**Scheme 1**). Also, unusual α-amino acids featuring a variety of substituents R are quite accessible through various synthetic methods.[8] Amino acids can be readily converted into amino aldehydes **III** that, in turn, are quite reactive toward organometallics.[9] Thus, stereoselective addition of a 2-metalated thiazole to the carbonyl group of **III** to give amino alcohol **IV**, followed by thiazole-to-formyl unmasking, is the simplest viable route for the synthesis of target aldehydes **I**.

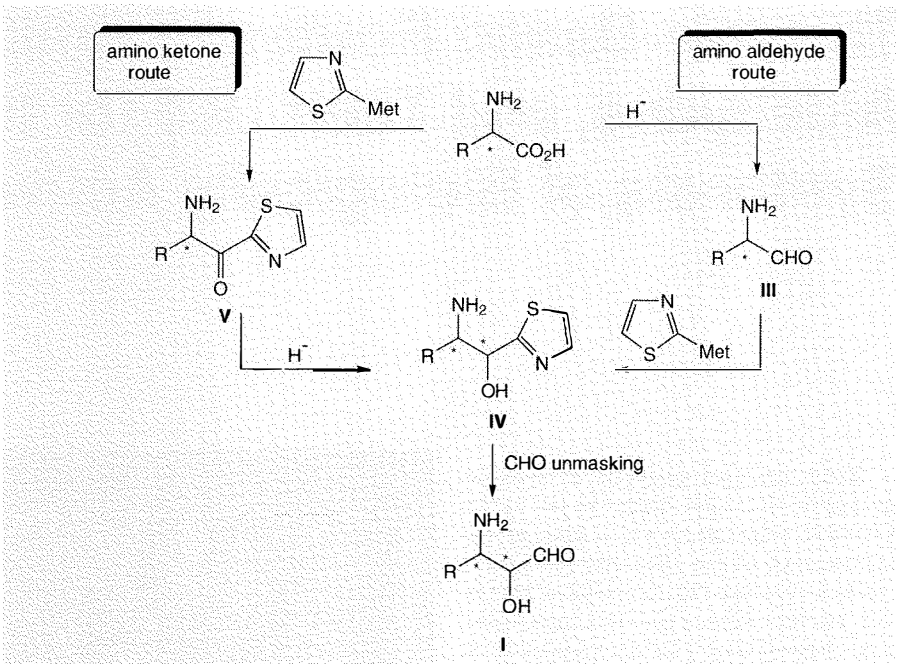
In contrast to the commonly held notion that α-amino aldehydes are plagued by high

chemical and configurational instability (a belief that we also shared at the beginning), we found the use of these reagents quite convenient in the course of our work over the years. Literature methods are available[9] for the preparation of these compounds with different amino protective groups and in satisfactory chemical and enantiomeric purities by starting from the most common and commercially available amino acids. However, in some cases we explored improving these preparative conditions.[10] The thiazole-based organometallic employed in the reaction with amino aldehydes was 2-(trimethylsilyl)-thiazole (2-TST, **2**). Earlier work in our laboratory demonstrated the excellent service of this readily available[11] (**eq 1**) and stable organosilane as a formyl carbanion equivalent for the homologation of chiral α-alkoxy aldehydes. The addition of **2** to aldehydes occurred readily in the absence of any fluoride ion catalyst[12,13] and led essentially to anti alcohols with high selectivity (ds 90-98%). The formyl group unmasking in these adducts completed the homologation sequence (**eq 2**).

Accordingly, the addition of **2** to *N-tert*-butoxycarbonyl-L-serinal acetonide (**3a**) and L-threoninal derivative **3b** occurred readily to give as major products the corresponding anti amino alcohols **4a** and **4b**, respectively (**Figure 2**).[14] On the other hand, the addition of **2** to the L-serinal (**6a**) and L-threoninal (**6b**) derivatives featuring the *tert*-butoxycarbonyl (Boc) as a single protecting group of the amino group afforded the corresponding syn amino alcohols **7a** and **7b** as major products. In all cases satisfactory levels of either anti or syn diastereoselectivity were observed. The compatibility of the formyl group unmasking protocol with the amino protective groups was demonstrated by the conversion of the thiazolyl amino alcohols **4a** and **7a** into aldehydes **5** and **8.** These compounds constitute a pair of C-2 epimeric β-amino-α-hydroxy aldehydes derived from the same amino acid (L-serine).

Hence it appeared that a reversal of diastereofacial selectivity was achieved in the addition of **2** to differentially *N*-protected serinal and threoninal. The validity of this observation was extended to aldehydes derived from phenylglycine, phenylalanine, leucine, and cyclohexylalanine with a single (*N*HBoc)- or a double [*N*(Bn)Boc]-protected amino group[14b] (**Figure 3**). Variation of the reactive aldehyde conformation as shown by the nonchelate Felkin-Anh and proton-bridged Cram cyclic models provided a simple explanation for the opposite diastereofacial selectivity. As demonstrated by the formyl group unmasking of the alcohol **4a** and **7a** (**Figure 2**), the overall procedure can result in the conversion of each α-amino aldehyde into a pair of diastereomeric one-carbon higher homologues.

As a first application of the foregoing results it is worth describing an efficient synthesis of the *N*-Boc-β-amino-α-hydroxy-4-phenylbutanal **9** since this aldehyde was considered[15] as a key intermediate for the preparation of the Phe-Pro mimic hydroxyethylamine isosteric dipeptide **11**.



Scheme 1. Thiazole-based homologation of α-amino acids.

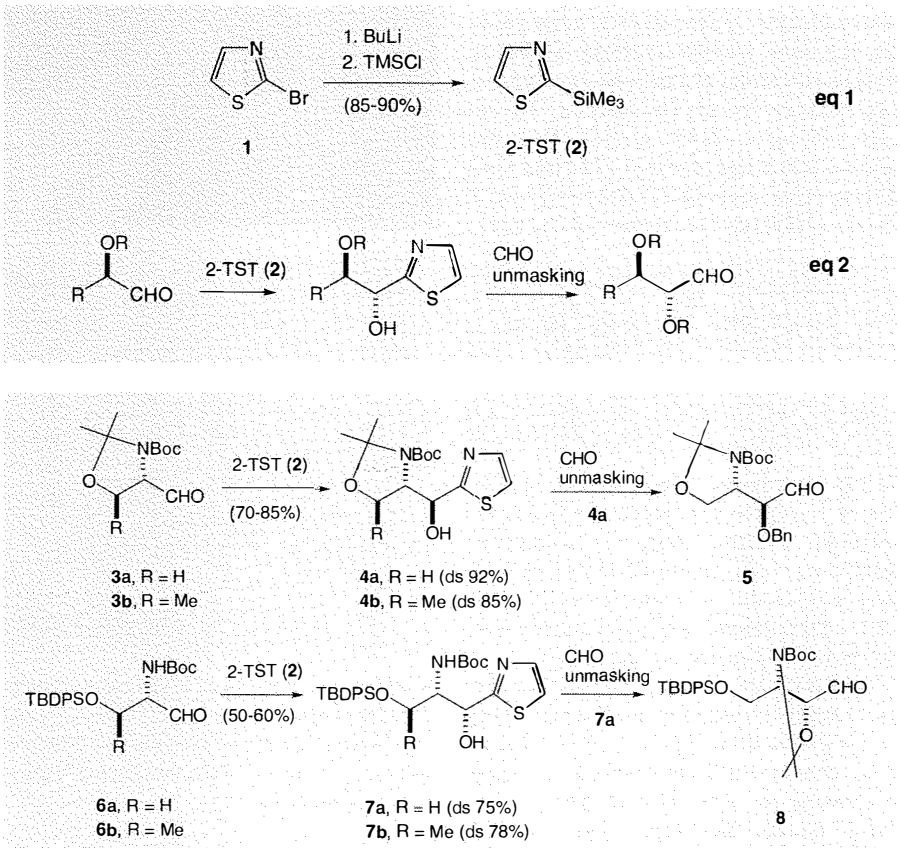


Figure 2. Representative anti and syn addition reactions of 2-TST (**2**) to α-amino aldehydes.

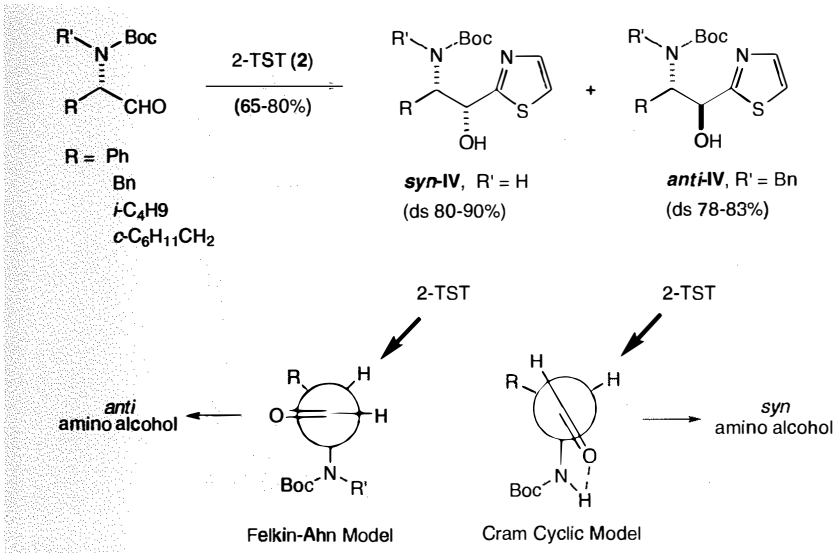


Figure 3. Diastereoselectivity and transition-state models in the addition of 2-TST (**2**) to α-aminoaldehydes.

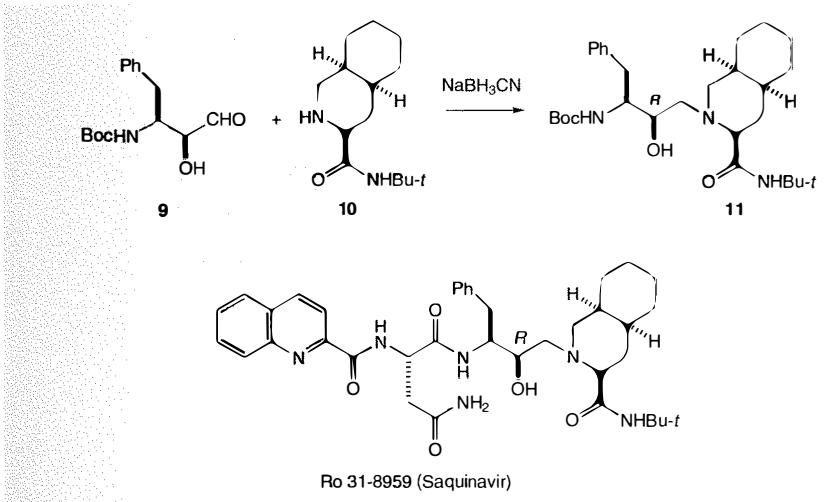
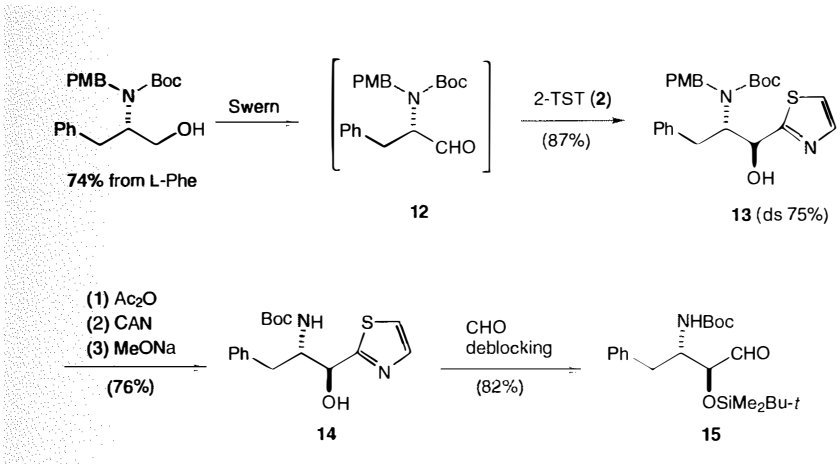


Figure 4. Approach to the dipeptide isostere moiety **11** of Ro 31-8959.[16]



Scheme 2

that in turn served as a precursor of the potent and selective HIV protease inhibitor Ro 31-8959 (Saquinavir)[16] (**Figure 4**). Phenylalanine was the logical starting material for the synthesis of **9** by the amino aldehyde route. It had to be considered that the relative stereochemistry of the OH and NHBoc group in **9** was anti while the above results showed a predominant syn addition of **2** to *N*-monoprotected L-phenylalaninal derivatives. The syn selectivity in favor of the undesired stereoisomer was in fact confirmed in an approach to **9** followed by a Roche group.[15] Hence, it was challenging to demonstrate a thiazole-based route to this aldehyde via anti addition of 2-TST (**2**) to a suitable L-phenylalaninal derivative bearing a doubly protected amino group. Toward this aim our attention became focused on the use of Boc and *p*-methoxybenzyl (PMB) since the former is part of the final product, and the latter could be removed under oxidative conditions that are compatible with the presence of the thiazole ring. Thus, *N*(Boc)PMB-L-phenylalaninal (**12**) was generated in situ by Swern oxidation of the corresponding alcohol and reacted with **2** at low temperature (**Scheme 2**). After desilylative workup of the reaction mixture, ^{1}H NMR analysis showed the presence of the anti adduct **13** and the syn isomer (not shown in the Scheme) in a 3:1 ratio. Compound **13** was isolated in 64% yield. Removal of the PMB group from **13** with cerium ammonium nitrate (CAN) required the temporary protection of the hydroxyl group as the *O*-acetyl ester, since the reaction with CAN led to the decomposition of the unprotected alcohol. Finally, the application of the standard one-pot thiazole-to-formyl deblocking protocol to the *N*-Boc anti amino alcohol **14** afforded aldehyde **15** (25% overall yield from L-phenylalanine) that is the *O*-TBDMS derivative of the target compound **9**. This stereoselective thiazole-based synthesis of this β-amino-α-hydroxy aldehyde bears considerable relevance not only to Ro 31-8959 but also to other protease inhibitors featuring a hydroxyethylamine isosteric dipeptide unit.[17]

Another illustration of the utility of this method is provided by the synthesis of hydroxyethylene isosteric dipeptides. The increasing interest in this class of dipeptide mimics stems from their inhibition of aspartic proteases,[18] the enzymes that are involved in various human diseases such as hypertension[19] and acquired immunodeficiency syndrome (AIDS).[20] An obvious approach to *N*-Boc isosteric dipeptides in either their open-chain or lactone form **16** was considered starting from α-amino acids through β-amino-α-hydroxy aldehydes **I**

featuring a syn relationship between the amino and hydroxyl groups (**Figure 5**).

Guided by the above observations we have carried out a new formal synthesis of **16a**, a hydroxyethylene dipeptide isostere of the potent renin inhibitor L-Leu-L-Leu, in 19% overall yield starting from L-leucine[21] (**Scheme 3**). Our method compares quite well with that of an earlier approach that employed ethyl propiolate as a three-carbon homologating system of the same amino acid.[22] In our case, the chain elongation of the amino acid was carried out in a stepwise fashion. In a first sequence, leucine was converted into *N*-Boc leucinal **17** that promptly added 2-TST (**2**) with correct, although moderate, syn stereoselectivity (ds 77%) to give amino alcohol **18** as the major product. Aldehyde **19** was then liberated by the usual thiazole-to-formyl deblocking protocol. It is worth noting that *t*-butyldimethylsilyl (TBDMS) was used as the hydroxyl protecting group in this step. This choice was dictated by the stability of this protective group on one hand and the ease of removal on the other, a condition that was exploited later on in the synthesis. The second chain elongation was carried out through Wittig olefination of **19** with a carbomethoxy-stabilized phosphorus ylide, and reduction of the mixtures of *E* and *Z* enoates **20** with nickel boride generated in situ from $NiCl_2$ hexahydrate and $NaBH_4$. This reagent did not affect the ester group of the enoates and therefore produced a single alkanoate which, upon desilylation with Bu_4NF, afforded γ-lactone **21.** The same compound was previously reported by Kleinman and co-workers[22] and converted into the target isosteric dipeptide **16a**.

The thiazole ring did not appear to be a convenient masked equivalent of the carboxylate group. The deblocking sequence (oxidation with singlet oxygen and then refluxing in aqueous 6N HCl) described by Ireland some years ago[23] constitutes a serious limitation in synthesis since these harsh reaction conditions can affect the integrity of stereocenters and remove labile protecting groups. We also found that the use of RuO_2-$NaIO_4$ gives unsatisfactory results.[24] Fortunately enough, the facile oxidation of the formyl to the carboxylate group under a variety of reaction conditions extends the scope of the thiazole-based strategy to the synthesis of carboxylic acid derivatives as well. Our synthesis[25] of the phenylisoserine C-13 side chain of the potent anticancer agents[26] Taxol® and Taxotere® (**Figure 6**) illustrates an important application of this chemistry. Considerable attention has been directed in recent years to the synthesis of this relatively simple β-amino-α-hydroxy

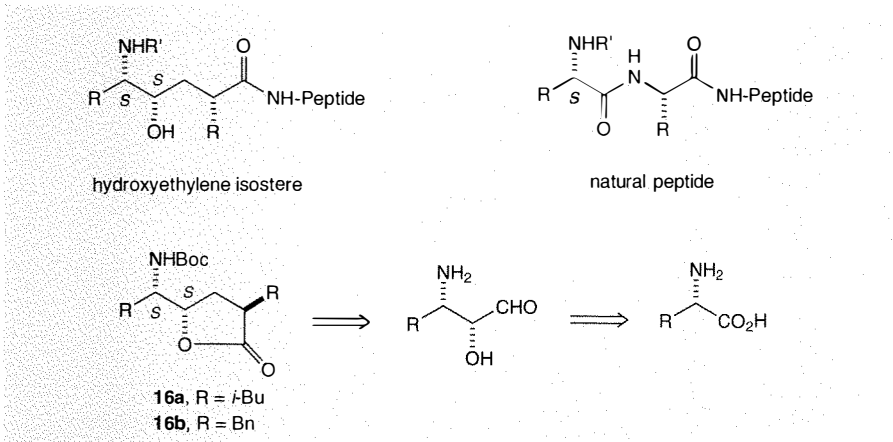
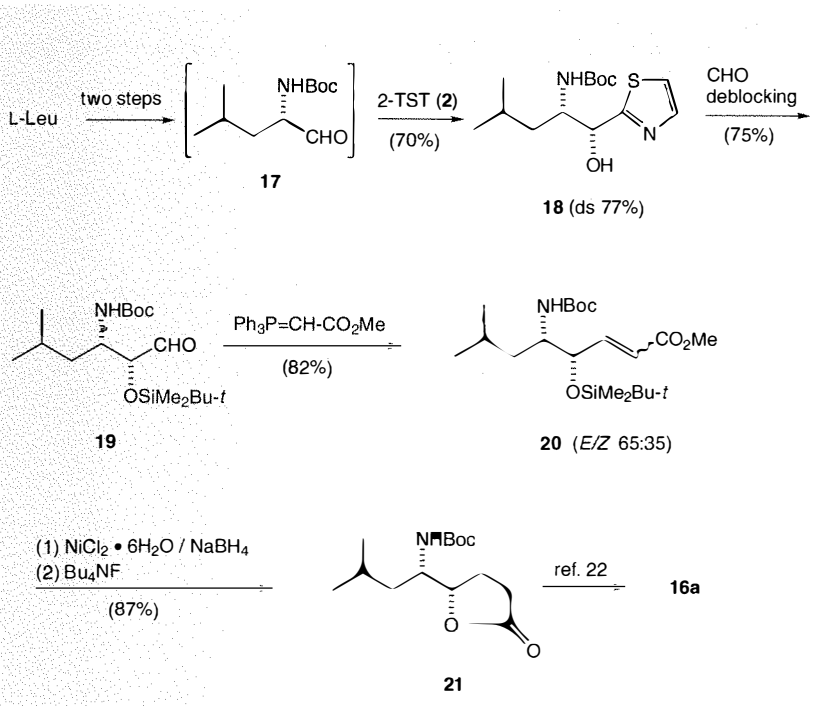


Figure 5. Hydroxyethylene isosteres and retrosynthetic plan.



Scheme 3

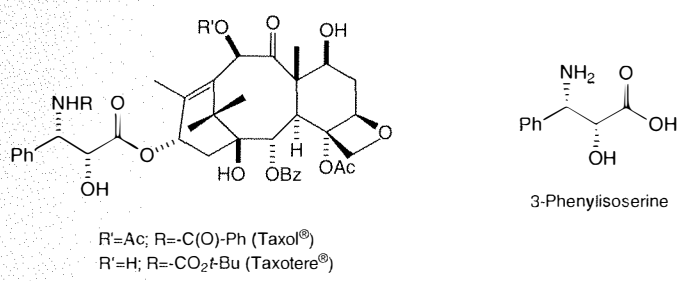
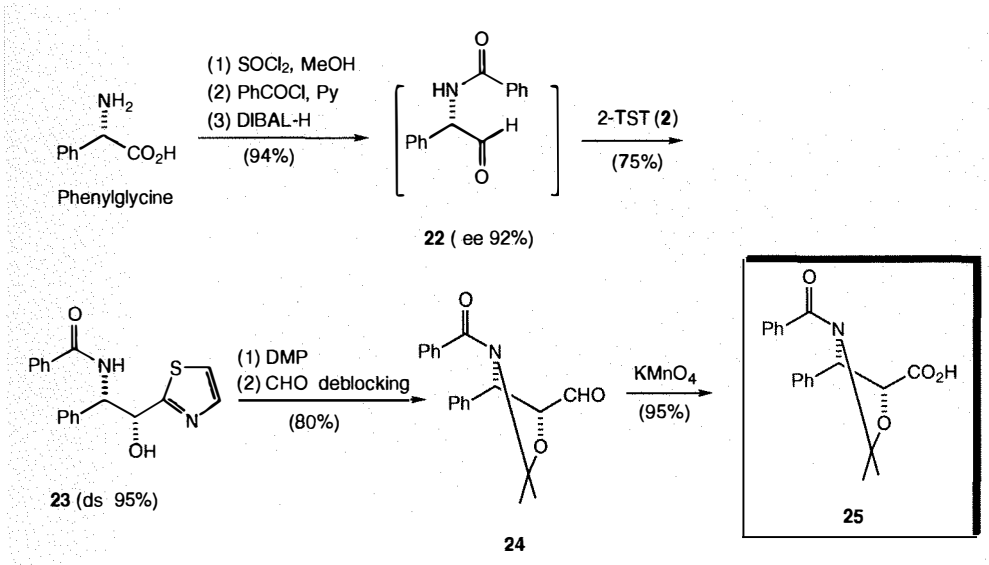


Figure 6. Taxol® and Taxotere® and their basic C-13 side chain.

acid starting from the most disparate starting materials.[27] This is justified by the essential role this moiety plays in the biological activity of Taxol® and Taxotere®,[26] and by its use in semisynthetic approaches to these compounds and their analogs.

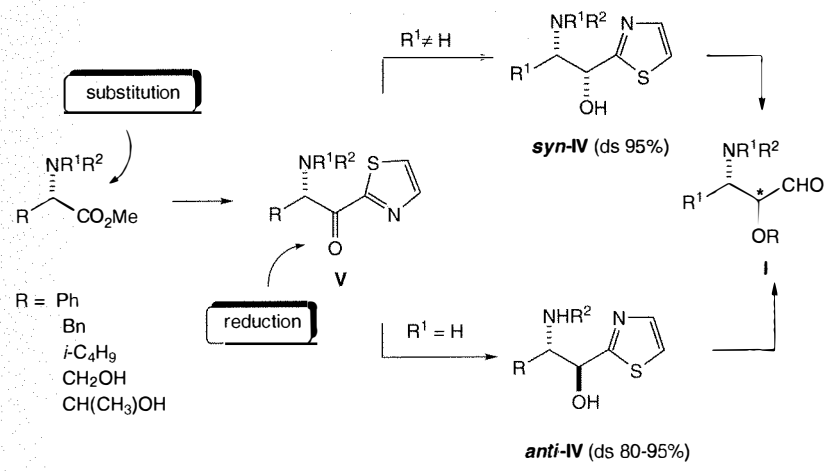
Our synthesis[25] of the Taxol® side chain *N*-benzoyl-3-phenylisoserine starting from L-phenylglycine is summarized in **Scheme 4**. The α-amino acid was converted into the *N*-benzoyl aldehyde **22** in good yield and enantiomeric purity as judged from the ^{1}H NMR of the Mosher ester of the corresponding alcohol. The reaction of this aldehyde with 2-TST (**2**) responded perfectly to the expectation of a chelation-controlled syn addition (ds 95%) since it afforded the amino alcohol **23** in good yield. Alcohol **23** was purified by acetonization to remove the small amount of anti isomer. Aldehyde **24** was then liberated in the usual way and oxidized under mild and neutral conditions ($KMnO_4$ / *t*-BuOH) to the carboxylic acid **25** in a quite rewarding overall yield (52%) from phenylglycine. In the same way, the Taxotere® side chain, *N-tert*-butoxycarbonyl-3-phenylisoserine, was prepared albeit in a lower overall yield (35%). The synthesis of the latter compound has been reviewed in a specialized journal of drug discovery.[28]



Scheme 4

B. Amino Ketone Route

In another plan for preparing thiazolyl amino alcohols **IV**, amino aldehydes **III** were replaced by amino ketones **V** (**Scheme 1**). This route employed the same reagents of the amino aldehyde route but in reversed order. In fact, it involved first the installation of the thiazole ring by a substitution reaction of a 2-metalated thiazole on the amino ester and then the stereoselective reduction of ketone **V** by a metal hydride[29] (**Scheme 5**). Tuning the stereoselectivity by singly and doubly protecting the amino group gave amino alcohols anti-**IV** and syn-**IV**, respectively. This stereochemical outcome is *opposite* to that of the addition of 2-TST (**2**) to the same differentially protected amino aldehydes (**Figure 3**). Hence, the two routes are nicely complementary for the preparation of stereoisomeric amino alcohols **IV** with the required stereochemistry. The application of the same transition-state models involving nonchelate and chelate conformations of the amino ketone explains the diastereoselectivity reversal (**Figure 7**).



Scheme 5

The amino ketone route was also successfully employed for the homologation of various amino acids into the corresponding pairs of C-α epimer β-amino-α-hydroxy aldehydes **I**. The representative homologation of L-threonine served to evaluate more closely the efficiency of the method. The amino acid was converted into amino ketone **27** by reaction of 2-lithiothiazole (2-LTT) with the protected methyl ester **26** (**eq 3**). The in situ generation of 2-LTT from 2-bromothiazole **1** and butyllithium (**eq 1**) and

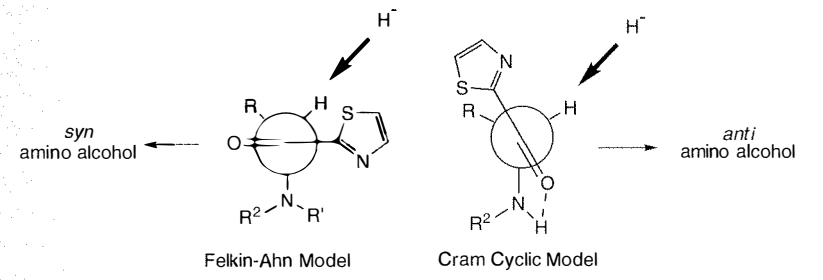


Figure 7. Diastereoselectivity and transition-state models in the reduction of α-amino ketones **V**.

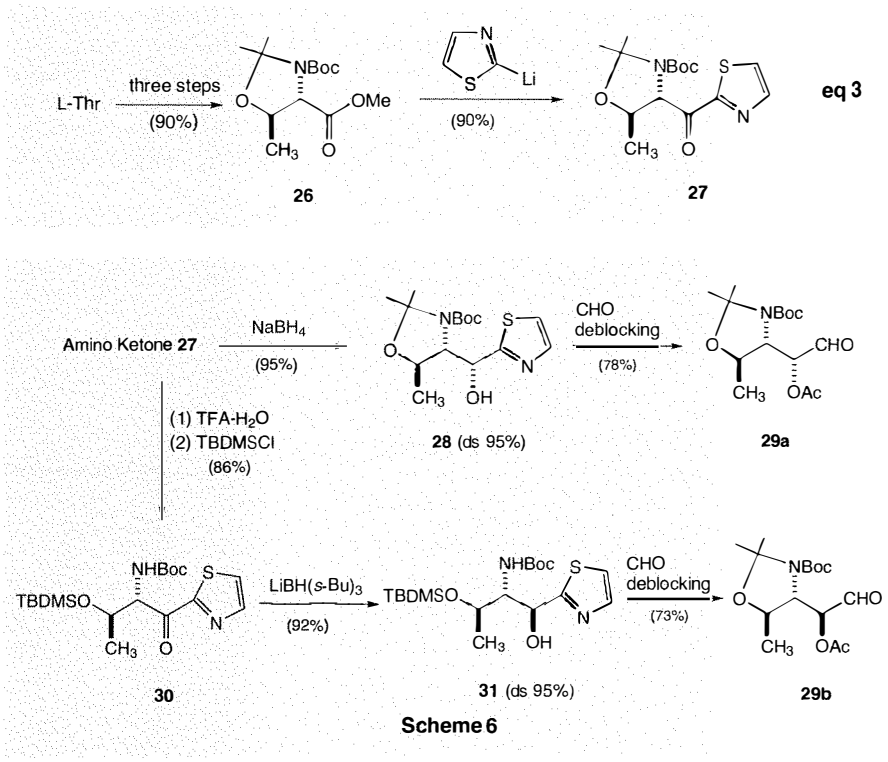
its subsequent reaction with **26** were quite simple operations even though they required some care.[30] The clean substitution of 2-LTT on the amino ester (Gilman-type ketone synthesis)[31] without the formation of tertiary alcohol arising from the addition of the organometal to the resulting ketone is noteworthy. The reason for this efficient acylation of the thiazole ring may be ascribed to the stability of the initial 2-LTT-ester adduct as a result of intramolecular chelation.[32]

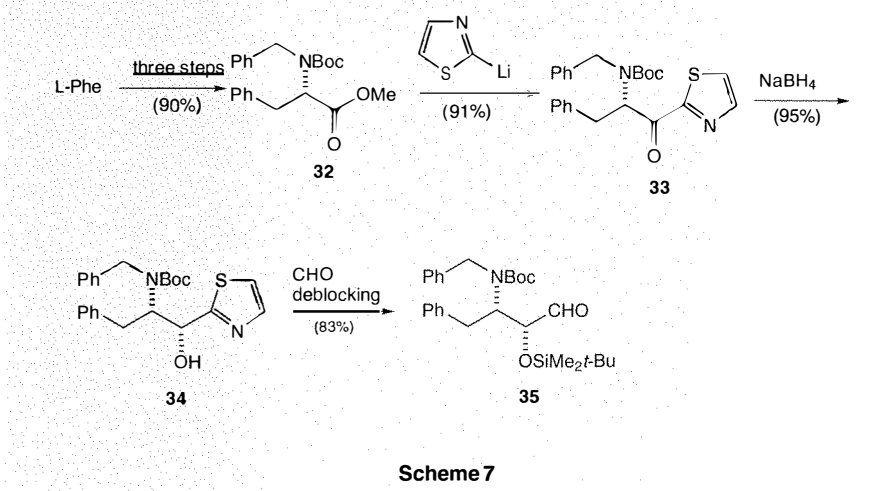
Reduction of amino ketone **27** with $NaBH_4$ produced the syn amino alcohol **28** (**Scheme 6**). Suitable elaboration of **27** into the differently protected amino ketone **30** and reduction of the latter with $LiBH(s\text{-}Bu)_3$ (L-Selectride®) gave, instead, the anti amino alcohol **31**. Both reactions occurred with high levels of diastereoselectivity (ds 95%). The use of L-Selectride® [or diisobutylaluminum hydride (DIBAL-H)] for the reduction of **30** rather than $NaBH_4$ was simply dictated by the high selectivity obtained with these reagents. Hence, the rich menu of available hydride-releasing reagents allowed substantial improvement of the carbonyl reduction when reaction results were unsatisfactory. Of course, the sequence was completed by liberation of the corresponding β-amino-α-hydroxy aldehydes **29a** and **29b** in fair yields.

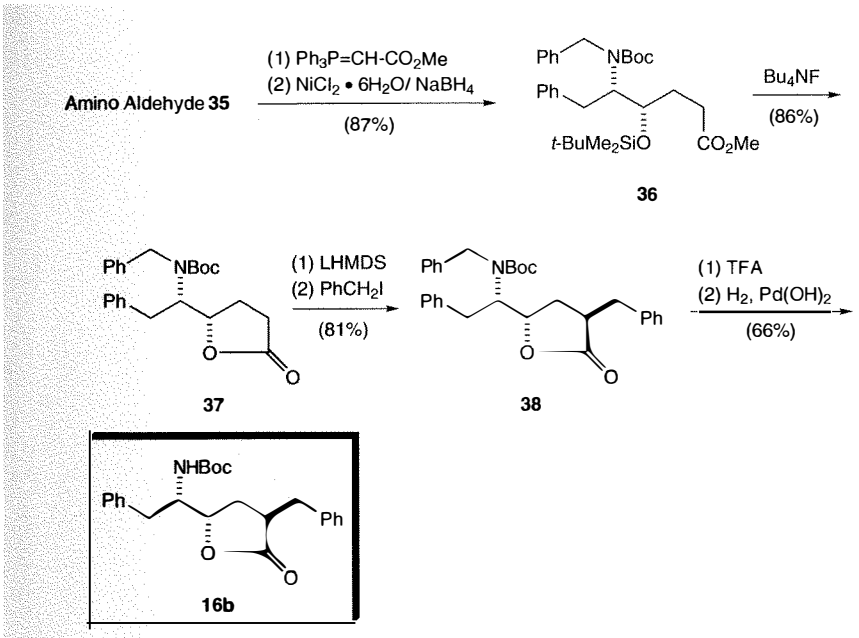
A good illustration of the strategic use of this amino ketone route is provided by our recent synthesis[21,33] of the L-Phe-L-Phe hydroxyethylene dipeptide isostere in the lactone form **16b** (**Figure 5**). An earlier synthesis of this short substrate peptide analog from D-mannose was reported by a Merck group.[34] Substitution of this subunit for a suitable dipeptide of oligopeptide enzyme substrate gave potent inhibitors of HIV-1 aspartic protease. A synthetic approach to the required β-amino-α-hydroxy aldehyde **I** via the amino ketone route appeared quite feasible based on the high levels of syn selectivity registered in the carbonyl reduction of compounds having a double-protected amino group. The *tert*-butoxycarbonyl (Boc) and benzyl (Bn) groups were considered as a pair of convenient protective groups in this approach, since conditions were known for the selective removal of the latter. **Scheme 7** summarizes the synthesis of aldehyde **35** from *N*-(Boc)Bn-L-phenylalanine methyl ester **32**. The expectation of an efficient synthesis of this aldehyde was completely fulfilled by the high yield observed in each step and the remarkable level of syn selectivity with which ketone **33** was reduced to amino alcohol **34**.

To continue construction of the carbon chain of the target isosteric dipeptide, aldehyde **35** was subjected to Wittig olefination by a carboxylate-bearing phosphorus ylide, and the resulting mixture of enoates was reduced with nickel boride to the γ-hydroxy-δ-amino ester **36** (**Scheme 8**). We sought an ideal elaboration of alkanoate **36** into **16b** by the direct stereoselective transfer of the benzyl group from nitrogen to the α-carbon. This rearrangement would have nicely fulfilled the Trost 'atom economy' concept[35] and would have been worth investigating. Instead, this transformation was carried out stepwise and, we must admit, in an expensive manner. First of all **36** was converted into lactone **37**. Stereoselective benzylation of the latter afforded the trans alkylated lactone **38** featuring the correct configuration at the new stereocenter. Finally, the one-pot removal of the *N*-benzyl group by sequential *N*-Boc deprotection and hydrogenolysis in the presence of $(Boc)_2O$ gave the target isosteric dipeptide **16b** in 23% overall yield from L-phenylalanine. After our first report[33] on the synthesis of **16b**, another amino ketone-based route to the same compound starting from L-Phe was succinctly described.[36] Other papers have also appeared showing the utility of amino ketones for amino acid homologation.[37]

The ease of access to various β-amino-α-hydroxy aldehydes **I** stimulated the synthesis of other biologically active nitrogen compounds. Compound **39** (**Figure 8**),







Scheme 8

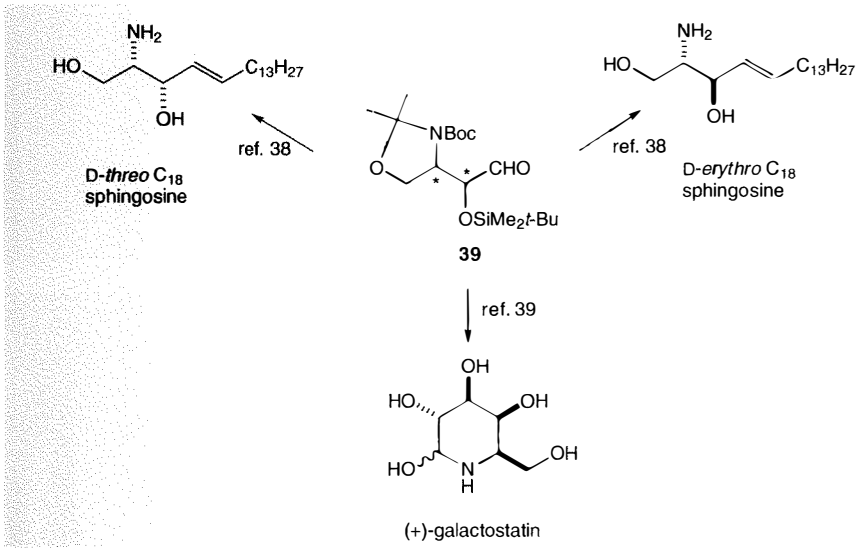


Figure 8. Representative natural products synthesized by thiazole-based homologation of serine.

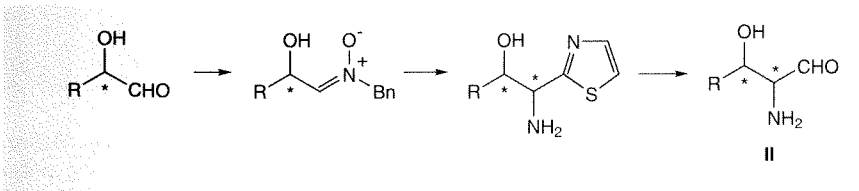


Figure 9. Homologation of aldehydes through *N*-benzyl nitrones (aminohomologation).

available in the four possible stereoisomers from serine through either the amino aldehyde or amino ketone route, proved to be a valuable building block for the gram-scale synthesis of threo and erythro sphingosines[38] and the model aza sugar galactostatin.[39] Aldehydes **I** derived from phenylalanine and leucine[29] were oxidized to the unusual amino acid components of the oligopeptides bestatin and amastatin.[40]

The use of these techniques for amino acid homologation has been considered by others.[41] Given the complementary nature of the two routes and the numerous variations which are possible within each one, the method becomes of interest for a combinatorial approach to a library[42] of compounds of type **I.**

Synthesis and Use of α-Amino-β-hydroxy Aldehydes II

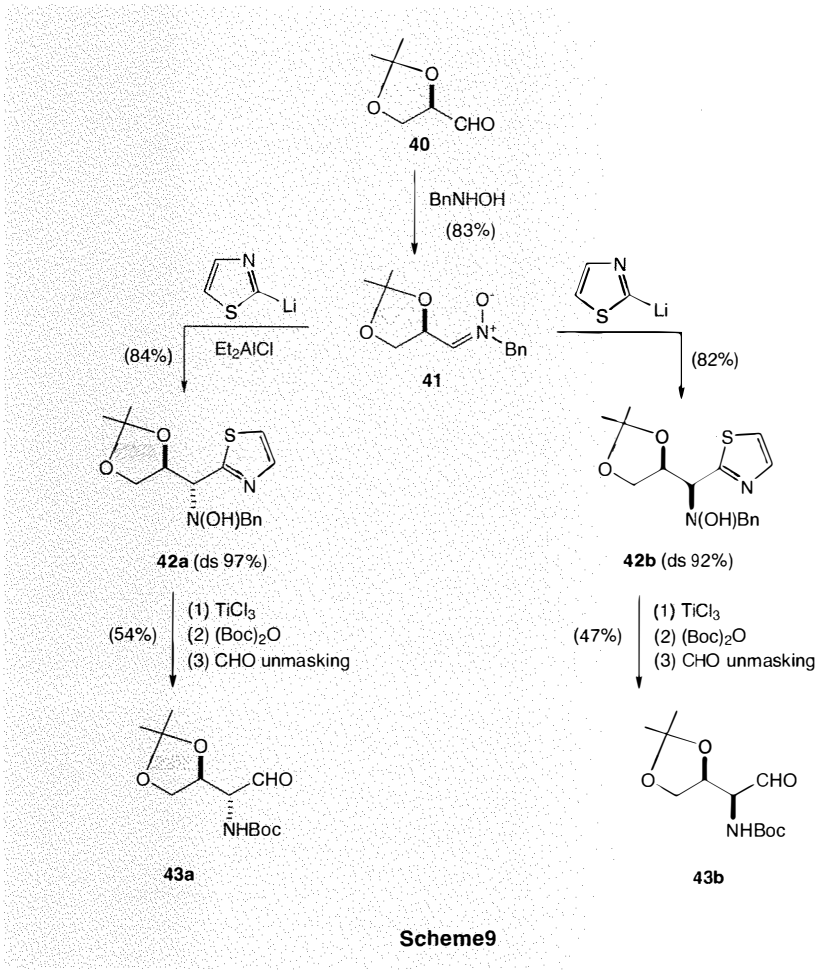
While the addition of a 2-metalated thiazole to the aldehyde carbonyl results in the formation of a secondary alcohol that, when subjected to the thiazole-to-formyl deblocking protocol, leads to an α-hydroxy aldehyde homologue, it is evident that the use of an imino derivative of the same aldehyde will provide a secondary amine and then an α-amino aldehyde homologue (aminohomologation). Preliminary results of this synthetic approach from our laboratory were not considered for some time. Hence, it was in mid-1991, when Pedro Merino was returning to Zaragoza after two years as a postdoctoral associate in our group, that we decided to continue our collaboration, although from a distance, and employ this approach for the synthesis of α-amino-β-hydroxy aldehydes **II** via α-hydroxy aldehyde nitrones (**Figure 9**). The use of nitrones as iminium derivatives of aldehydes[43] turned out to be quite convenient since various compounds derived from acyclic chiral aldehydes and dialdoses were easily prepared and proved to be stable enough for handling and storage,[44] but, nevertheless, were sufficiently reactive towards various 2-metalated thiazoles.[45]

A model stereocontrolled aminohomologation sequence is summarized in **Scheme 9**. D-Glyceraldehyde acetonide (**40**) was transformed into the corresponding *N*-benzyl nitrone **41** simply by condensation with benzylhydroxylamine in the presence of a heterogeneous drying agent such as sodium or magnesium sulfate. Then the addition of 2-lithiothiazole (2-LTT) to **41** was carried out with opposite diastereofacial selectivity by using the free nitrone (syn addition) or the Et_2AlCl-precomplexed derivative (anti addition).[46] The overall yields and levels of diastereoselectivity that were registered are noteworthy (92-97%). Similar results were obtained with $TiCl_4$, whereas other Lewis acids ($MgBr_2$, $ZnBr_2$) were scarcely efficient. The elaboration of the individual anti and syn *N*-benzylhydroxylamines **42a** and **42b** to epimeric α-amino aldehydes **43a** and **43b**, respectively, followed the same procedure, i.e., reduction of the hydroxylamino to the amino group by $TiCl_3$ (Murahashi method),[47] and unmasking of the aldehyde by the usual cleavage of the thiazole ring.

The convenient use of thiazole became apparent in the reduction step since other acid-sensitive formyl protective groups, such as the 1,3-dithiane ring, did not tolerate the $TiCl_3$ treatment and the reaction produced essentially tarlike material.

The key feature of the above aminohomologation sequence was the excellent stereocontrol exerted by Lewis acids on the addition of 2-LTT to nitrone **41**. The opposite diastereofacial selectivities observed in the absence or in the presence of Lewis acids indicated strong interactions of these catalysts with the nitrone. The syn addition to the free nitrone[48] suggested a transition-state model **A** (**Figure 10**) similar to those developed for reactions of alkenes and enolates.[49] On the other hand, the anti addition to the Et_2AlCl-precomplexed nitrone was tentatively explained by model **B**.

The scope of the above aminohomologation route was studied by considering various poly(alkoxy) aldehydes of different complexities. The method worked quite well in most of the cases so that various pairs of epimeric α-amino aldehydes **II** [R = poly(alkoxy) chain or pyranose or furanose ring] were obtained in satisfactory yields. Exceptions were found by increasing the complexity of the substituent R. For instance the addition of 2-LTT to the arabinose nitrone **45** was moderately anti selective (ds 70-76%) either in the absence or presence of complexing agents (**Scheme 10**). *N*-Benzylhydroxylamine **46** was the major product in every case. Fortunately enough, this compound was correctly assembled for conversion into D-mannosamine, a rare and biologically important amino sugar. The elaboration of **46** by the established procedure ($TiCl_3$-based reduction to amine and aldehyde unmasking) afforded *N*-acetyl-D-mannosamine diacetonide **47** that was converted into the free sugar **48** by deacetonization with aqueous trifluoroacetic acid. A chemical synthesis of **47** from D-gluconolactone[50] and an enzymatic synthesis of **48** by epimerization of glucosamine[51] have been reported. Both compounds have been used as precursors to *N*-acetyl neuraminic acid by coupling with pyruvic acid or synthetic equivalents.



Scheme9

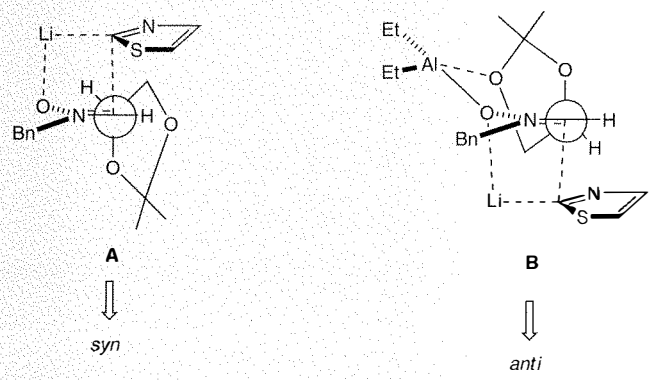
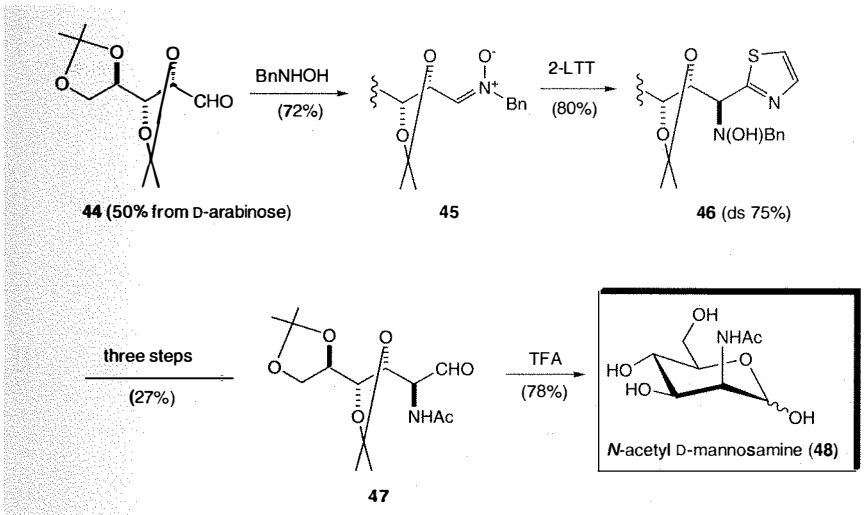


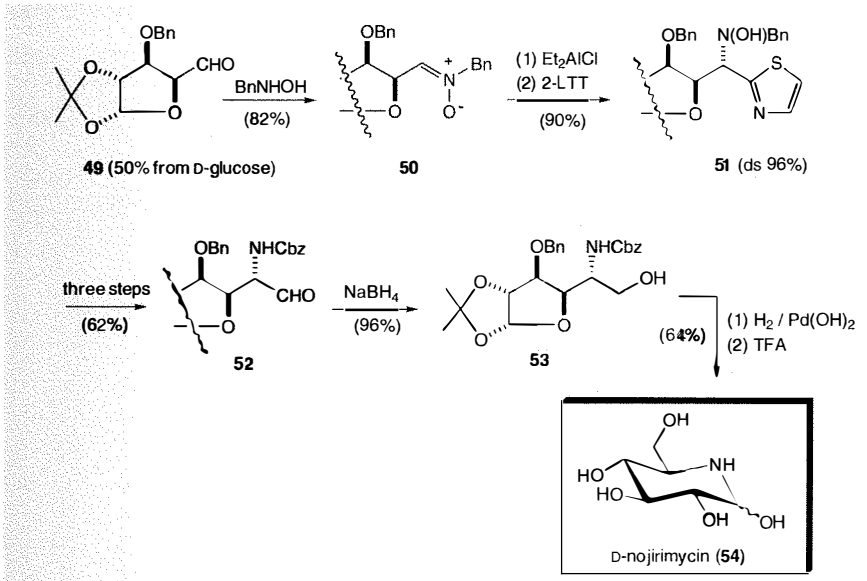
Figure 10. Model transition states for the addition of 2-LTT to nitrone **41**.

Another example of aminohomologation of a sugar-derived aldehyde to give an amino sugar whose nitrogen atom is part of the ring (aza sugar) is shown in **Scheme 11**. The precomplexed *C*-glycosyl nitrone **50** derived from the protected D-*xylo*-dialdose **49** was converted into the anti hydroxylamine **51** with excellent diastereoselectivity. Amino aldehyde **52** was liberated by the usual technique and reduced to amino alcohol **53**. Removal of the benzyloxycarbonyl (Cbz) and isopropylidene protective groups afforded D-nojirimycin (**54**), a quite common member of the aza sugar class.[52] The successful synthesis of this compound demonstrates the potential of the method for the synthesis of other aza sugars of natural origin as well as unnatural analogs.

From the above example it became apparent that the aminohomologation of dialdoses was a powerful method for assembling a chiral α-amino aldehyde side chain in a pyranose or furanose ring. Hence, we considered the synthesis of the polyhydroxylated ε-amino acid **55** (destomic acid)[53] and the amino sugar **56** (lincosamine)[54] by a stereocontrolled aminohomologation of D-*galacto*-hexodialdopyranose (**Figure 11**). These compounds have been the target of various synthetic approaches,[55] but very few, to the best of our knowledge, have dealt with a stereoselective method leading to both products from a single precursor.[56]



Scheme 10



Scheme 11

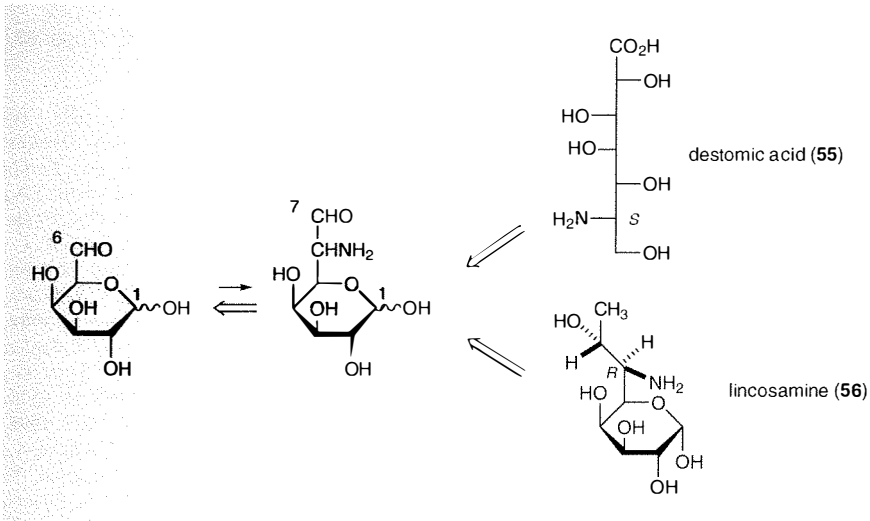


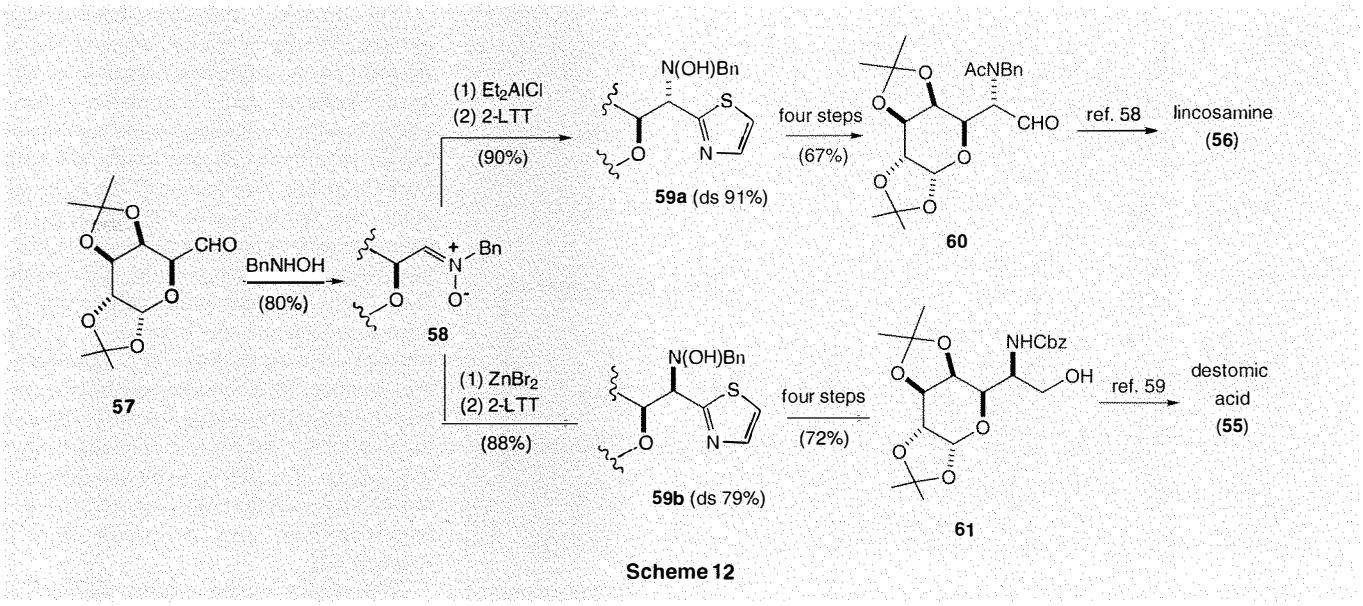
Figure 11. Destomic acid (**55**) and lincosamine (**56**) : retrosynthesis.

The protected D-*galacto*-hexodialdopyranose **57** was the starting material for our stereodivergent aminohomologation procedure[57] (**Scheme 12**). Opposite stereoselectivities were obtained in the addition of 2-LTT to nitrone **58** precomplexed with Et_2AlCl in one case and with $ZnBr_2$ in the other. The former reaction produced the *N*-benzylhydroxylamine **59a** as the major product, whereas the latter gave the epimer **59b.** Very likely, different modes of Lewis acid-nitrone association are responsible for the reversal of diastereoselectivity. These hydroxylamines were transformed into the corresponding sugar α-amino aldehydes through the usual $TiCl_3$ dehydroxylation and formyl unmasking. The aldehyde **60** and the alcohol **61** had been previously converted into lincosamine[58] and destomic acid,[59] respectively.

We recently sought a further application of the aminohomologation method in the synthesis of pseudo C_2-symmetric 1,3-diamino alcohol core units of HIV protease inhibitors. The great interest in this class of new inhibitors stems from the recent recognition that aspartic proteinase encoded by HIV-1 exists in its active form as a twofold symmetric homodimer.[60] We have tested our synthetic method by preparing the known pseudo C_2-symmetric dibenzyl 1,3-diamino-2-propanol (*S,S*)-**63** and two meso isomers **63a** and **63b** by adding benzylmagnesium chloride to nitrone **62** with either 2*R* or 2*S* configuration (**Figure 12**).[61] These nitrones were obtained from the corresponding aldehydes that were, in turn, prepared by the amino aldehyde or amino ketone route. The syn/anti stereoselectivity (ds 94-95%) of the BnMgCl addition to these nitrones was efficiently controlled by precomplexation with Et_2AlCl. It was suggested that the antipode (*R,R*)-**63** was equally accessible starting from a suitable chiral nitrone. Hence, by using nitrones of various β-amino-α-hydroxy aldehydes **I** and other organometals as alkylating agents, the method appears highly promising for the production of numerous C_2-symmetric diamino alcohols.

Conclusion

This brief research report has highlighted methods that allow a number of aminohydroxy aldehydes to be synthesized in a stereoselective fashion. Target compounds have been prepared and transformed into biologically active products of different types, including isosteric peptides, sphingosines, aza sugars, and long-chain amino sugars. The methods employ either α-amino acids or monosaccharides as starting materials and 2-metalated thiazoles as reagents for



Scheme 12

the installation of the formyl group. Attractive features of these formylation reactions are their efficiency and flexibility in that they appear amenable to the preparation of chiral aldehyde building blocks with structural diversity. The superb role of the thiazole ring as a formyl group equivalent is attested to by its compatibility with numerous functionalities and reaction conditions, thus establishing the broad applicability of this chemistry. Only 2-metalated thiazoles have been employed in these methods: the stable, yet very reactive, trimethylsilyl derivative[62] 2-TST, and the lithio derivative 2-LTT, which is easily generated in situ. Both reagents function as formyl carbanion equivalents; therefore, the methods described here are just specific tactics of a general strategy for the synthesis of aldehydes that employs different types of thiazole-based reagents. The methods allow the installation of two- and three-carbon atom moieties bearing the formyl group and, subsequently, provide a solid foundation for a more rapid synthesis of complex molecules, particularly carbohydrate derivatives. This topic will be exhaustively described in a forthcoming review.[63]

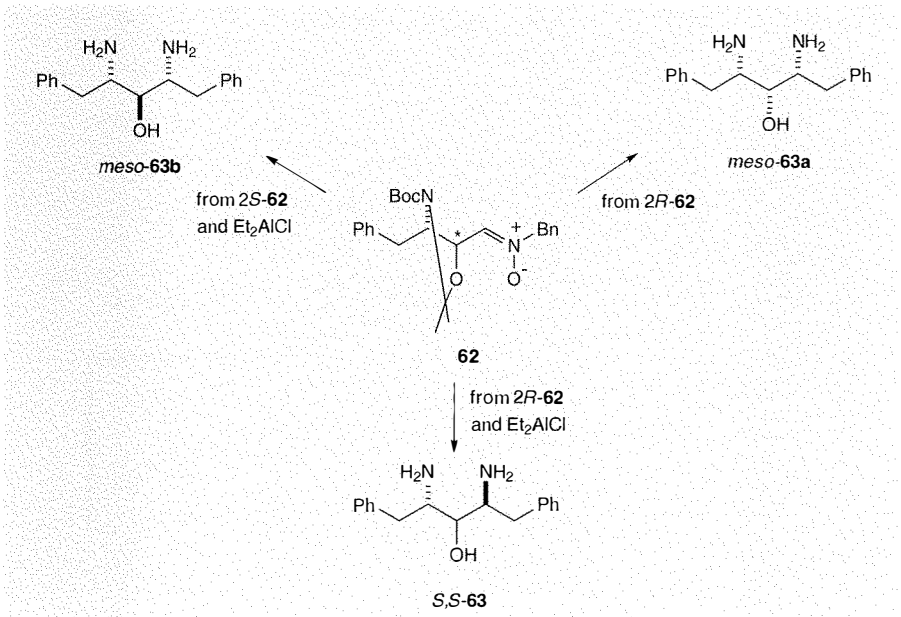


Figure 12. Dibenzyl 1,3-diamino-2-propanols (**63**) prepared by addition of BnMgCl to nitrones **62**.

Acknowledgments

It is a pleasure to thank all who have contributed to the chemistry reviewed here and whose names appear in the cited references. The financial contribution of various agencies reported in the original papers, is also warmly thanked.

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About the Authors

Alessandro Dondoni has been Professor of Organic Chemistry at the University of Ferrara since 1975. He was born in northern Italy and studied chemistry at the University of Bologna where he received the 'Laurea' in Industrial Chemistry (1960) under the guidance of Professor F. Montanari. He undertook postdoctoral work at the same institution with Professor G. Modena (1961) and then at the Illinois Institute of Technology in Chicago (1962-1963) with Professor S.I. Miller. In 1964 he was appointed Assistant Professor at the University of Bologna and joined the research group of Professor A. Mangini at the Department of Industrial Chemistry. For the teaching activity and research work carried out there, he earned the habilitation in Physical Organic Chemistry (1969). In 1970 he became Associate Professor at the University of Ferrara, and in 1975 he was promoted to the rank of Professor and appointed to the chair of Organic Chemistry at the same university.

Professor Dondoni worked initially on reaction mechanisms of 1,3-dipolar and [2+2] cycloadditions, and the synthesis of heterocycles. His present research interests are in new synthetic methods, asymmetric and diastereoselective synthesis, use of heterocycles as synthetic auxiliaries, and carbohydrate chemistry. Most of the recent work has been centered on the use of the thiazole ring as a synthetic equivalent to the formyl group. This concept stimulated the design and synthesis of various thiazole-based reagents for the stereoselective synthesis of biologically active compounds. Very recently he started new work on sugar-calixarene chemistry.

Professor Dondoni has published about 200 communications, papers, and reviews. He has been an invited lecturer at many international congresses in Europe, the USA, Canada, and Japan. In addition, he has been the Upper Rhine Lecturer (1994) at the Universities of Basel, Freiburg, Karlsruhe, Mulhouse, and Strasbourg; the Rhône-Poulenc Rorer Lecturer (1995) at Ohio State University in Columbus; the Ciba-Geigy Lecturer (1996) at the Academy of Science in Prague and in Budapest; and the Great Lakes Lecturer (1996) at the Research Centers of five pharmaceutical companies in the Chicago area. He has held visitor professorships at the University of Rennes (1982), Hamburg (1983), Osaka (1988, Japan Society for the Promotion of Science Award), and Lyon (1994). He has been awarded the 1996 A. Mangini Memorial Medal for creative work in organic chemistry by the Italian Chemical Society.

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Esterifications, Transesterifications, and Deesterifications Mediated by Organotin Oxides, Hydroxides, and Alkoxides

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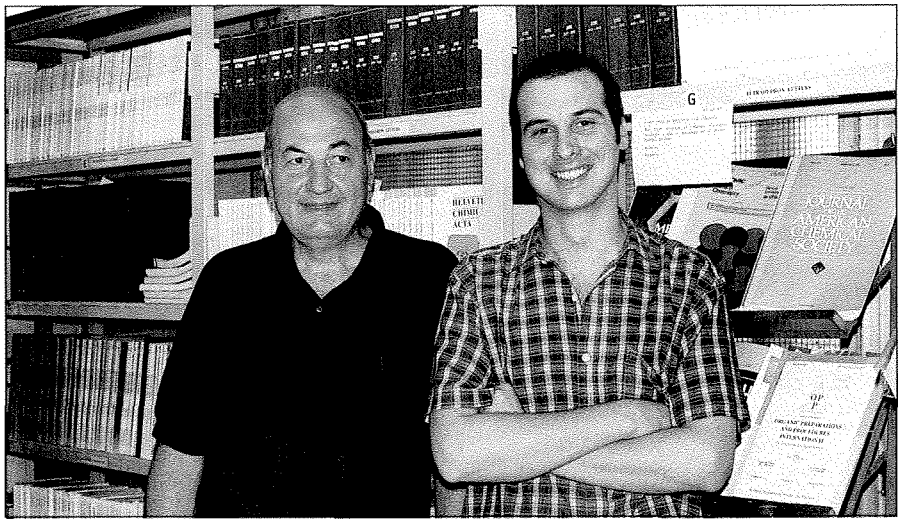
1. Introduction

This review deals with synthetic aspects of carboxylic acid esterification, medium- and large-ring (macro) lactonization, transesterification of carboxylic esters, and cleavage of carboxylic esters by organotin oxides, hydroxides, and alkoxides. The literature has been surveyed up to July 1996. Throughout this review, the common nomenclature system, in which "tin" is used as a suffix, is being followed rather than the nomenclature system used by *Chemical Abstracts* (**Table 1**).



2. Structure and Bonding of Organotin Compounds

Organotin compounds are substances in which at least one *tin-carbon* bond is present. Since tin has the electronic configuration (Kr) $4d^{10}\ 5s^2\ 5p^2$, organotin compounds are found in one of two oxidation states, Sn(II) and Sn(IV). The most common oxidation state of tin in organotins is Sn(IV), but the coordination number may vary from four to eight.[1] The structure and bonding in bivalent and tetravalent organotin compounds are briefly reviewed here, since the structural aspects of organotin chemistry in the solid state and in solution have been comprehensively studied.[1-3]

In dicyclopentadienyltin(II) (**1**), the tin atom is sp^2 hybridized: Two of the hybrid orbitals are involved in bonding, while the third contains an unshared pair of electrons as illustrated in **Figure 1**. Tetrahedral, four-coordinated sp^3 hybridization is observed for tin in symmetrical tetraorganotins (**2**), hexaorganoditins (**3**), organotin hydrides (**4**) and in R_3SnX (**5**), where X = OH or Cl, and R is a bulky organic ligand such as the 2,2-dimethyl-2-phenylethyl (neophyl) group (**Figure 2**). Thus, trineophyltin hydroxide is monomeric in chloroform and acetone, and the tin atom in this molecule has a coordination number of four.

Table 1. Some examples of the nomenclature of organotin compounds.

Formula	Common System	Chemical Abstracts System
n-Bu_3Sn–Cl	Tri-*n*-butyltin chloride	Tributylchlorostannane
$(CH_3)_3Sn$–OH	Trimethyltin hydroxide	Hydroxytrimethylstannane
Ph_3Sn–N_3	Triphenyltin azide	Azido triphenylstannane
$(CH_3)_3Sn$–OOH	Trimethyltin peroxide	Hydroperoxytrimethylstannane
n-Bu_3Sn–OCH_3	Tri-*n*-butyltin methoxide	Tributyl(methoxy)stannane
$(n\text{-}Bu_3Sn)_2O$	Bis(tri-*n*-butyltin) oxide	Hexabutyldistannoxane
$(n\text{-}Bu_3Sn)_2S$	Bis(tri-*n*-butyltin) sulfide	Hexabutyldistannathiane
$[Cl(n\text{-}Bu)_2Sn]_2O$	Bis(chloro-di-*n*-butyltin) oxide	1,1,3,3-Tetrabutyl-1,3-dichlorodistannoxane
n-Bu_2SnO	Di-*n*-butyltin oxide	Dibutyloxostannane
n-BuSn(O)–OH	*n*-Butyltin hydroxide oxide	Butylhydroxyoxostannane

When tin bears more electronegative substituents its Lewis acidity increases and coordination with electron-rich sites leads to sp^3d (trigonal bipyramidal) or sp^3d^2 (octahedral) hybridization. Of the two possible five-coordinate geometries, trigonal bipyramidal and square-based pyramidal, the former predominates. Five-coordinate triorganotin complexes R_3SnX_2 may exist in three trigonal bipyramidal isomeric forms: the trans structure (**6**), which is the most common; the cis isomer (**7**); and the mer form (**8**). Few triorganotin derivatives of oxygen ligands such as hydroxides, alkoxides remain tetrahedral at tin atoms; rather, they show a

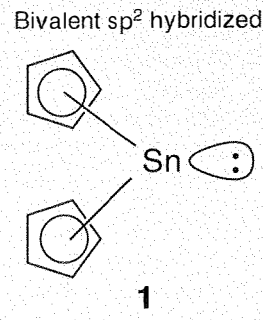


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Figure 1. Structure and bonding in organotin(II) compounds.

marked tendency to associate into one-dimensional chain dimers or polymers in which planar or near-planar [R_3Sn] units are bridged by oxygen atoms as in the crystal structure of trimethyltin hydroxide (**Figure 3**). X-ray studies have shown that trimethyltin fluoride and trimethyltin methoxide consist of planar trimethyl groups and fluorine atoms arranged alternately, with nonlinear Sn–F–Sn or Sn–O(CH_3)–Sn bridges, respectively. The compound [$Cl(CH_3)_2Sn]_2O$ has a dimeric structure in the solid state in which the tin geometry is close to a cis trigonal bipyramid. This structure has been termed a "ladder" or "staircase" structure.

The structure and bonding for coordination number 6 (octahedral tin) are shown in **Figure 4**. Dimethyltin difluoride (**11**) consists of infinite two-dimensional sheets of tin and fluorine atoms. Each tin atom is linearly bridged to the four neighboring fluorine atoms with methyl groups above and below this plane completing a trans octahedral tin atom configuration.

Lewis Acidity

Sn(IV) halides (SnX_4) and organotin halides ($R_{4-n}SnX_n$), are good Lewis acids. The Lewis acidity in these halides increases with electronegativity, in the order I < Br < Cl < F and 1 < 2 < 3 < 4. The Lewis acid, in the presence of a Lewis base (amine, phosphine, phosphine oxide), forms a complex, frequently of the composition R_nSnX_{4-n}•L when n=3 or R_nSnX_{4-n}•L_2 when n=2, 1, or 0. There are two simple techniques that allow a qualitative comparison of the coordinating ability of organotin Lewis acids. In the first, the IR frequencies of phosphine oxide or sulfoxide ligands undergo a shift toward lower frequencies in the presence of organotin or other Lewis acids, because coordination of an electrophilic atom with the P=O or S=O oxygen electron pairs reduces the double bond character of the P=O or S=O bond.[4] **Table 2** shows the IR frequency shifts for triphenylphosphine oxide (TPPO) complexed with tin tetrachloride and several organotin halides, bis(tri-*n*-butyltin) oxide (BBTO) (**12**), bis(chlorodi-*n*-butyltin) oxide (**13**) and tri-*n*-butyltin methoxide (**14**).[5,6]

The electron-withdrawing nature of a phenyl group attached to tin is reflected in a higher shift value for the dichlorodiphenyltin complex than for the dichlorodimethyltin counterpart (entries 3 and 5, **Table 2**).

In the other technique, the Lewis acidity of organotin compounds toward TPPO or triethylphosphine oxide (TEPO) is determined by recording the ^{31}P chemical shift on a mixture of the organotin Lewis acid and the Lewis base TPPO or TEPO in benzene or toluene. Lewis acidities of R_3SnX (R = CH_3,

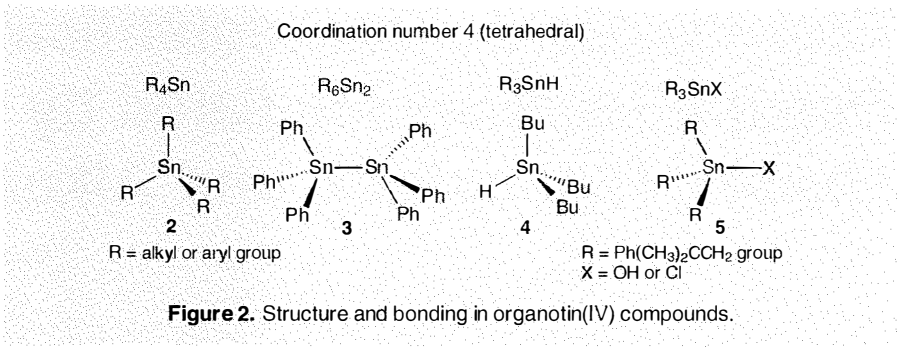


Figure 2. Structure and bonding in organotin(IV) compounds.

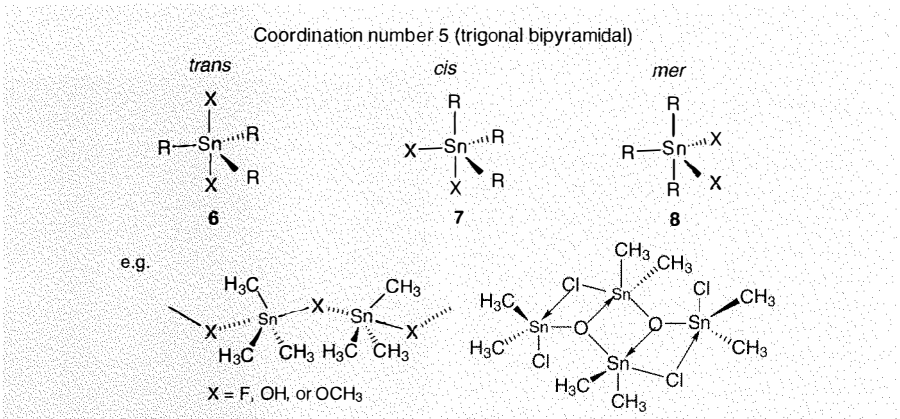


Figure 3. Structure and bonding in organotin(IV) compounds.

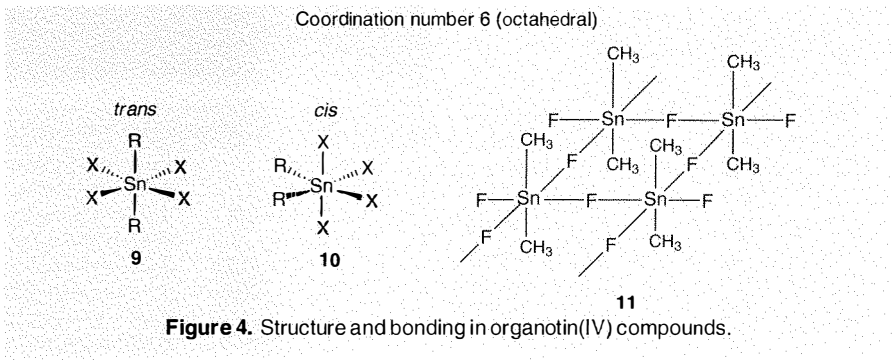


Figure 4. Structure and bonding in organotin(IV) compounds.

Table 2. Lewis acidity according to the $Ph_3P=O$ frequency shift method.

Entry	Lewis Acid (LA)	LA:$Ph_3P=O$	Δν (cm^{-1})[a]	ref
1	$SnCl_4$	1:2	67[b]	4
2	$SnCl_4$	1:1	50[c]	5
3	Ph_2SnCl_2	1:2	53[b]	4
4	Ph_3SnCl	1:1	43[b]	4
5	Me_2SnCl_2	1:2	39[b]	4
6		1:1	26[c]	6
7	$(ClBu_2Sn)_2O$ (**13**)	1:1	13[c]	5
8	$(Bu_3Sn)_2O$ (**12**)	1:1	8[c]	5
9	Bu_3Sn-OCH_3 (**14**)	1:1	4[c]	5

[a]The shifts were determined relative to a wave number of 1,180cm^{-1}, assigned to P=O in TPPO. [b]Nujol. [c]0.08*M* $CHCl_3$ solution.

C_2H_5, C_3H_7, C_4H_9, C_6H_5; X = Cl, Br, I) relative to TPPO,[7] and of a series of tributyltin carboxylates and one triphenyltin carboxylate toward TEPO,[8] have been determined by the ^{31}P NMR shift technique.

3. Esterifications Mediated by Organotin Oxides and Derivatives

3.1. Stoichiometric Esterifications

Sasin first reported the preparation of triethyltin acetate (**19**), propionate, butyrate, trifluoroacetate, and benzoate (**17**) by reaction of bis(triethyltin) oxide (**16**) with the corresponding carboxylic acid (**eq 1**).[9] Sasin's preparations were preceded by Anderson's studies, which had shown that bis(triethylgermanium) oxide reacts with formic and acetic acids to form the corresponding esters.[10] In 1954 Anderson[11] demonstrated the formation of triethyltin acetate **19** in high yield in the reaction of trimethylsilyl acetate (**20**) with **16** (**eq 3**).

Three years later, Anderson reported[12] the preparation of twelve triethyltin esters of haloacetic, halopropionic, and propenoic acids through the reaction developed by Sasin.[9] However, Anderson reported that this methodology was not suitable for the preparation of triethyltin acrylate, probably due to polymerization of acrylic acid. Instead, Anderson employed the transesterification reaction between methyl acrylate and **16** for the synthesis of triethyltin acrylate. He found that neither of these methods was suitable for the esterification of hydroxyacetic acid; he accomplished this latter esterification by reacting silver hydroxyacetate with triethyltin iodide.

In 1962, Valade and Pereyre reported that tri-*n*-butyltin methoxide (**14**) and related compounds react with acyl chlorides or anhydrides to give carboxylic esters under very mild conditions.[13]

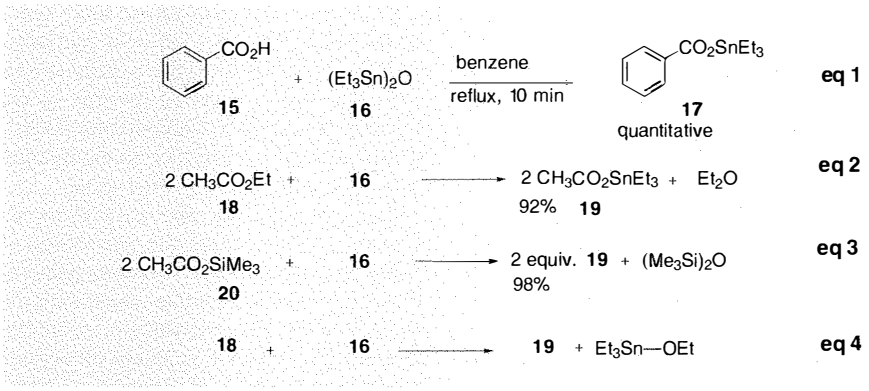
In the same year, Alleston and Davies prepared organotin carboxylates by treating sodium or triethylammonium carboxylates with an equivalent amount of the organotin halide.[14]

Later, Davies and co-workers[15] found that the products of the reaction between carboxylic esters and bistrialkyltin oxides were trialkyltin carboxylates and trialkyltin alkoxides rather than trialkyltin carboxylates and dialkyl ethers (compare **eq 2** and **4**) as had been reported earlier by Anderson.[11,12]

3.2. Catalytic Esterifications

Kumar and Chattopadhyay described the catalytic role of diphenyltin and dimethyltin dichlorides in the esterification of various carboxylic acids with methanol, ethanol, *n*- and isopropanol. The yields were fair to very good (41-97%).[16] The catalytic role of R_2SnCl_2, where R = Ph or Me, was tentatively explained on the basis of the formation of an intermediate weak donor-acceptor complex between the acid carbonyl oxygen and the organotin compound. Subsequent nucleophilic attack of the alcohol oxygen atom on the electron-deficient carbonyl carbon results in the formation of the ester. The approach of a bulky alcohol to the electrophilic carbonyl carbon is sterically hindered, thereby reducing the yield of the corresponding ester.

Otera and co-workers reported in 1991 that exposure of a carboxylic acid to a large excess of an alcohol in the presence of a catalytic amount of several bis(1,3-disubstituted tetraalkyltin) oxides **20a-e** (**Figure 5**) provides the corresponding esters.[17] Good yields of esters were obtained from



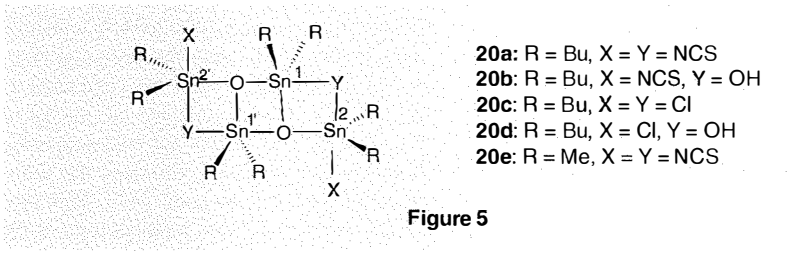
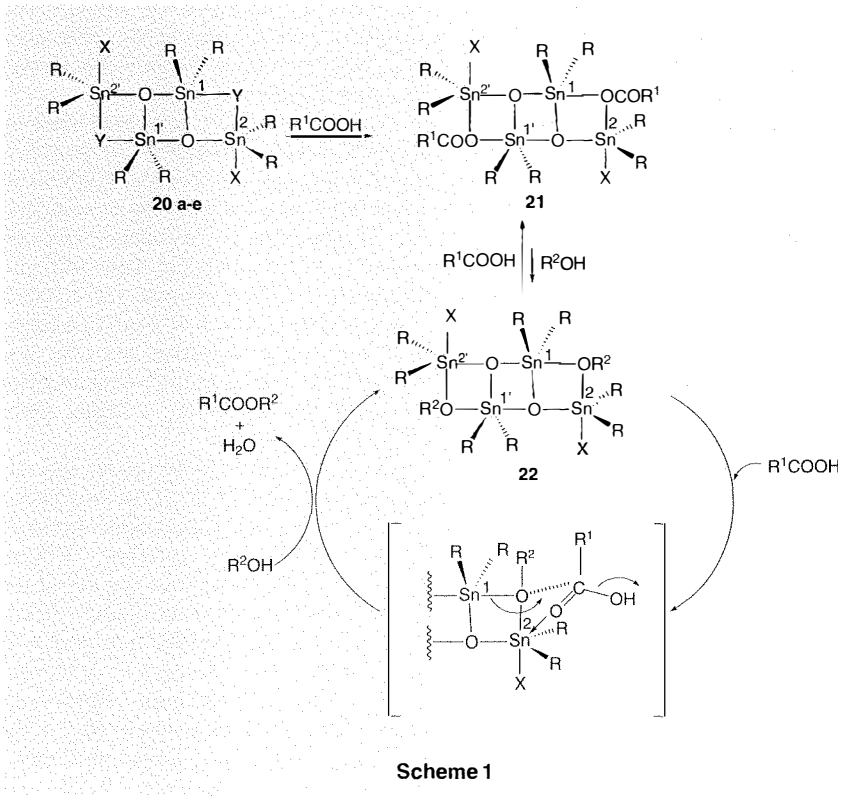


Figure 5



Scheme 1

α-alkyl- and α,α-dialkylcarboxylic acids. However, pivalic acid and benzoic acid afforded esters in only low yields. In contrast to primary alcohols, secondary and tertiary alcohols reacted sluggishly.

Several bis(1,3-disubstituted tetra-*n*-butyltin) oxides **20a-e** have been attributed a stable rigid-ladder structure (**Figure 5**).[17] This structure exists both in the solid state and in solution, and presents two kinds of pentacoordinate tin atoms: Sn(1 or 1') is bonded to two alkyl groups, two oxygen atoms and one Y group; Sn(2 or 2') is bonded to two alkyl groups, one oxygen atom, one X group, and one Y group.

A mechanism for the esterification process was proposed (**Scheme 1**). It was suggested that the catalyst **20a-e** initially reacts with the carboxylic acid rather than with the alcohol. The alkoxy(1,3-disubstituted tetraalkyltin) oxide **22** would be produced by ligand exchange with carboxy(1,3-disubstituted tetraalkyltin) oxides **21**. However, the equilibrium is biased thermodynamically in favor of **21**. These authors reasoned that the ester would probably not be formed via the reaction of **21** with the alcohol since the reactivity of the carboxyl carbon of **21** toward nucleophilic attack by the alcohol would be decreased by the presence of the tin atom, and also because the ability of the alcohol to coordinate with Sn(2) would be less than that of a carbonyl group. On the other hand, the nucleophilicity of the alkoxy group of **22** would be sufficiently enhanced by bonding to the electropositive tin atom to enable it to attack the carbonyl group. Thus, reaction of the (1,3-disubstituted tetraalkyltin) oxides with a carboxylic acid would shift the equilibrium in favor of **22**. Otera and co-workers mentioned that this organotin-catalyzed esterification is quite different from conventional esterification methods in that the reverse reaction (hydrolysis) cannot occur. Removal of the water that is formed is unnecessary, and the absence of hydrolysis was attributed to the double-layered structure of **20a-e**, the surface alkyl groups of which prevent water from approaching the catalytically important core sites, i.e., the tin atoms.

3.3. Synthetic Applications and Structural Studies of Organotin Carboxylic Esters

Synthetic applications of trialkyltin carboxylates for the protection of the carboxyl group were first reported in 1965 by Frankel and co-workers[18] who prepared tri-*n*-butyl- and triethyltin esters of free and *N*-acyl amino acids by heating equivalent amounts of the amino or *N*-acylamino acids with BBTO or triethyltin hydroxide in benzene or toluene, and azeotropically removing the water formed in the reaction. The instability of these esters towards water, ethanol, mild acids, and bases made them impossible to use in peptide synthesis that uses a coupling reaction in the presence of dicyclohexylcarbodiimide (DCC), because the free acid present in the mixture easily cleaved the trialkyl ester group.

In 1968, Bamberg and co-workers attempted to demonstrate the usefulness of trialkyltin carboxylates.[19] 6-Aminopenicillanic acid (6-APA), a starting material for the preparation of all semisynthetic penicillin antibiotics, is insoluble in almost all organic solvents commonly used in synthesis. These authors made use of its tri-*n*-butyltin ester to increase the solubility of 6-APA in a desired organic solvent allowing the acylation reaction of the amino group to be conducted as usual. Subsequent cleavage of the tri-*n*-butyltin ester was carried out with potassium thiophenoxide in DMF, affording the semisynthetic penicillin in good yield. This protection and deprotection methodology of the carboxyl group has not found applications in the industrial preparation of semisynthetic penicillins, probably due to the difficulties encountered in freeing the penicillin derivatives from organotin residues.

Tri-*n*-butyltin esters have been used by MacMillan and co-workers[20] to protect a carboxyl group in the chemical synthesis of 2,2-dimethylgibberellin A_4. The tri-*n*-butyltin ester of gibberellin is conveniently prepared by heating bis(tri-*n*-butyltin) oxide with gibberellin in refluxing benzene for 2 hours, with azeotropic removal of water in a Dean-Stark trap. Upon alkylation, the ester was cleaved with acetic acid to give the required 2,2-dimethylgibberellin A_4, a highly active plant growth promoter.

Organotin monocarboxylate and dicarboxylate esters have attracted interest in studies of the relationships between biocide activity and structure. Consequently, a large increase in reports of the synthesis and structural elucidation of various organotin carboxylates has been seen in recent years. In addition to their biocidal importance, organotin carboxylates have occupied a prominent position in the development of our understanding of structural organotin chemistry.[21]

A recent review by Tiekink[22] reveals that triorganotin carboxylates basically belong to three structural classes in the crystalline state: **a**, **b**, and **c**. Structure class **a** is characterized by a four-coordinate, distorted tetrahedral tin atom; a typical example of class **a** is triphenyltin salicylate. Structure class **b** contains a five-coordinate tin atom with a bidentate carboxylate moiety. This geometry is based on a distorted trigonal bipyramid with the carboxylate oxygen atom spanning one apical and one equatorial position. A typical example of class **b** is triphenyltin *o*-(dimethylamino)benzoate. Both structure **a** and **b** are monomeric. Structure class **c** is polymeric, with bidentate carboxylates bridging the five-coordinate tin atoms of the polymeric chain. A typical example is triphenyltin acetate.

Di- and triorganotin derivatives of *N*-protected dipeptides[23] have been studied recently as well as the reactions of di-*n*-butyltin oxide (**23**);[24] BBTO;[25] bis(triphenyltin) oxide (**24**);[26] and triphenyltin,[25] trimethyltin and tricyclohexyltin[25] hydroxides (**25** to **27** respectively) with several carboxylic acids.

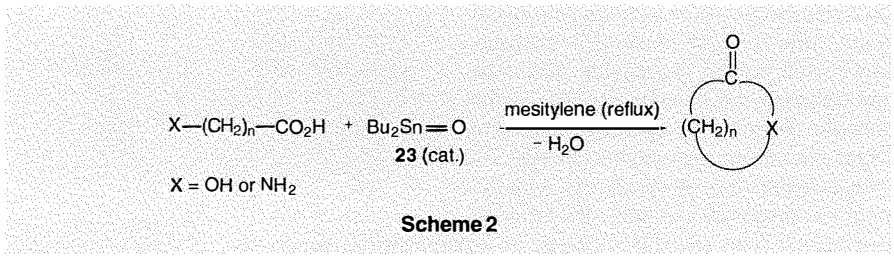
3.4. Macrocyclic Lactone Synthesis

Medium- and large-size rings contain 8–11 and 12 or more atoms respectively. The term *macrocyclic* most commonly refers to large-ring compounds, but in a broader sense sometimes denotes those with medium-size rings as well. Intramolecular esterification of ω-hydroxy carboxylic acids provides the most direct synthetic method for macrolactonization. To this end, however, high dilution techniques or preliminary activation of the carboxyl and/or hydroxyl groups are generally required for retarding intermolecular reactions. A wide variety of methods have been described for the cyclization of ω-hydroxy carboxylic acids to medium and large polyfunctional cyclic lactones.[27,28]

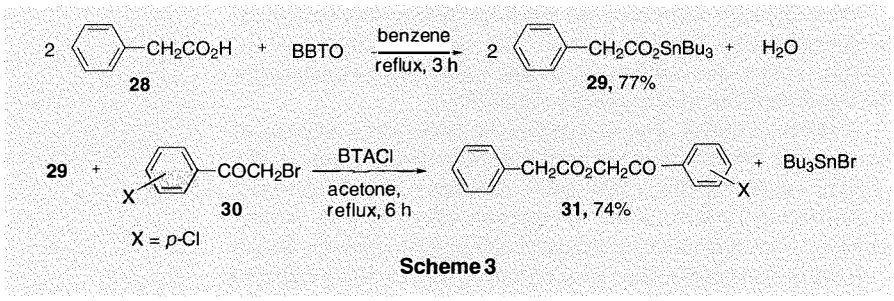
Organotin oxide derivatives are effective not only for the intermolecular esterification of carboxylic acids but also for macrolactonization of ω-hydroxy carboxylic acids. Shanzer and co-workers reported in 1980 the novel synthesis of macrocyclic tetralactones by the reaction of various diacyl halides[29] or cyclic anhydrides[30] with cyclic distannoxanes prepared by treatment of diols, such as ethylene glycol, with di-*n*-butyltin oxide (**23**).

In an extension of the above method, Shanzer and Libman described[31] the use of cyclic organotindithianes as activating agents and templates for the efficient preparation of macrocyclic dithiolactones and tetrathiolactones. Ethanedithiol and 1,3-propanedithiol were converted into cyclic organotindithianes by treatment with di-*n*-butyltin dichloride. Cyclic organotindithianes underwent reaction with several diacyl halides to give macrocyclic dithialactones and tetrathialactones. Later, Shanzer's group reported the synthesis and structure of macrocyclic mixed *S,O*-lactones by treatment of the cyclic organotin compound derived from 2-mercaptoethanol with diacyl halides.[32] In 1992, Mandolini and co-workers reported the synthesis of monomeric and dimeric macrocyclic poly(thialactones) by reaction of an organotindithiane (prepared by treatment of

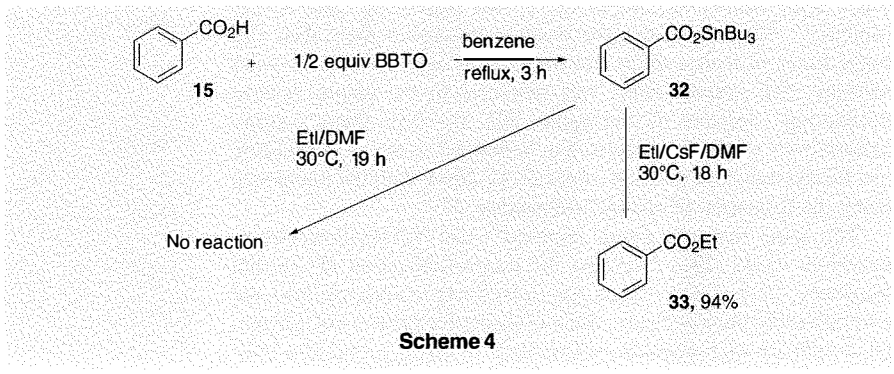
Table 3. Organotin oxides and hydroxides.	
$(Bu_3Sn)_2O$ (BBTO)	12
$(Bu_2ClSn)_2O$	13
Bu_2SnO	23
$(Ph_3Sn)_2O$	24
$Ph_3Sn–OH$	25
$(CH_3)_3Sn–OH$ (TMTOH)	26
$(c\text{-}C_6H_{11})_3Sn–OH$	27



Scheme 2



Scheme 3



Scheme 4

ethanedithiol with di-*n*-butyltin oxide) with several diacyl chlorides.[33]

The organotin-mediated lactonization process of cyclic organotin derivatives developed by Shanzer and co-workers[30] was applied to the synthesis of (+)-dicrotaline, an 11-membered dilactonic pyrrolizidine alkaloid.[34]

Steliou and co-workers reported that di-*n*-butyltin oxide (**23**) promoted ring closure of ω-hydroxy carboxylic acids and ω-amino carboxylic acids to macrocyclic lactones and lactams, respectively, and proposed a mechanism that accounts for the macrocyclization process and the "template" effect of the tin oxide.[35] From their experimental results, they concluded that tin-mediated esterification is particularly well suited for the formation of 13- to 17-membered macrolactones. Lactam formation, on the other hand, occurs in excellent yields only for five-, six-, and seven-membered rings (**Scheme 2**). Although they tried various diorganotin oxides, the best macrocyclization results were obtained with **23** or dimethyltin oxide. Diphenyltin oxide preferentially led to polymerization, while dicyclohexyltin oxide reacted too sluggishly to be of any value. They applied this methodology to the macrocyclization step of the macrolide antibiotics zearalenone, ingramycin, and nodusmicin.[35b]

In 1986, Otera's group reported that bis[1-hydroxydi-*n*-butyltin-3-(iso-thiocyanato)di-*n*-butyltin] oxide **20b** and bis(1-hydroxydi-*n*-butyltin-3-chlorodi-*n*-butyltin) oxide **20d** were effective catalysts and templates for the lactonization of ω-hydroxy carboxylic acids.[36] The catalyzed macrolactonization was irreversible and proceeded smoothly without recourse to the azeotropic removal of water.[17]

This catalytic lactonization methodology was applied by Schreiber's group to the synthesis of brefeldin[37] and a kadsurenone-ginkgolide hybrid.[38]

More recently, White and co-workers described[39] a macrolactone synthesis employing 1,1,1-trifluoroethyl ω-hydroxycarboxylate and various catalytic organotin reagents, such as tri-*n*-butyltin methoxide, BBTO, hexa-*n*-butylditin, tri-*n*-butyltin chloride, and *n*-Bu_3SnH/AIBN. This procedure was applied to the synthesis of ricinelaidic lactone. The authors proposed a mechanism involving exchange of alkoxytrialkyltin species and suggested that a tin template is probably not involved.

3.5. Transesterification via a Trialkyltin Carboxylic Ester Intermediate

The use of trialkyltin esters to activate a carbonyl group towards esterification has gained particular prominence in the past decade.

In 1985, Vijayaraghavan and Balasubramanian reported the synthesis of several phenacyl ester derivatives of phenylacetate using tri-*n*-butyltin phenylacetate (**29**) and the appropriate phenacyl bromide in the presence of benzyltriethylammonium chloride (BTACl) (**Scheme 3**).[40] The initial organotin byproducts were removed as insoluble tri-*n*-butyltin fluoride when ammonium fluoride was added.

More recently, Otera's group reported a general procedure for the alkylation of tri-*n*-butyltin carboxylates.[41] A DMF solution of tri-*n*-butyltin carboxylate (1 equiv) and the appropriate alkyl halide (1.5 equiv) was stirred in the presence of CsF (1.5 equiv) at 30 °C for 18 – 30 hours. Aqueous workup afforded the alkyl carboxylates in good to excellent yields (**Scheme 4**).

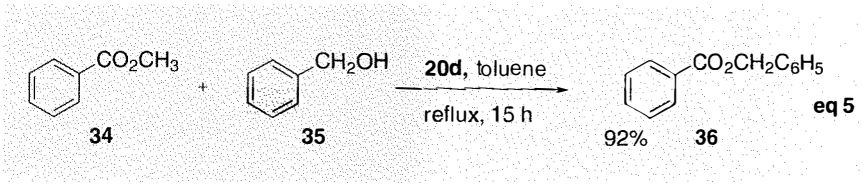
The role of CsF is apparent from the observation that exposure of $Bu_3SnOCOPh$ to ethyl iodide in the absence of CsF under similar conditions failed to afford ethyl benzoate (**33**) (**Scheme 4**). Attack of the fluoride ion on tin apparently drove the reaction of the organotin carboxylate.

3.6. Organotin-Catalyzed Transesterification

In 1969, Pereyre and co-workers first reported that tri-*n*-butyltin methoxide and ethoxide act as transesterification catalysts.[42] Several alkyl and vinyl carboxylic esters were treated with the appropriate alcohol (methyl, ethyl, or isopropyl alcohol) in the presence of a catalytic amount of tri-*n*-butyltin methoxide or ethoxide at 120 °C for 40 – 100 hours; the corresponding transesterified products were obtained in low to moderate yields (31-72%).

Poller and Retout[43] reported the relative catalytic activity of several diaryl- and

dialkyltin oxides, diaryl- and dialkyltin dichlorides, diaryl- and dialkyltin sulfides, triphenyltin acetate, diphenyltin dichloride, and tetraphenyltin in promoting the reaction between *n*-propyl acetate and methanol. Organotin sulfides, triphenyltin chloride, and tetraphenyltin were without activity. A mechanism was proposed, indicating that the effective catalyst is the alkoxide; however, no experimental evidence was provided.

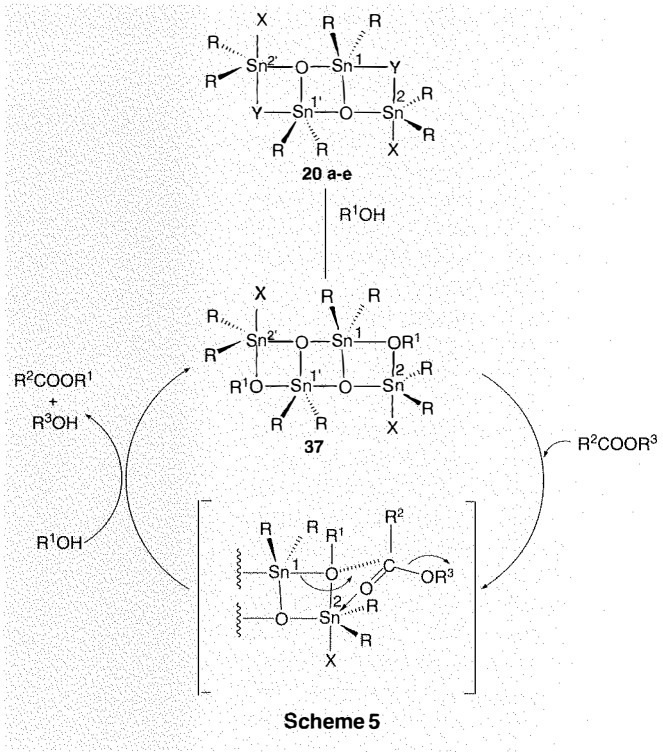


Otera and co-workers reported that bis[l-hydroxydi-*n*-butyltin-3-(isothiocyanato)di-*n*-butyltin] oxide **20b** and bis(1-hydroxydi-*n*-butyltin-3-chlorodi-*n*-butyltin) oxide **20d** were effective catalysts for the transesterification of carboxylic esters.[44]

A toluene solution of several carboxylic esters and a diversity of alcohols, e.g. **34** and **35,** were heated at reflux in the presence of a catalytic amount of **20b** or **20d** (**eq 5**). Secondary alcohols gave rise to satisfactory results, while no reaction occurred with tertiary alcohols. The reaction proceeded under almost neutral conditions and a variety of functional groups were tolerated well. Otera's group also studied the effect of solvent on the transesterification rate of butyrate esters with benzyl alcohol at 80 °C and employing **20a** as the catalyst.[45] They found that the reaction proceeded more than 100 times faster in hydrocarbon and halocarbon solvents than in polar solvents. This solvent effect was attributed to the unique reverse micelle-type structure of compound **20a**. In 1991, Otera's group proposed the mechanism depicted in **Scheme 5** as the most probable one for the transesterification catalyzed by **20a-e** with the initial step being the formation of alkoxydistannoxane **37**.

The same research group reported[46] that 1,3-dichlorotetra-*n*-butylditin oxide (**20c**) catalyzed the transesterification of 1,n-diol diacetates (n = 2,3,4) which are selectively converted into the corresponding monoacetates. Such unique selectivity is not encountered with 1,n-diol diacetates where n≥5.[47] Otera's group also indicated that the analogous compounds **20a**, **20b,** and **20d** also serve as catalysts, and they described the template effect of the catalyst in terms of cooperation between two different tin atoms which are in close proximity.[47]

In 1989, Shimizu and co-workers[48] used **20b** and **20d** as catalysts in the transesterification of ethyl 4,4,4-trifluoroacetoacetate with allylic alcohols to give the corresponding allylic carboxylic esters.



Scheme 5

4. Deesterification by Organotin Oxides, Hydroxides, and Alkoxides

4.1. Background

Carboxylic esters can be considered as protecting groups for carboxylic acids or alcohols, depending on which component is of interest. Carboxylic acids can be protected as a wide range of esters such as, benzyl (Bn), phenacyl (Pac), allyl, *t*-butyl, methyl, ethyl, and silyl esters among others. Esters such as acetate, benzoate, *p*-nitrobenzoate and pivalate are frequently used as hydroxyl protecting groups.[49]

Since a carboxylic ester has two sites that can be potentially attacked by a nucleophile, one should choose a nucleophile that exhibits a preference for attacking at either the carbinol carbon or the carbonyl carbon. In a recent review, we provided an update on methods for chemical deprotection of carboxylic esters.[50] Using the principle of hard/soft acid/base,[51] soft nucleophiles are expected to show a preference for attacking on the carbinol carbon (soft-soft interaction), while hard nucleophiles should prefer the carbonyl carbon (hard-hard interaction) (**Figure 6**). Whatever strategy is chosen for the cleavage of carboxylic esters, the mechanistic implications have to be considered along with the steric hindrance around the carbinol and carboxyl carbons, as well as the chemical properties and drawbacks of each reagent. If you would like to isolate a chiral alcohol with retention or inversion of configuration, it is particularly important to select the reagent that would cleave either the *O*-acyl (path a) or the *O*-alkyl bonds (path b) (**Figure 6**).

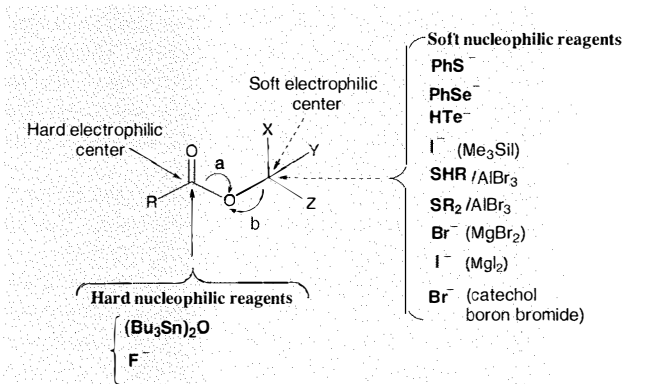
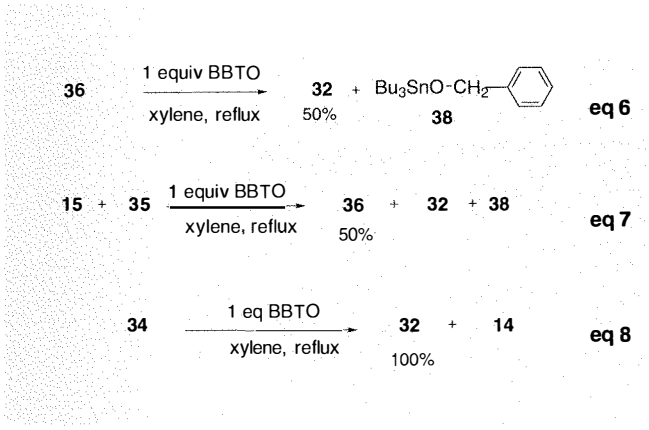


Figure 6. Guide for the choice of methods for the cleavage of carboxylic esters in nonhydroxylic solvents.

4.2. O-Acyl Cleavage of Carboxylic Esters

In 1980, Steliou and co-workers reported[35a] the *O*-acyl cleavage of carboxylic esters by BBTO to afford the corresponding organotin carboxylates. These authors indicated that treatment of benzyl

benzoate (**36**) with an equivalent amount of BBTO in refluxing xylene gave a 1:1 mixture of tri-*n*-butyltin benzoate (**32**), unreacted benzyl benzoate, and tri-*n*-butyltin-*O*-benzyl ether (**38**) (**eq 6**). On the other hand, when benzoic acid (**15**) and benzyl alcohol (**35**) were treated with an equimolar amount of BBTO, an equal distribution of **36**, **32** and **38** was achieved (**eq 7**). The transesterification of benzyl benzoate to form an organotin carboxylate and the reverse reaction — the esterification of benzoic acid under the same conditions — are a particular example of the principle of *microscopic reversibility*.

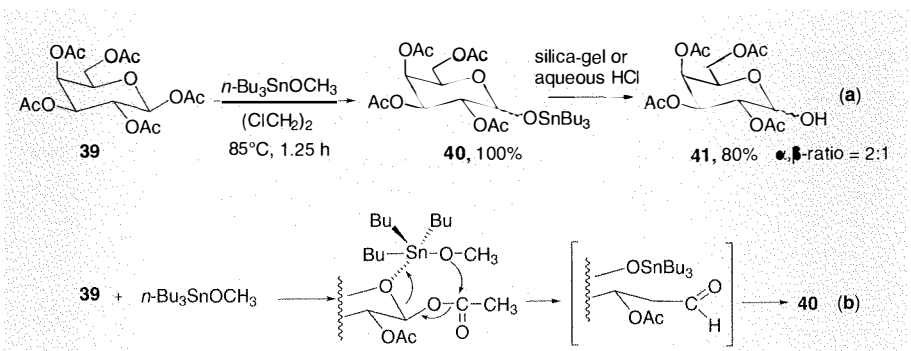


The authors found that treatment of methyl benzoate (**34**) with an equivalent amount of BBTO in refluxing xylene gave a mixture of **32** and **14** in quantitative yield (**eq 8**).

The same authors also reported that lactones, such as propiolactone or caprolactone and equimolar amounts of BBTO in refluxing mesitylene, readily undergo ring opening to yield bifunctional tri-*n*-butyltin carboxylate-tri-*n*-butyltin ethers. However, γ-butyro- or δ-valerolactone were recovered unchanged under the same conditions.

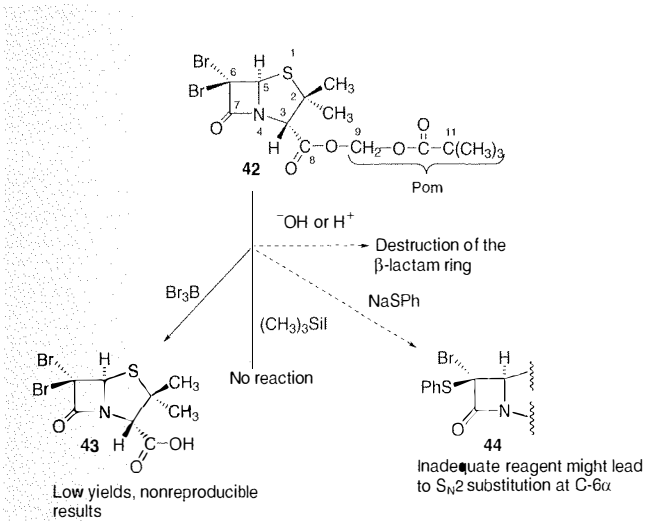
Nudelman and co-workers reported[52] regioselective ester cleavage of anomeric sugar acetates following treatment with an equimolar amount of BBTO or tri-*n*-butyltin methoxide in a refluxing non-hydroxylic solvent such as THF, 1,2-dichloroethane, benzene, or toluene (**Scheme 6**). A variety of acetylated sugars selectively afforded the Bu_3SnO-1 derivatives; these were readily hydrolyzed to the HO-1 unsubstituted products. They found that the β-form of these acetylated sugars reacted faster and gave higher yields of deacetylated products than the α-form. The authors explained these results by the mechanism depicted in **Scheme 6**, part b.

In an extension of this work, Nudelman's group reported[53] the use of Bu_3SnOMe or Bu_2SnO in methanol for the transesterification of several acetylated sugars having an anomeric acetate group. As was previously indicated, the anomeric acetates were more reactive than primary and secondary acetates, thereby enabling selective removal to give HO-1 unsubstituted products in good yields. Again, the reactivity of the β-acetates was higher than that of the corresponding α-acetates.



Scheme 6

In the course of our search for an assay of β-lactamase activity, we needed a chemically efficient method of removing the (pivaloyloxy)methyl (Pom) protecting group in the Pom 6,6-dihalo- and 6-halopenicillanate derivatives. Among the reported methods for the cleavage of esters, classic saponification and acidic methods seemed unsuitable because they brought about the destruction of the β-lactam ring. Sodium thiophenoxide, a nucleophilic, nonbasic reagent, was inadequate since, in the 6,6-dihalo- and 6-halo- penicillanate series, it might lead to S_N2 substitution at carbon 6[54] (**Scheme 7**). Our search led us to several recently reported procedures that allow the cleavage of carboxylic esters under neutral conditions such as by using iodotrimethylsilane (TMSI) or boron tribromide. We found that TMSI did not produce cleavage of Pom 6,6-dibromopenicillanate ester (**42**), while attempted Pom ester cleavage with BBr_3 was not reproducible and gave low yields of **43**. Although enzymatic methods had been available in the literature,[55] they were not tested by us at that time.



Scheme 7. Attempts to cleave the double ester of Pom 6,6-dibromopenicillinate.

Simultaneously, and in connection with a reductive radical dehalogenation of **42** by tri-*n*-butyltin hydride in the presence of catalytic AIBN, we observed that when we used an aged bottle of tin hydride the Pom ester underwent partial cleavage to the corresponding acid **43**, presumably through the agency of adventitious BBTO (**Scheme 8**). Indeed, when this reaction was carried out with pure BBTO, we found that this organotin oxide cleanly and effectively cleaves the (pivaloyloxy)methyl double ester of several penicillanate derivatives (**Scheme 9**) as well as several methyl, ethyl, and phenyl carboxylic esters in nonhydroxylic solvents with yields ranging from 43 to 100%.[56]

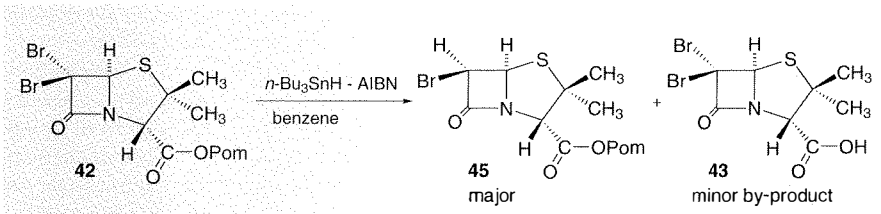
Later on[57] we documented the utility of BBTO as a nonacidolytic reagent for the selective cleavage of primary alkyl and *p*-nitrobenzyl carboxylic esters, as well as for the cleavage of primary alkyl esters of *N,N*-dimethyl dipeptides, without affecting a wide range of functional groups within the molecules used. As a limitation, we found that attempts to effect the cleavage of the Pom ester groups in 6α-fluoro- and 6β-bromo-6α-fluoro-penicillanates with BBTO brought about destruction of the β-lactam ring. It seemed to us that a fluoro-destannylation reaction might be occurring. This result was preceded by the work of Harpp and co-workers,[58] who stated that the hard atom of tin had a great tendency to interact with the hard fluorine atom.[59] Eventually, we overcame this limitation by using pig liver esterases.[55]

4.3. Simple Primary Alkyl Esters

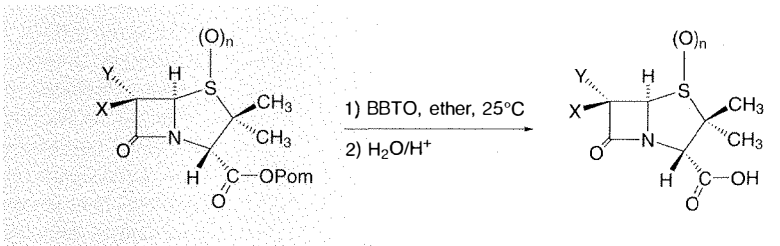
In 1994, we published[60] a more detailed study of the scope, limitations, and mechanism of deprotection of carboxylic esters by BBTO. The generality of the procedure for cleaving primary alkyl carboxylic esters was tested by carrying out the reaction on a variety of methyl and ethyl esters of aliphatic and aromatic carboxylic acids containing representative functional groups. The procedure was generally applicable to the conversion of primary alkyl carboxylic esters into carboxylic acids in moderate to good yields (**eq 9-11**). The reagent BBTO was compatible with a broad range of functional groups including lactones, alkenes, cyclic ketals, acyclic and cyclic dithioketals, and vinyl bromides. The optical purities of acids **53**, **55**, and **57** were completely retained.

It is particularly noteworthy that treatment of methyl (*S*)-(+)-5-oxotetrahydro-2-furoate (**56**) with BBTO in acetonitrile at 60°C for 24 hours led to the (*S*)-(+)-5-oxotetrahydro-2-furoic acid (**57**) (**eq 11**). A similar chemoselectivity was reported by Yamamoto and co-workers for the hydrolysis of methyl (*R*)-5-oxotetrahydro-2,3-dimethyl-2-furoate with lithium hydroxide.[61]

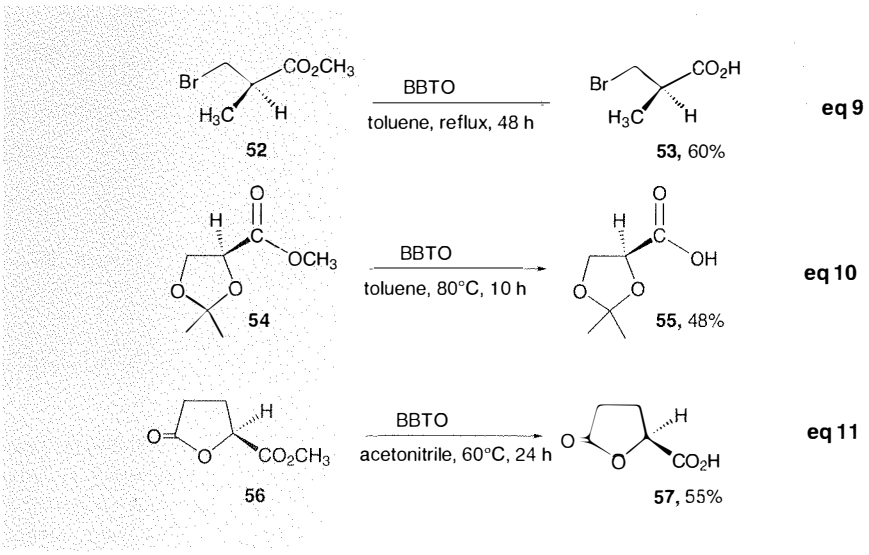
Methyl and ethyl esters are commonly encountered in organic synthesis because they are simple and easy to prepare. As previously mentioned, methyl and ethyl, as well as other alkyl carboxylates, have been prepared in good to excellent yields by reaction of tributyltin carboxylates (obtained by heating an equimolar mixture of carboxylic acid and BBTO in refluxing benzene) with alkyl halides in the presence of CsF.[41] The significance of the synthetic versatility of BBTO lies in the fact that it is now possible to mask carboxylic acids temporarily as

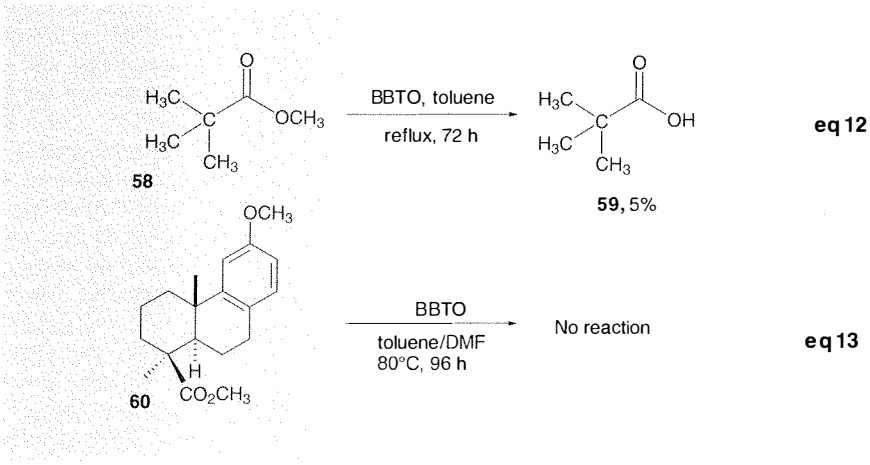


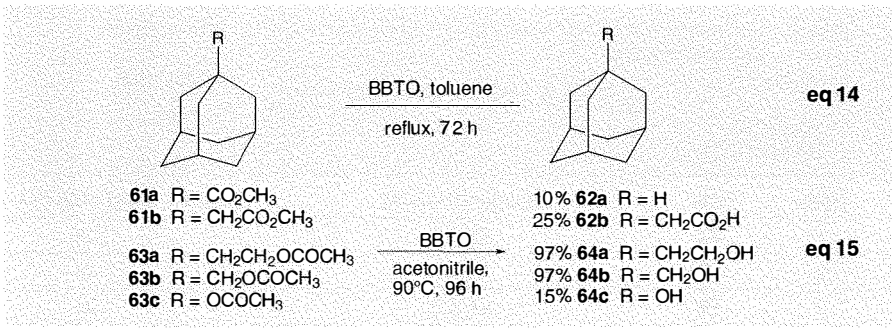
Scheme 8. Reductive free-radical dehalogenation by aged tri-*n*-butyltin hydride.

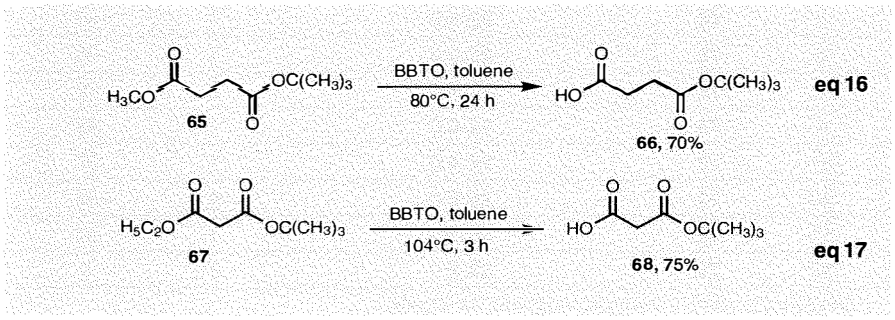


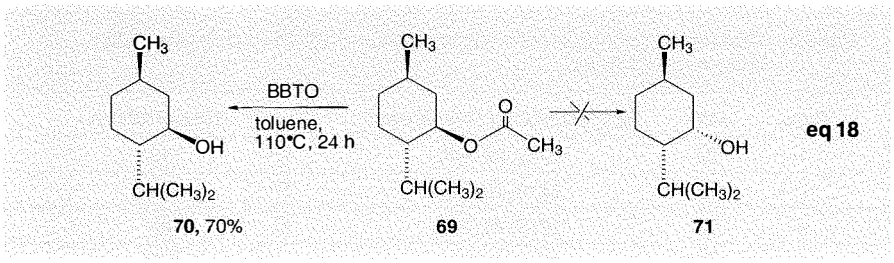
Scheme 9. Cleavage of (pivaloyloxy)methyl penicillanate derivatives by BBTO.











methyl or ethyl esters in the course of a multistep synthesis of polyfunctional molecules and then selectively deprotect these esters in the presence of diverse functional groups under mild conditions. Another aspect of this method is that the reaction is carried out under essentially neutral conditions and thus it can serve as an ideal procedure for the cleavage of esters of acid- or base-sensitive compounds.

4.4. Sterically Hindered Esters

We have examined the applicability of the BBTO cleavage reaction to methyl esters that are sterically hindered around the carboxyl carbon (**eq 12-14**). In addition, and in order to gain an understanding of the effects of steric hindrance on the carboxyl versus the alcohol groups, we selected acetates of primary, neopentyl, and tertiary alcohols (**eq 15**). BBTO did not cleave the methyl ester of pivalic acid (**58**), *O*-methylpodocarpic acid (**60**), or 1-adamantanecarboxylic acid (**61a**). Furthermore, when methyl 1-adamantaneacetate (**61b**) was treated with BBTO under similar conditions, the reaction was not complete, giving only 25% of 1-adamantaneacetic acid (**62b**). In contrast, the phenylselenide-induced cleavage at the carbinol center of the hindered methyl esters **58** and **60** afforded the corresponding carboxylic acids in excellent yields.[62]

Cleavage of the acetate of primary alcohol **63a** and primary neopentyl-type alcohol **63b** was accomplished almost quantitatively. When this reaction was used to cleave the tertiary 1-adamantyl acetate (**63c**), the yield was considerably lower (15%).

The results obtained with **61b** and **63b** led to the conclusion that steric hindrance at the carboxyl carbon inhibits the deesterification reaction more than steric hindrance at the carbinol center. Thus, the reagent selectively cleaved the *methyl* ester of *tert*-butyl methyl succinate (**65**) (**eq 16**) and the *ethyl* ester of *tert*-butyl ethyl malonate (**67**) (**eq 17**), in the presence of the *tert*-butyl ester group. The isolated yields of the corresponding acids were 70% and 75%, respectively. This finding that methyl and ethyl esters could be cleaved selectively by BBTO in the presence of *tert*-butyl esters complements the selective cleavage of *tert*-butyl esters by catechol boron bromide in the presence of methyl and ethyl esters.[63] The chemoselectivity of the BBTO and the catechol boron bromide for orthogonal deprotection of these esters is clearly valuable in multistep syntheses involving carboxylic acids protected both as primary and tertiary alkyl esters.

4.5. Cleavage of Esters with Recovery of the Alcohols

Studies on esters of chiral alcohols showed that BBTO promotes regioselective cleavage at the **acyl-oxygen** bond. Thus, (1*R*,2*S*,5*R*)-(–)-menthyl acetate (**69**) affords exclusively (1*R*,2*S*,5*R*)-(–)menthol (**70**) (**eq 18**).[57,60] This represents a simple method for the deprotection of chiral alcohols *with complete retention of configuration.*

4.6. Cleavage of Methyl and Isopropyl Phenylacetate

Recently, we investigated the cleavage of methyl and isopropyl phenylacetate (**72** and **73,** respectively) with trialkyltin, triaryltin, and dialkyltin oxides, as well as with triaryltin and trialkyltin hydroxides (**Table 3**) under classical heating and microwave irradiation conditions.[64a,b]

When **72** was heated at 100 °C without solvent and with 1 equivalent of BBTO, it was converted into phenylacetic acid (**28**) in quantitative yield (entry 1, **Table 4**). Upon treatment of 0.5*M* toluene solutions of **72** with 1 equivalent of organotin oxides **24, 23** and hydroxides **25–27** at 100 °C for 6.0 hours (entries 3–7), the acid **28** was produced in high to moderate yields. When the ester **72** was treated with bis(chlorodi-*n*-butyltin) oxide (**13**), it remained unaffected even over a longer period of heating (entry 2 in **Table 4**, see also entry 6 in **Table 5**). Presumably, the strongly electron-withdrawing nature of the chlorine atoms affects the nucleophilicity of the oxygen atom bonded to two tin atoms (-Sn–O–Sn-) in this compound.

Treatment of **73** with 1 molar equivalent of **12** or **26** (entries 8 and 11) afforded **28** in high yield. This result indicates that, in these cases, the steric demand of the secondary alkyl group is not important. However, for organotin oxide **24** and hydroxides **25** and **27** this steric hindrance appears to be important (compare entries 3:9, 5:10, and 7:12 in **Table 4**).

Table 5 summarizes the results obtained when the same deesterification reaction was carried out under microwave irradiation conditions. Here, the concentration of the organotin reagent greatly affected the yield of **28**.

The order of reactivity towards deesterification of methyl and isopropyl phenylacetate is thus: **BBT● ≅ 26 > 24 ≅ 27 > 25 ≅ 23 >> 13**.

4.7. Selective Ester Cleavage in N-Protected Amino Acids and Peptides

More recently we became interested in the use of organotin oxides and hydroxides for the chemoselective deprotection of benzyl, phenacyl, and methyl esters of *N*-protected amino acids and dipeptides; andbenzyl and phenacyl esters of *N*-protected amino acids and peptides linked to polystyrene resins.[65]

Phenacyl, methyl, and benzyl esters of various *N*-α-Boc-, *N*-α-Cbz-, or *N*,*N*-dimethylamino-protected amino acids and dipeptides, as well as esters of *N*-α-protected amino acids linked to Wang and Pam resins were efficiently and chemoselectively cleaved by BBTO in aprotic solvents to give the corresponding carboxylic acids in good yields. Moreover, the absence of racemization during the deprotection was demonstrated. A limitation of the method was the instability of the *N*-ε-Fmoc and Cbz protecting groups. In the case of *N*-α-protected dipeptides, there was no evidence of free amino acids which indicated that the peptide bond was unaffected.

Pac, Bn, and methyl esters of *N*-α-Boc-L-phenylalanyl-L-proline were cleaved in good yield by BBTO in toluene (**Table 6**). The absence of racemization during the deprotection of *N*-Boc-L-phenylalanyl-L-proline methyl ester (**77**) was checked — the product was found to be enantiomerically pure.

The ester linkage of the growing peptide chain to the resin is crucial in solid-phase synthesis (SPS). It has to be easily formed, stable to repeated cycles of acylation and deprotection reactions, and yet easily cleaved at the end of the synthesis without damaging the newly formed peptide bonds. To evaluate the use of BBTO in the cleavage of esters of the resin-linked *N*-α-protected amino acids, we studied Boc-*O*-benzyl-L-serine linked to Merrifield resin (**78**), Fmoc-L-alanine linked to Wang resin (**80**), and Boc-L-alanine linked to Pam resin (**83**) (**Figure 7**). Attempts to cleave the benzyl ester of Boc-*O*-benzyl-L-serine bound directly to the crosslinked polystyrene-*co*-divinylbenzene resin (Merrifield resin) using BBTO met with little success. Only 12% of Boc-*O*-benzyl-L-serine (**79**) was obtained after 5 days of reflux in chloroform (**Table 7**). The reaction failed, presumably due to inaccessibility of the carboxyl carbon reactive site to the bulky BBTO reagent. This difficulty was overcome by using linker-resins (handles) such as the Wang or *p*-alkoxybenzyl alcohol resin and the Pam or 4-(oxymethyl)phenylacetamidomethyl resin (**Figure 7**).

Table 4. Cleavage of carboxylic esters by organotin oxides and hydroxides under classical heating.

$PhCH_2CO_2R$ (**72** R=CH_3, **73** R=$CH(CH_3)_2$) —1 equiv. of organotin oxide or hydroxide, 100 °C→ $PhCH_2CO_2H$ (**28**)

Entry	Ester	Reagent/Time (h)	Solvent[a]	Yield of **28** (%)
1	**72**	**12**; 2.5	–	100
2	**72**	**13**; 20	T	0
3	**72**	**24**; 6.0	T	94
4	**72**	**23**; 6.0	T	65
5	**72**	**25**; 6.0	T	60
6	**72**	**26**; 2.5	T	96
7	**72**	**27**; 6.0	T	76
8	**73**	**12**; 6.0	–	82
9	**73**	**24**; 6.0	T	27
10	**73**	**25**; 6.0	T	22
11	**73**	**26**; 6.0	T	84
12	**73**	**27**; 6.0	T	0

[a]Solutions 0.5mmol/mL of organotin reagents. T = toluene.

Table 5. Cleavage of carboxylic esters by organotin oxides and hydroxides under microwave irradiation.

Entry	Ester	Reagent/Mol. eq./Time/Power[a]	Solvent[b]	Yield of **28** (%)
1	**72**	**12**; 2; 20; 900	T[c]	13
2	**72**	**12**; 2; 20; 900	T[d]	49
3	**72**	**12**; 2; 20; 900	T[e]	100
4	**72**	**12**; 2; 16; 900	–	100
5	**72**	**12**; 1; 29; 500	–	100
6	**72**	**13**; 1; 45; 750	T[c]	0
7	**72**	**24**; 1; 45; 750	T[c]	20
8	**72**	**23**; 1; 45; 750	T[c]	7
9	**72**	**25**; 1; 45; 750	T[c]	14
10	**73**	**12**; 2; 20; 900	–	83
11	**73**	**24**; 1; 45; 750	T[c]	0
12	**73**	**25**; 1; 45; 750	T[c]	0

[a]Time in min; power in watts. [b]Solutions in mmol/mL of organotin reagents. [c]0.5; [d]0.9; [e]2.0. T = toluene.

Table 6. Deprotection of selected Pac, Bn, and methyl esters in *N*-protected amino acids and dipeptides by BBTO in toluene at 90°C.

Entry	Starting Material	Product	Reaction Time (h)	Yield (%)
1	*N*-Boc-L-phenylalanyl-L-proline phenacyl ester (**74**)	*N*-Boc-L-phenylalanyl-L-proline (**75**)	48	76
2	*N*-Boc-L-phenylalanyl-L-proline benzyl ester (**76**)	**75**	96	69
3	*N*-Boc-L-phenylalanyl-L-proline methyl ester (**77**)	**75**	36	69

Treatment of Fmoc-L-alanine bound to the Wang resin (**80**) with BBTO liberated 40% of L-alanine (**81**) and 18% of Fmoc-L-alanine (**82**) (**Table 7**). The benzyl ester of Boc-L-alanine-Pam resin (**83**) was cleaved with BBTO to Boc-L-alanine (**84**) in 63% yield. This orthogonal deprotection, which did not affect the *tert*-butyloxycarbonyl group, is in accord with earlier results obtained for the unlinked, protected dipeptides.

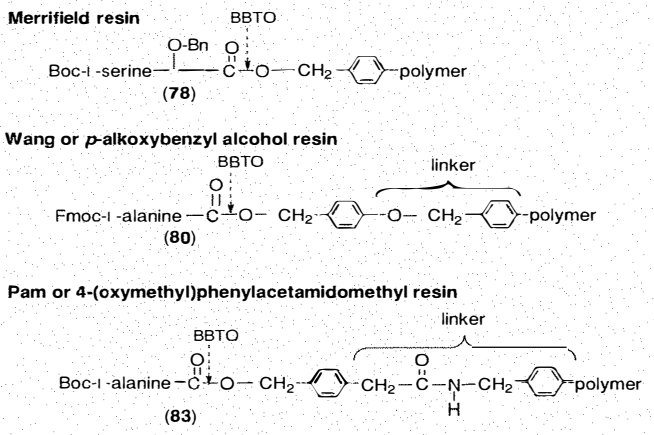
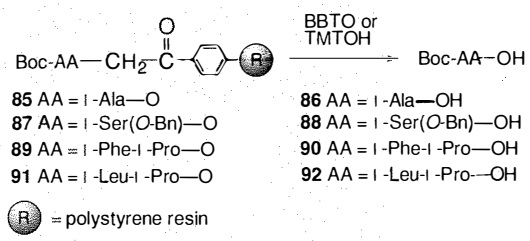


Figure 7. Protected amino acids linked through benzyl esters to Merrifield, Wang, and Pam polystyrene resins.

Table 7. Cleavage of resin-linked esters of *N*-protected amino acids by BBTO in chloroform at 61 °C.

Entry	Starting Material	Product	Reaction Time	Yield (%)
1	Boc-*O*-benzyl-L-serine Merrifield-resin linked (**78**)	Boc-*O*-benzyl-L-serine (**79**)	5d	5
2	Fmoc-L-alanine Wang-resin linked (**80**)	L-Alanine (**81**) Fmoc-L-alanine (**82**)	60h	58
3	Boc-L-alanine Pam-resin linked (**83**)	*N*-Boc-L-alanine (**84**)	96h	63



Scheme 10

Table 8. Cleavage by BBTO and TMTOH of Boc-amino acid and dipeptide phenacyl esters linked to polystyrene resin.

Entry	Starting Material	Product	Conditions[a]	Yield (%)
1	**85**	**86**	BBTO, 25h	100
2	**85**	**86**	BBTO, 50min[b]	83
3	**85**	**86**	TMTOH, 15h	96
4	**87**	**88**	BBTO, 22h	45
5	**87**	**88**	TMTOH, 15h	96
6	**89**	**90**	BBTO, 15h	58
7	**89**	**90**	TMTOH, 13h	80
8	**91**	**92**	BBTO, 15h	67
9	**91**	**92**	TMTOH, 15h	78

[a]All reactions were performed using 2.2 equiv of reagent in 1,2-dichloroethane at 83°C.
[b]Reaction performed in DMF under microwave irradiation at 650W of power.

In a recent study,[66] we found that TMTOH and BBTO cleanly and efficiently cleave *N*-Boc amino acids and peptides (linked through a phenacyl ester to a polystyrene resin) to the corresponding Boc amino acids or peptides in high yield (**Scheme 10**). Treatment of Boc-L-Ala-Pac-polystyrene resin (**85**) with BBTO in refluxing 1,2-dichloroethane afforded Boc-L-Ala-OH **86** in quantitative yield (**Table 8**, entry 1). When a mixture of **85**, BBTO and dimethylformamide (DMF) was subjected to microwave irradiation at 650 W of power for 50 minutes, **86** was isolated in 83% yield (entry 2). Treatment of **85** with TMTOH in refluxing $(ClCH_2)_2$ for 15 hours afforded **86** in 96% yield (entry 3). The Pac ester of Boc-L-serine(*O*-benzyl)-polystyrene resin (**87**) was also cleaved with TMTOH yielding Boc-L-serine(*O*-benzyl)-OH (**88**) in 96% yield (entry 5). This result demonstrated that the cleavage of the Pac ester by TMTOH proceeded with complete retention of both the *N*-Boc and the side-chain *O*-Bn protecting groups of serine. Cleavage of **87** with the sterically hindered BBTO (entry 4) required a longer reaction time and resulted in a lower yield of **88**. Treatment of Boc-L-Phe-L-Pro-Pac-resin (**89**) with TMTOH in refluxing $(ClCH_2)_2$ for 13 hours detached Boc-L-Phe-L-Pro-OH (**90**) from the solid matrix in 80% yield (entry 7), while the cleavage with BBTO provided **90** in 58% yield after 15 hours (entry 6). In the cleavage of **89** with TMTOH or BBTO there was no evidence of free Pro-OH. A similar result was obtained in the cleavage of Boc-L-Leu-L-Pro-Pac resin (**91**) by TMTOH and BBTO: The corresponding Boc-L-Leu-L-Pro-OH **92** was obtained in 78% and 67% yield, respectively (entries 9 and 8). Anchoring Boc amino acids and dipeptides through Pac esters to the 2-bromoacetyl resin and the subsequent cleavage with TMTOH occurs without noticeable racemization. For example, the optically active Boc-amino acids **86**, **88** (entries 3 and 5) and Boc-dipeptides **90** and **92** (entries 7 and 9) were obtained without loss of enantiomeric purity.

4.8. Mechanism of Ester Cleavage With BBTO and TMTOH

With BBTO. We have proposed a mechanism that rationalizes the regioselective acyl-oxygen cleavage of carboxylic esters. Mechanism (1) involves the polar transition state **93** (**Scheme 11**), and implies that a nucleophilic hard oxygen coordinates with the hard electrophilic carbonyl carbon center, followed by an attack of the hard nucleophilic oxygen of the carbinol moiety on the hard electrophilic tin atom.

The following experimental results support this mechanism:

• The deesterification rate is influenced by steric hindrance around the carboxyl and carbinol centers and by steric congestion in BBTO.[60]

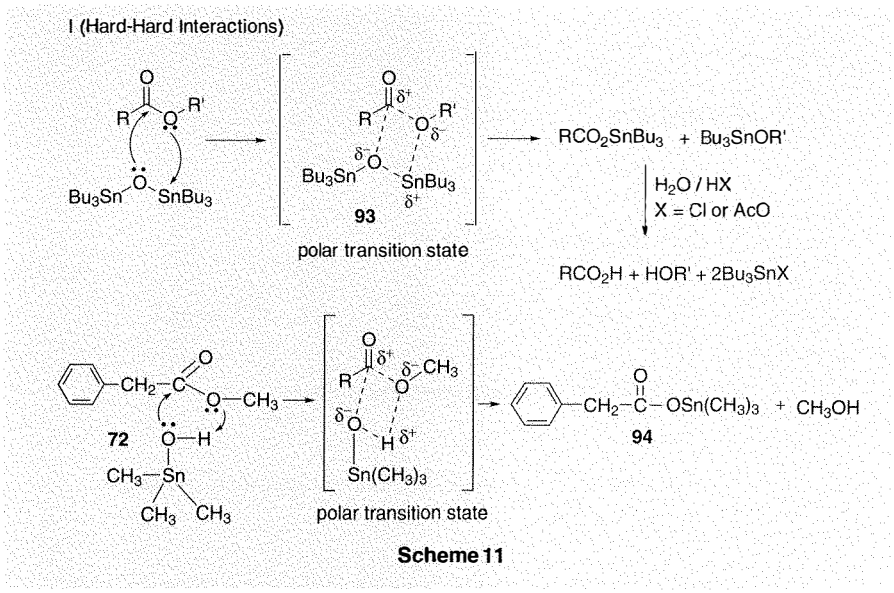
• Retention of configuration in going from **69** to **70**.[60]

• Methyl benzoate (**34**) was not cleaved to benzoic acid (**15**) by bis(tri-*n*-butyltin) sulfide (BBTS), a softer analog of BBTO. The starting ester **34** was recovered quantitatively. Under identical experimental conditions using BBTO, **15** was isolated in 80% yield. These results support the assumption that a hard oxygen atom is needed to achieve cleavage.[60]

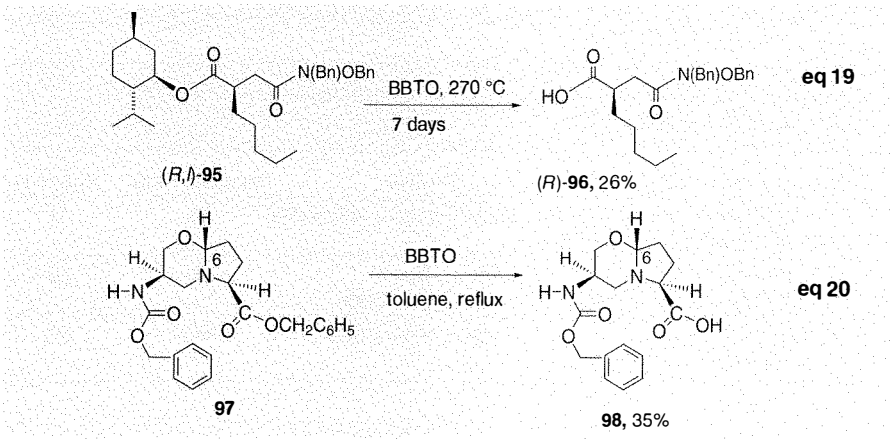
• The findings that methyl and isopropyl phenylacetates **72** and **73** were converted into phenylacetic acid **(28)** in very good or quantitative yields by using 1 equivalent of BBTO (**Table 4**, entries 1 and 8 and **Table 5**, entry 5).

• The qualitative estimation of the acidity of BBTO and bis(chloro-di-*n*-butyltin)-oxide **13** (**Table 2**), and the observation that when ester **72** was treated with **13**, it remained unaffected over a long period of heating or under microwave irradiation (entry 2 in **Table 4** and entry 6 in **Table 5**).[64a]

With TMTOH. The regiochemistry of the acyl oxygen bond cleavage was documented when methyl phenylacetate **72** was treated with TMTOH and the reaction product analyzed by IR and ^{1}H, ^{13}C, and ^{119}Sn NMR spectroscopy to reveal that $C_6H_5CH_2CO_2Sn(CH_3)_3$ (**94**) was the only organotin product isolated[67] (**Scheme 11**). It is likely that the mechanism of cleaving carboxylic esters with the weakly basic TMTOH is similar to that occurring with BBTO, a weak Lewis acid.



Scheme 11



4.9. Synthetic Applications

In 1992, Deb and Basu[68] applied our method to the BBTO-mediated cleavage of several primary alkyl, benzyl, and aryl carboxylates, through the intermediacy of tri-*n*-butyltin esters. More recently, Pérez and Maier have successfully used BBTO for the selective deprotection of steroid esters.[69]

Farina and Huang[70] studied the selective debenzoylation at C-2 of baccatin III with tri-*n*-butyltin methoxide-lithium chloride. Meanwhile, in their asymmetric synthesis of (–)-actinonin and (–)-*epi*-actinonin, Davies and co-workers found cleaving the menthyl group of the intermediate (R,*I*)-(–)-menthyl 2-(*N*-benzyl-*N*-benzyloxycarbamoylmethyl)heptanoate (**95**) problematic.[71] After several unsuccessful attempts using such reagents and conditions as TMSI, phenylmethanethiolate, or BBTO at reflux in benzene or toluene, they succeeded using BBTO under very drastic conditions — although the desired acid **96** was obtained in low yield (**eq 19**). Baldwin and co-workers reported[72] the use of BBTO to deprotect the benzyl ester of the bicyclic Cbz-lactam **97** and its C-6 epimer. The corresponding bicyclic lactam acid **98** (and the C-6 epimer) were obtained in 35% yield. The low yield for the deprotection reaction was attributed to the simultaneous cleavage of the Cbz protecting group. This problem was circumvented by using the *N*-Boc protecting group instead of Cbz.

In 1994, in a publication of their total synthesis of (±)-myrocin C, Danishefsky and co-workers reported that an unexpected formate ester cleavage of an iodoformate ester intermediate occurred when they attempted a radical reductive dehalogenation with bis(tri-*n*-butyltin) hydride and catalytic AIBN.[73] The authors explained that this abnormal minor compound could arise from the presence of an oxidized product in tri-*n*-butyl hydride and mentioned our similar finding.[56]

5. Purification

Most of the organotin oxides and hydroxides and their byproducts are highly soluble in nonpolar solvents and very insoluble in water. TMTOH is the only organotin compound that is soluble in water and very insoluble in most organic solvents. We have used these properties extensively to purify carboxylic acids and alcohols. We have also found that filtration through a short pad of C-18 reversed-phase silica gel and elution with mixtures of acetonitrile-water is one of the most useful ways to remove organotin derivatives.

In 1979, Berge and Roberts reported a purification method for organotin compounds based on the preferential partitioning in the acetonitrile-hexane two-phase system.[74] The same year, Leibner and Jacobus reported[75] a purification procedure based on converting organotin chlorides, bromides, or iodides

into an insoluble organotin fluoride which was separated by filtration.

More recently, Farina[76] reported a simple procedure for the separation of organotin derivatives by column chromatography using reversed-phase silica gel. Last year, Crich and Sun[77] published a practical method for the removal of organotin byproducts formed in Bu_3SnH and Ph_3SnH reductive radical dehalogenations. It consists of the reductive conversion of organotin compounds by $NaBH_3CN$ prior to silica gel chromatography.

6. Outlook

One of the major developments in the last 25 years has been understanding the structure and reactivity of organotin oxides, hydroxides, and alkoxides. The well-established techniques of ^1H, ^{13}C, and ^{119}Sn NMR spectroscopy, as well as ^{119}Sn Mössbauer spectroscopy and X-ray diffraction, have provided a wealth of structural information both in the solid state and in solution.

During the last decade substantial progress has been achieved in the development of useful organic functional group transformations mediated by organotin oxides, hydroxides, and alkoxides. Recent studies by Otera and co-workers have contributed to the development of a number of bis(1,3-disubstituted di-*n*-butyl)tin oxides as very effective template-catalysts for esterification of carboxylic acids, transesterification, acetalization of carbonyls, and deprotection of acetals and silyl ethers. The key to rationalizing these processes has been provided.

We discovered serendipitously that BBTO cleaved carboxylic esters. Since the time we made this observation, we have reported that a number of organotin oxides and hydroxides are effective stoichiometric reagents for the nonhydrolytic cleavage of simple carboxylic esters, such as methyl, ethyl, benzyl and phenacyl esters. Recently we have found that TMTOH efficiently cleaves benzyl and phenacyl esters linked to polystyrene resins, such as Merrifield, Pam, Wang as well as other linker resins. This we believe will be useful in future applications to solid-phase synthesis and to the production of combinatorial libraries — in particular to the production of organic compounds containing acid-sensitive functional groups.

We highly recommend the use of TMTOH since:

- It is less sterically congested than BBTO, thus overcoming one of the limitations of the reaction of BBTO with sterically hindered esters.
- The separation of TMTOH and its byproducts is straightforward.
- Carboxylic acids are produced in high yields.
- *N*-Boc amino acids and *N*-Boc peptides are isolated with complete retention of enantiomeric purity.
- It is compatible with an *N*-Boc/*O*-Bn strategy, yielding protected peptides suitable for further manipulation in segment condensations or cyclization strategies.

We are confident that significant developments in this active field will continue apace.

7. Acknowledgments

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About the Authors

Oreste A. Mascaretti holds the position of Full Professor of Medicinal Chemistry at the University of Rosario and Senior Researcher at the Institute for Organic Synthesis of Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET).

Professor Mascaretti was born, raised, and received most of his formal education in Argentina obtaining the Doctorate in Pharmacy from Buenos Aires University under Professor Edmundo A. Rúveda in 1975. After postdoctoral training with Heinz G. Floss at Purdue University, he was appointed Assistant Professor of Organic Chemistry at Buenos Aires University (1978-1983).

Professor Mascaretti is the author of more than 45 scientific papers and is President (1996-1997) of the Organic Chemistry Research Association (Argentina) and an Associate Fellow of The Royal Society of Chemistry (London).

His current research interest is the design and synthesis of β-lactam compounds as β-lactamase and elastase inhibitors, as well as the use of organotin oxides and hydroxides for the cleavage of carboxylic esters.

Ricardo L.E. Furlán was born in Lucas Gonzalez (Argentina). He graduated with a B. Pharm. in 1993 from the Faculty of Biochemistry and Pharmacy of Rosario University, Argentina. He is presently pursuing his doctoral research on cleavage of carboxylic esters by organotin oxides and hydroxides under the direction of Professor Oreste Mascaretti. He holds a fellowship from CONICET and a teaching assistantship in Pharmacognosy at the University of Rosario.

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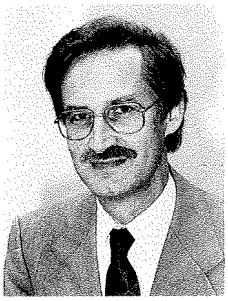
62279 Lipase, immobilized in Sol-Gel-AK from *Pseudomonas cepacia*, ~ 60 U/g, 1 g / 5 g
62281 Lipase, immobilized in Sol-Gel-AK from *Aspergillus niger*,~ 2.7 U/g, 1 g / 5 g
62277 Lipase, immobilized in Sol-Gel-AK from *Candida antarctica*,~ 1.6 U/g, 1 g / 5 g
62278 Lipase, immobilized in Sol-Gel-AK from *Candida cylindracea*,~ 16 U/g, 1 g / 5 g
62324 Lipase, immobilized in Sol-Gel-AK from hog pancreas, ~ 65 U/g, 100 mg / 500 mg
62282 Lipase, immobilized in Sol-Gel-AK from *Mucor miehei*, ~7 U/g, 1 g / 5 g
62283 Lipase, immobilized in Sol-Gel-AK from *Pseudomonas fluorescens*, ~ 55 U/g, 1 g / 5 g

The Prize Winner 1997:



Manfred T. Reetz received his PhD from the University of Göttingen in 1969. After postdoctoral studies with Prof. R. W. Hoffmann he qualified as university lecturer at the University of Marburg in 1974. In 1978 he became C3-Professor at the University of Bonn and only 2 years later, in 1980, obtained a full professorship in organic chemistry at the University of Marburg. In 1993 he was appointed director of the *Max-Planck-Institut für Kohlenforschung* at Mülheim an der Ruhr, Germany. For his work in the field of organic chemistry he was awarded a *Dozentenstipendium des Fonds der Chemischen Industrie* (1976), the *Otto-Bayer-Preis* (1986), and the *Leibniz-Preis der Deutschen Forschungsgemeinschaft* (1989).

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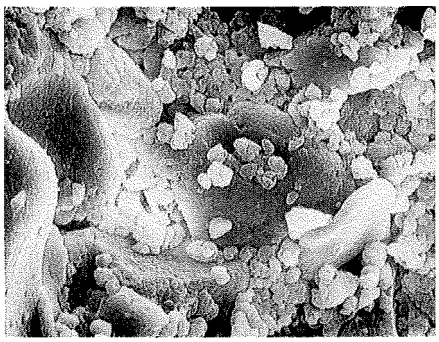

Scanning electron-micrograph of a sol-gel immobilisate with *Aspergillus niger* lipase, Fluka No. **62281**

The development of immobilized lipases produced by inclusion of the enzyme in sol-gel materials has been awarded the 1997 Fluka prize. Lipases play an important role in organic synthesis. Two major problems, however, are the decreased enzyme activity in organic solvents and difficult recovery. These problems can be solved with a new immobilization procedure in which lipases are incorporated in hydrophobic organic-inorganic hybrid materials with the help of a sol-gel process.[1-3] This new class of heterogeneous biocatalysts has several advantages:

- increased enzyme activity (up to a factor of 100) for esterifications in organic solvents.[1-3]
- conservation and increase of enantioselectivity in acylation reactions.[1-5]
- remarkably high long-term stability.[1-3]
- increased temperature stability.[2]
- convenient recovery.[1-3]

The porous and lipophilic character of the lipase-containing gels[6] (see scanning electron micrograph) results in unexpectedly high activity. The new gels can be coated onto glass beads (e.g., SIRAN®) and used as heterogeneous biocatalysts in fluidized bed reactors.[7] Preliminary experiments show that catalytic reactions are also possible in water.[8] A review article will be published soon.[9]

SIRAN is a registered trademark of Schott Glaswerke, Mainz.

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The painting on our cover is *The Country School* (oil on canvas, 54.3 x 97.5 cm) by Winslow Homer (1836-1910). In this painting, the artist depicts a rural schoolroom in an upstate New York town he had visited in 1870. The sunlight streaming through the window curtains suggests the fresh atmosphere of the country day and contrasts with the controlled geometry of the classroom.

Winslow Homer developed his interest in scenes of everyday life as a magazine illustrator in the 1850s in Boston, where he worked primarily in the medium of wood engraving. His earliest paintings feature humble scenes rendered in contrasting lights and darks. Homer's images of American life show authentic characters in their native environments, without the overly sentimental qualities that mark many contemporary genre scenes.

This painting is in the collection of The Saint Louis Art Museum.

Lab Notes

Protocol for Purifying α-Ketocarboxylic Acids

Over previous years we have had to prepare some α-ketocarboxylic acids. These compounds are key intermediates in the synthesis of many pharmaceutical products. Their purification has previously been carried out using Kugelrohr distillation or flash column chromatography. Whilst these are excellent and useful techniques in their own right, they are (1) less suited to thermally unstable compounds since recovery losses occur, and (2) it is often more difficult to elute very polar compounds in a pure state since the polar eluent, frequently needed to effect the separation, "drags down" impurities. In addition, these compounds are sometimes unstable on silica gel.

The following protocol that we have used to purify these materials is fast and reliable, and gives virtually quantitative recoveries.

The reaction solvents are removed from the reaction mixture by evaporation. The crude mixture is then treated with diethyl ether followed by potassium carbonate. The potassium ketocarboxylate salt rapidly precipitates out leaving the impurities in solution. The supernatant liquid is then decanted, and the residue is triturated with a little diethyl ether. This ether wash is also decanted. The precipitate is suspended in diethyl ether and acidified with aqueous hydrochloric acid to pH 3. After shaking, the ether layer is separated, dried, and evaporated to yield the pure α-ketocarboxylic acid almost quantitatively.

Dr. Craig J. Roxburgh
Christopher Ingold Laboratories
University College London, University of London
20 Gordon Street
London, WC1H OAJ, England

Holding GC Capillary Columns with a Piece of Parafilm®

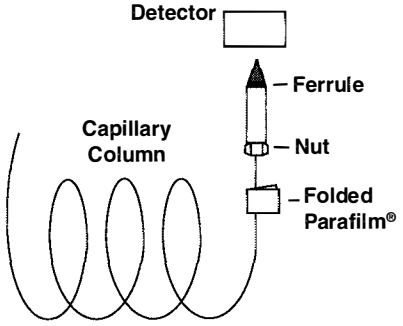
Installing a glass capillary column in a gas chromatograph is often a frustrating process. I find that Parafilm® can help in connecting the column to the detector or inlet. A small piece (about 3 x 6 cm) is folded in half behind the ferrule and nut to hold these parts still and can be used to position the end of the column more precisely (see diagram).

The Parafilm® won't slip and is a good finger hold on the column itself. Removal is easy and leaves no adhesive residue.

Sincerely,

David Van Horn, graduate student
Department of Chemistry
University of Utah
Salt Lake City, UT 84106

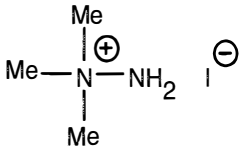
Diagram



"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President

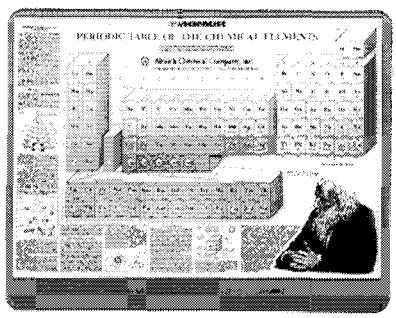


Dr. Philip Pagoria of the Lawrence Livermore National Laboratory kindly suggested we offer 1,1,1-trimethylhydrazinium iodide (TMHI). This compound acts as an aminating agent in the vicarious nucleophilic substitution of hydrogen, and is superior to other nucleophilic aromatic aminating reagents.

Chem. Eng. News **1996**, *Apr. 15*, 34.

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, *Aldrichimica Acta*). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. **Z15,000-2**). If we publish your *Lab Note*, you will also receive an Aldrich periodic table turbo mouse pad (Cat. No. **Z24,409-0**). It is Teflon®-coated, 8½ x 11in., with a full-color periodic table on the front. We reserve the right to retain all entries for future consideration.



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Synthesis of Biologically Important Oligosaccharides and Other Glycoconjugates by the Glycal Assembly Method*

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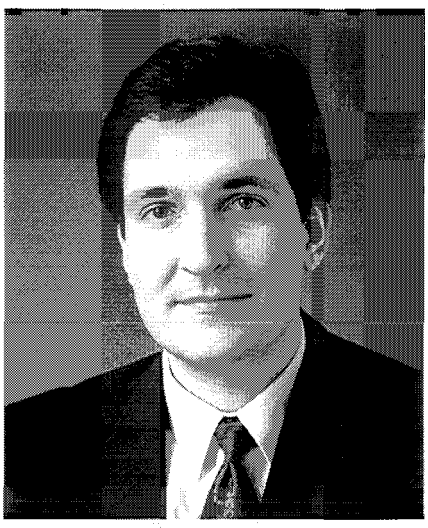
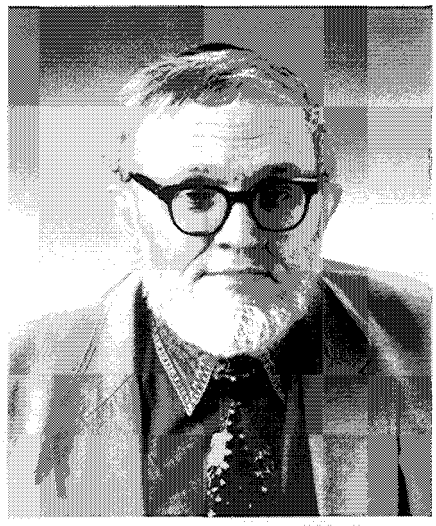
Abstract

A review is provided here of the work in our laboratory on the synthesis of oligosaccharides and glycoconjugates. The use of glycals both as glycosyl donors and glycosyl acceptors led to the strategy of glycal assembly of oligosaccharides and other glycoconjugates. Several new glycosylation techniques were developed to provide access to a range of synthetic targets.

Moreover, glycal assembly—both in solution and the solid phase—has been used to gain concise and efficient entry into a variety of biologically interesting and potentially valuable constructs. Some of these syntheses, particularly in the field of tumor antigens, have led to novel compositions which are in clinical assessment.





1. Introduction

The synthesis of carbohydrate-based structures is emerging as a major frontier area in organic chemistry. In addition to their well-appreciated roles in supporting structural matrices, in energy storage, and as biosynthetic starting materials, carbohydrates are cast in a variety of interesting settings as glycoconjugate antibiotics,[1] antitumor agents[2] and cardiotonic glycosides.[3] The gangliosides are being increasingly implicated as tumor antigens and cellular differentiation markers.[4] The importance of the carbohydrate domains (in the context of glycoproteins and glycolipids) as elements in cell surface recognition is manifested by their role in cellular adhesion[5,6] and as blood group determinants.[7] Another incentive for focusing on carbohydrates is their usefulness as enantiomerically pure starting materials for the synthesis of various natural products and other types of target molecules.[8]

The Lewis acid catalyzed diene-aldehyde cyclocondensation (LACDAC) reaction provides a rapid route to novel dihydropyrones of type **2**. 1,2-Reduction of such dihydropyrones with sodium borohydride mediated by cerium(III) chloride results in alcohols such as **3** in which the hydroxyl group is in an equatorial position (**Scheme 1**).

Several pathways were successfully followed to produce enantiomerically enriched or enantiomerically pure dihydropyrones and glycals by means of the LACDAC reaction and have been reviewed previously.[9]

Our enthusiasm for the LACDAC methodology notwithstanding, naturally occurring sugars still provide the best source of glycals which bear the usual hexose functionality at C-3, C-4, and C-6. In particular, glycals closely related to D-glucal, D-galactal and D- or L-fucal are readily accessible from commercially available precursors. It is only when the required functionality of the target glycal is not reasonably accessible from carbohydrates that total synthesis via the LACDAC chemistry can be superior to partial synthesis.

The synthesis of glycals from carbohydrate precursors bearing axial hydroxyl

* This article is based on a more comprehensive review published in *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

† Dr. Seeberger's new address as of January 1998: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139-4307

groups at C-3 (e.g. D-allal and D-gulal) can be achieved by reductive elimination of C-1-C-2 hetero groups.[10] However, in several important instances, the starting hexoses bearing axial alcohols at C-3 were themselves very difficult to access. A route was devised to deal with this type of situation. Our method exploits a form of the Ferrier type displacement of glycals.[11,12] As will be seen, the classical Ferrier rearrangement leading to pseudoglycals was valuable to our developing program (**Scheme 2**). For the case at hand, reaction of a C-3 equatorial glycal with thiophenol gives rise to an axial thiophenyl "pseudoglycal." The latter, upon oxidation, is converted to a C-3 axial glycal, presumably via rearrangement of its sulfoxide.[13,14]

2. Glycals in the Synthesis of Oligosaccharides–General Considerations

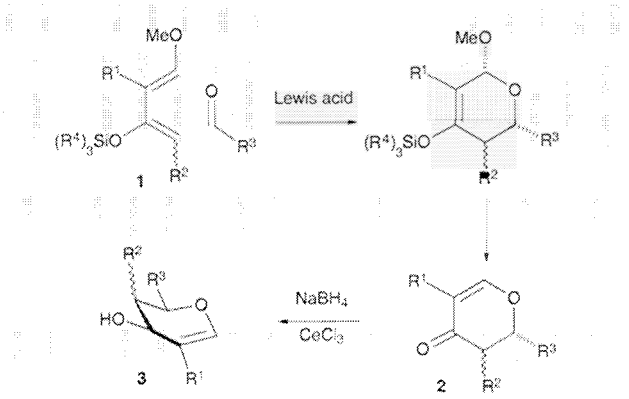
In the glycosylation reactions described below, *the component that contributes the anomeric carbon of the resultant glycoside is described as the glycosyl donor* (**Scheme 3**). The donor reacts with a glycosyl acceptor to establish a glycoside. In the majority of glycosylation reactions, *the acceptor is a nucleophile that furnishes the oxygen of the resultant glycoside* by replacement of a leaving group on the anomeric carbon of the electrophilic glycosyl donor. However, the novel glycosylations of Schmidt,[15] David and Lubineau,[16] Vasella,[17] and Kahne[18] attest to the need to decouple the terms "glycosyl donor" and "glycosyl acceptor" from mechanistic descriptors such as "nucleophile" and "electrophile".

It is also well to distinguish two modalities by which glycals can function as glycosyl donors (**Scheme 3**). In one motif the glycal is first converted, through a reaction or sequence of reactions, to an isolable, or at least identifiable, glycosyl donor (for instance, via epoxidation, azidonitration[19] or sulfonamidoglycosylation). In essence the glycal is a precursor to a structurally defined glycosyl donor. Alternatively, in situ electrophilic activation might mobilize the glycal to function as the donor in the form of a substoichiometric nonisolable intermediate rather than as a defined reaction component.

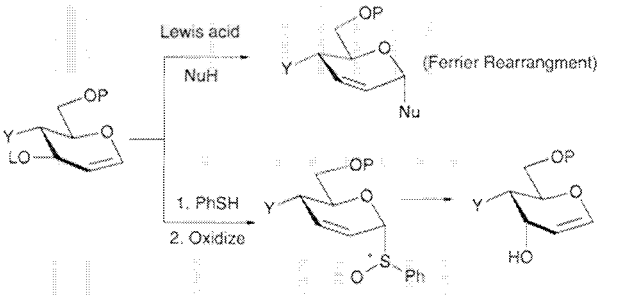
The possibility of utilizing glycals as glycosyl donors in disaccharide synthesis had been demonstrated in the pioneering research of Lemieux[20] and Thiem[21] via halonium-mediated coupling to suitably disposed acceptors. These particular reactions had been shown to have a high proclivity for trans diaxial addition and provided a crucial route to α-linked disaccharides bearing an axial 2-iodo function on the nonreducing end. Owing to the difficulty of effecting a nucleophilic displacement of the iodine in such systems,[22] this methodology has found its most useful application in the synthesis of 2-deoxyglycosides.[21,23]

If glycals could serve both as glycosyl donors and as glycosyl acceptors in a broad range of couplings, a reiterative strategy for the synthesis of complex glycoconjugates, including oligosaccharides, could be contemplated. A potentially important advantage of glycal-based glycosylations was to be the simplification of achieving differentiated hydroxyl protection and presentation (compare **Schemes 4** and **5**).

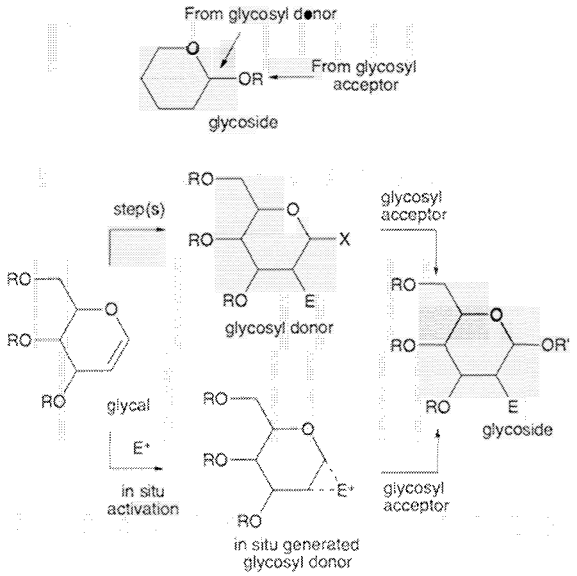
Scheme 4 portrays, globally, the classical strategy of glycosylation,[24] using fully oxygenated pyranose donors and acceptors. In the very simple case of coupling hexoses D (donor) and A (acceptor) to produce the protected DA disaccharide, several challenges must be overcome. The anomeric hydroxyl function in the eventual donor sugar must be distinguished as a leaving group from the other four hydroxyls. In the eventual acceptor, a particular free hydroxyl (one of five such groups) must be identified for glycosylation, while the anomeric area of the "acceptor" system is properly protected. If one is to proceed toward the DAA' trisaccharide, the "exo" glycoside moiety of the DA disaccharide must be distinguished from its "endo" counterpart. With this accomplished, a leaving group (i.e., a glycosyl donating function) is installed on the erstwhile A sugar, and this ensemble must be appended to



Scheme 1. Synthesis of glycals via the LACDAC reaction (gluco-series: R^2= β-oxygen, galacto-series: R^2= α-oxygen).



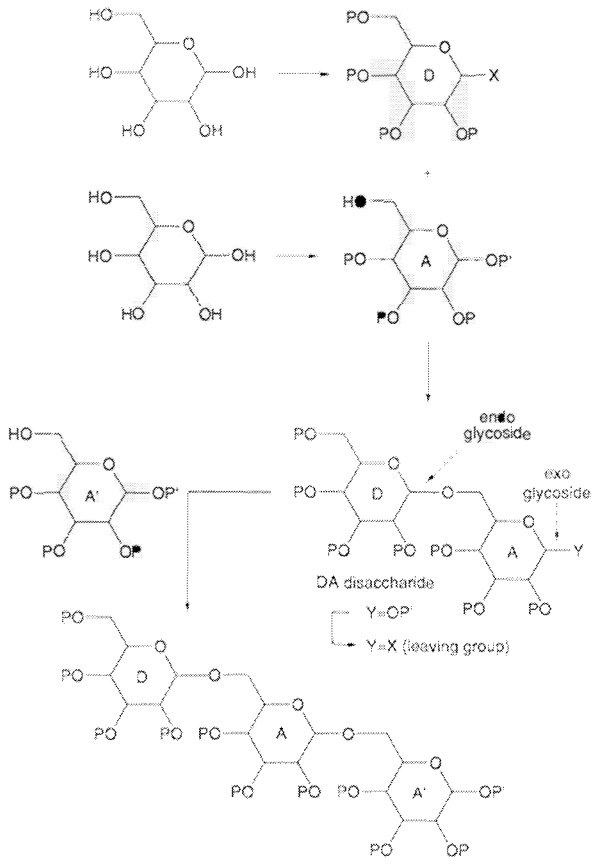
Scheme 2. Ferrier rearrangements of glycals and utilization of subsequent sulfoxide rearrangements (LO= leaving group; for allals: Y=α-OR, for gulals: Y= β-OR).



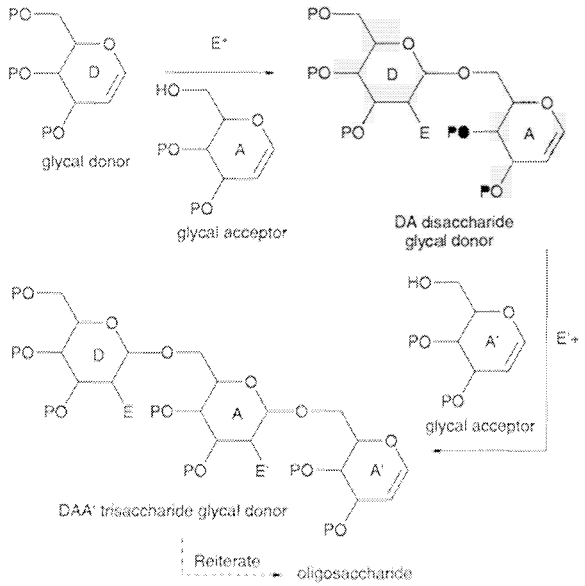
Scheme 3. Glycals as glycosyl donors.

glycosyl acceptor A' in which one of five hydroxyls had been identified as the acceptor for the glycosylation.

We contrast this situation with the projected formation of the DAA' trisaccharide by reiterative coupling of glycals (**Scheme 5**). Thus the activatable olefinic linkage of uniformly protected D functions as the



Scheme 4. Trisaccharide (DAA') synthesis via conventional methods (the stereochemistry of glycosidic linkages is not specified).



Scheme 5. Trisaccharide (DAA') synthesis via a glycal assembly strategy (the stereochemistry of glycosidic linkages is not specified).

donor. One of three hydroxyls of acceptor glycal A is to be presented for glycosylation in reaching the DA disaccharide. After coupling, the glycal linkage of DA is activated (either in situ or in a discrete process) to produce a DA donor vis-à-vis a new acceptor glycal, A'. In this way, trisaccharide DAA' is obtained. It can be readied for elongation by priming of the glycal in the A' sector en route to the tetrasaccharide or higher oligomers.

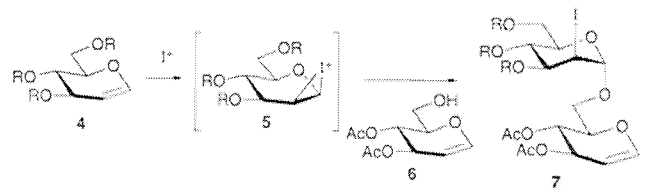
For the reiterative method described in **Scheme 5** to be viable and widely applicable, glycals must also function as glycosyl acceptors. Furthermore, for extended applications it would be necessary for glycal linkages at the putative reducing end of larger oligosaccharides also to function as viable donors. For maximum applicability, it would be necessary to fashion a variety of coupling methods with glycals serving both as donors and as acceptors. To use these concepts in the construction of unnatural glyconjugates and oligosaccharides, unnatural glycals, obtained by synthesis, must be amenable to the methodology being developed.

3. Glycosylation Reactions Involving Glycals

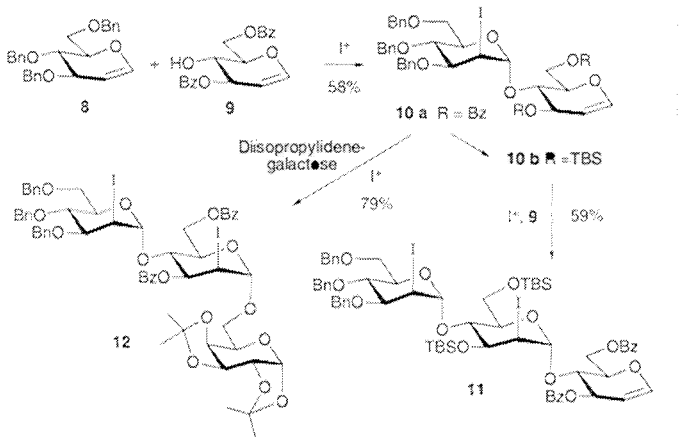
3.1. Haloglycosylation

The iodoglycosylation reaction developed by Lemieux[20] and Thiem[21] has been carried out with a glycal serving as a donor. The glycal linkage is attacked by an "I^+ equivalent" reagent (e.g., *N*-iodosuccinimide or *sym*-collidine iodonium perchlorate). In the ordinary case, the presumed substoichiometric **5** (**Scheme 6**), arising from attack of I^+ on the glycal, is attacked by a coexisting nonglycal acceptor, in which the reducing end is suitably capped. The stereochemistry of glycosylation is governed by *trans*-diaxial addition and the α-linked disaccharide **7** is produced.

An interesting possible solution presented itself. *The thought was that the pattern of protecting groups of the glycal might be used to direct the events.*[25,26] For the case at hand, consider the case of two glycals, projected donor **4** and projected acceptor **6** (**Scheme 6**). The oxygen atoms of **6** are



Scheme 6. The use of glycal donors and acceptors in iodoglycosylations (OR= ether linkage)



Scheme 7. Polysaccharide assembly employing the iodoglycosylation reaction.

acylated, while those of **4** are alkylated (or silylated). It seemed likely that **4** would be more nucleophilic towards the iodonium electrophile than would **6**. Hence, I^+ will attack **4**, thereby generating the mechanistically operative glycosyl donor **5**. Furthermore, **4** is deprived of a free hydroxyl group, hence, it cannot be an acceptor. Glycal **6**, which is equipped with the free hydroxyl group can function as the glycosyl acceptor, giving rise to iodoglycoside **7**. It is necessary that the rate of formation and the effective concentration of **5** be much greater than those of the corresponding iodonium species derived from **6** or from the disaccharide product **7**.

This possibility was reduced to practice as outlined in **Scheme 7** (see **8** + **9** → **10**).[27] To reiterate the process, it was necessary to enhance the nucleophilicity of disaccharide **10a** glycal toward I^+ so that it would function as a glycosyl donor to the next acceptor, hydroxydibenzoate **9**. For this purpose, **10a** was converted to **10b**. Indeed, iodinative coupling of **10b** with **9** gave rise to **11**. The iodinative coupling of glycal **10a** with a nonglycal—acceptor diisopropylidenegalactose—was of interest. This case, which led smoothly to **12**, again demonstrated that glycals bearing acyl protecting groups are certainly competent donors in iodoglycosylation reactions with nonglycal acceptors. The essence of this finding was that the otherwise active 1,2-double bond of the diester-protected glycal substrate does not compete with the analogous double bond in the triether for attack by the iodonium species. The control of the glycal-glycal coupling was exploited in a synthesis of ciclamycin 0.[28,29]

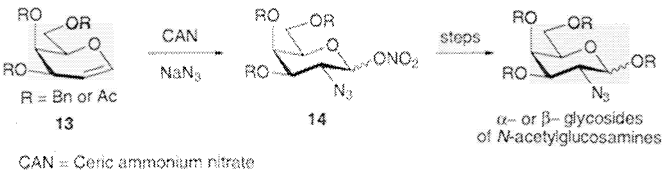
3.2. Azaglycosylation

Given the excellent access to natural and unnatural glycals by either total synthesis or partial synthesis, it seemed appropriate to investigate the possibility of their use as precursors to glycosides of 2-acylamino sugars.

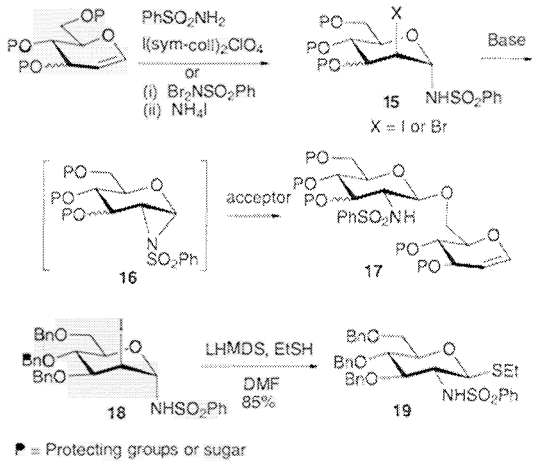
Two methods for introducing a nitrogen at C-2 via a glycal had been studied earlier by Lemieux. An important first advance employed nitrosochlorination of glycals.[30] While this route constituted significant progress in its time, the methods to convert the oximino products to desired goal structures were not optimal with regard to yield and stereoselectivity. Greater progress was achieved via azidonitration (**13** → **14**, **Scheme 8**).[19]

New methods were sought for reaching goal system **17** (**Scheme 9**) in which *stereoelectronic factors rather than issues of local steric hindrance govern the outcome.* The key reaction to deal with this problem was sulfonamidoglycosylation.[31] The method, which involves trans diaxial addition of an *N*-halobenzenesulfonamide to a glycal, leads to **15**. Under appropriate conditions, a range of nucleophiles is capable of converting **15** to glycosides of 2-α-benzenesulfonylglycosamine derivatives. It was demonstrated that the incoming *acceptor* can be a pyranose with a suitably differentiated hydroxyl group, or it could be a glycal thus allowing for reiteration of the process (cf. **17**). Also, the *donor* could be a di- or higher saccharide terminating in a glycal linkage that would undergo sulfonamidoglycosylation.

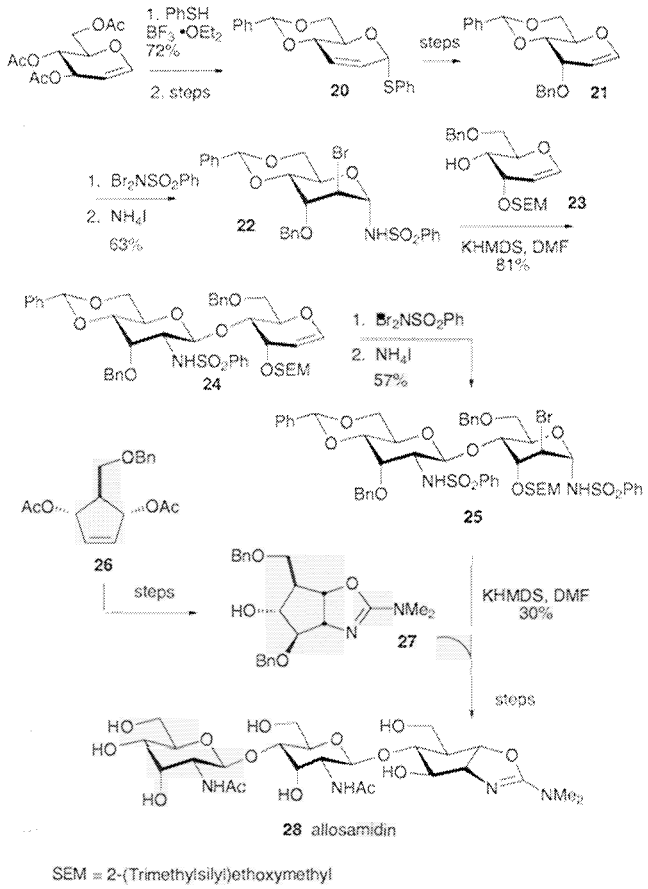
While we have not been successful in properly characterizing the intermediate between the 2β-halo-1α-sulfonamidopyranosides (e.g., **15**) and the product **17**, the 1,2-sulfonylaziridine **16** is believed to be the active glycosylating entity. This moiety functions as a very powerful electrophile, prompting clean β-attack by the nucleophile at the anomeric carbon. Several protocols have been developed for liberating the amino system from its 2-sulfonamide precursor. Furthermore, an iodosulfonamide can be readily converted to a corresponding ethyl thioglycoside (**18** → **19**, **Scheme 9**). The latter can subsequently be employed as an



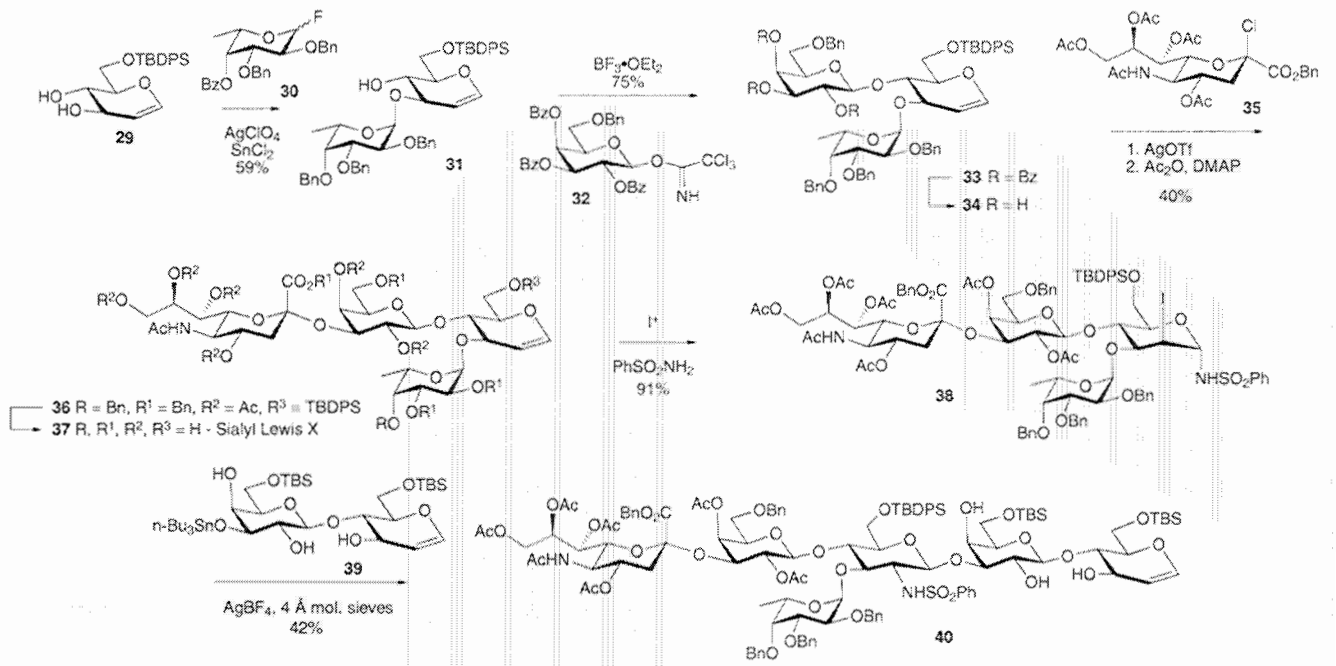
Scheme 8. Azidonitration of glycals.



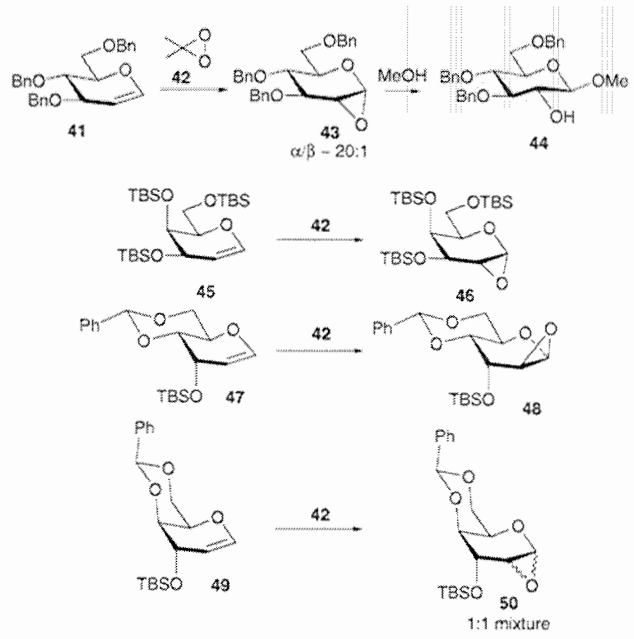
Scheme 9. Iodosulfonamidation of glycals.



Scheme 10. The synthesis of allosamidin.



Scheme 11. Synthesis of a sialyl Le^x glycal.



Scheme 12. Epoxidation of glycals by 3,3-dimethyldioxirane (**42**).

azaglycosyl donor to some advantage. This conversion has proven very useful in several important cases where the direct glycosylation of iodosulfonamides fails.

The first application of this new chemistry was in the total synthesis of the very powerful chitinase inhibitor allosamidin.[32] The route to allosamidin exploited sulfonamidoglycosylation at two stages. In the first application, allal type glycal **21** was used (**Scheme 10**). This glycal is available either from allose or by rearrangement of the α-thiophenyl derivative **20**.[11] Bromosulfonamidation of **21** afforded **22** which was coupled to glycal **23** in the presence of KHMDS to give **24**. The latter then functioned as an azaglycosyl donor. Bromosulfonamidation of **24** afforded **25**. Reaction of **27** with aglycone derivative **25** afforded, after several steps, allosamidin (**28**).

A second early application came in the important field of sialyl Le^x glycosides.[33,34,35] It is the sialyl Le^x substructure present at the nonreducing end of cell surface glycoproteins which comprises the key recognition element in E-selectin- and P-selectin-mediated adhesion.[36] The goals focused on the synthesis of an intermediate which could serve as a launching point to reach various glycosides of sialyl Le^x. Such glycosides could be screened as potential inhibitors of the natural ligand.

Toward this end, sialyl Le^x glycal derivative **36** was identified as a suitable target candidate (**Scheme 11**). We also hoped to study the properties of the fully deprotected derived glycal **37** in an ELAM binding assay. Moreover, if the azaglycosylation chemistry described above could be extended to the protected system **36**, we could gain access to a range of more extended oligomers from a late structure. In this way we would obviate the need for a separate lengthy synthesis for each assay candidate.

A key discovery in this regard was that glycal **29**, containing silyl protection only at the primary (C-6) hydroxyl group, undergoes selective fucosylation with **30** at the allylic alcohol center (C-3). Conveniently, after fucosylation, the C-4 hydroxyl was available to serve as the acceptor toward the galactosyl trichloroacetimidate donor **32**, thus affording Le^x derivative **33** (and, after deprotection, **34**). Sialylation of **34** with the known sialyl donor **35** and acetylation led to protected product **36**, and eventually to the deprotected sialyl Le^x glycal **37**.

Furthermore, **36** underwent iodosulfonamidation to afford **38** (**Scheme 11**). This compound served as an *N*-sulfonylglucosaminyl donor toward stannyl-activated glycosyl acceptors. For instance, reaction of **38** with **39** led to **40**. The prospect of exploiting the glycal linkage for still further derivatization is obvious.

3.3. Applications of 1,2-Anhydrosugars to Glycoside Synthesis

While iodoglycosylation and sulfonamidoglycosylation provide valuable capabilities for the conversion of glycals to various glycosides,

there was a need for a very general route which would serve to convert glycals to common glycosides of glucose, galactose and mannose. Ideally the new methodology would embrace both α and β glycosides. In the hope that this type of result would be achieved, the possibility of direct conversion of glycals **41** to glycal epoxides **43** (**Scheme 12**) was considered. Two serious impediments to the broad applicability of 1,2-anhydrosugars presented themselves. First, there had been no reported methodology wherein a glycal could be converted directly to its 1,2-oxirane derivative. Previous attempts to prepare 1,2-anhydro systems from the reactions of various peracids with glycals led not to the 1,2-oxiranes, but to heterolysis products.

Also, the record of using α-epoxides such as **43** as stereoselective β-glycosylating agents for the formation of compounds such as **44** was none too promising.[37] Previous attempts to prepare disaccharides by employing a 1,2-oxirane as a glycosyl donor with various acceptors often resulted in nonstereoselective glycoside formation although such a donor was applied in the historic construction of sucrose by Lemieux.[38]

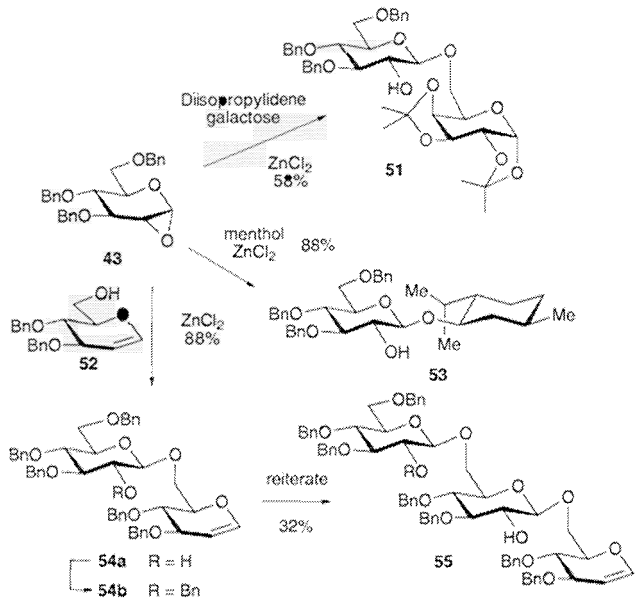
We, therefore, focused on several goals. One was that of finding a general method for the conversion of a glycal to a 1,2-anhydrosugar. The second goal was that of investigating whether glycals, which do not bear potential neighboring group participants of their resident functionalities, might serve as more stereoselective and efficacious donors in the formation of β-glycosides. Furthermore, we would investigate whether suitably differentiated glycals could function as glycosyl acceptors in glycosylations using glycal epoxide donors.

A major advance in our technology was the finding that a variety of glycals react smoothly with 3,3-dimethyldioxirane (**42**, DMDO),[39] prepared as a solution in methylene chloride.[40] For instance, glucal derivative **41** reacted with **42** to afford a near quantitative yield of **43** (**Scheme 12**). Solvolysis of **43** with neat methanol provided a methyl glycoside whose structure was shown to be **44**. Based on the methanolysis reaction, the stereoselectivity of the epoxidation was estimated to have been at least 20:1 in favor of the α-isomer. However, with resident acetate protecting groups, the stereoselectivity of the epoxidation was much reduced. Epoxidation of galactal derivative **45** provided **46**.

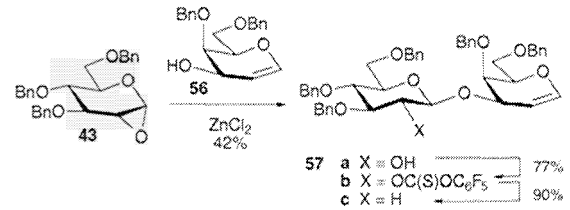
In the allal series, glycal **47** bearing the axial 3-TBSO function underwent quite selective epoxidation from its β-face providing **48**. On the other hand, the gulal derivative **49**, with hindering substituents on both faces of the double bond, gave a 1:1 mixture of epoxides **50**.

Based on these results, the glycosyl donating properties of these epoxides, particularly those derived from glucose and galactose, were investigated. The glycosylation of acceptors more complex than methanol, which are present to a roughly stoichiometric degree, was slow and required promotion. A universal promoter has not been discovered. With moderately acidic acceptors (e.g., phenols[41] and indoles)[42] the best results were obtained under basic conditions (vide infra). With ordinary alcohol acceptors the most widely used promoter has been anhydrous zinc chloride. In some applications, stannyl derivatives generated in situ, gave the best results (vide infra).

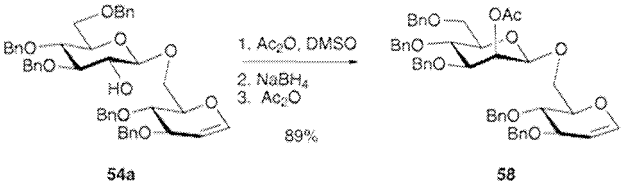
The earliest results from the use of **43** as a glycosyl donor are summarized in **Scheme 13**. Subsequent to the experiments summarized here, it was found that this particular oxirane is among the poorest of the donors[43,44] and, depending on the case, some α-glycoside is produced. It has since been learned that glycosylation yields can be improved by constraining the C3 - C4 or C4 - C6 oxygen functions into a cyclic motif. Nonetheless, the method had already enabled an easily executed two-step pathway from glucal derivatives to β-glycosides. That these products are fashioned with a uniquely distinguished free hydroxyl group adjacent to the β-glycosidic bond became a crucial element in our synthesis of complex branched saponins and the blood group determinants (vide infra). Also, the



Scheme 13. Coupling of an anhydrosugar with representative acceptors.



Scheme 14. Coupling of epoxides with secondary acceptors and phenols.



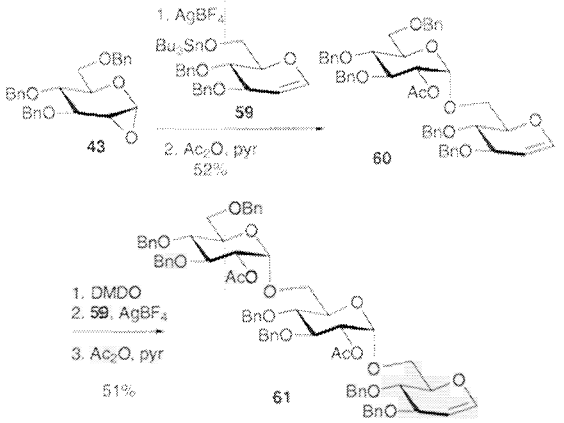
Scheme 15. Creation of β-mannosyl linkages via oxidation and reduction.

finding that the glycosyl acceptor for the glycal epoxide can itself be a glycal (see formation of **54**) had indeed established the basis for a reiterative strategy for the synthesis of repeating β-glycosides (see transformations **54a** → **54b** → **55**). This type of repeatability was in turn a central component of our approach to oligosaccharides with the glycosyl donor mounted into a solid support.

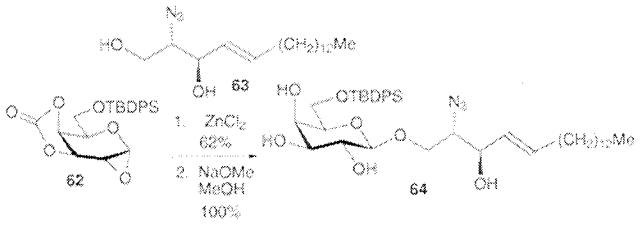
We also demonstrated the applicability of the glycal epoxide method to the synthesis of 2-deoxy-β-glycosides.[44,45] Here we took advantage of the uniquely placed C-2 free hydroxyl group as a target for deoxygenation. This was accomplished by free-radical reduction of the derived pentafluorophenyl thionocarbonate (**Scheme 14**).[45b]

Again, the basis for ready repeatability of the sequence is seen in the progression **43** + **56** → **57**. This demonstrates the feasibility of a Barton deoxygenation in the presence of a glycal linkage.

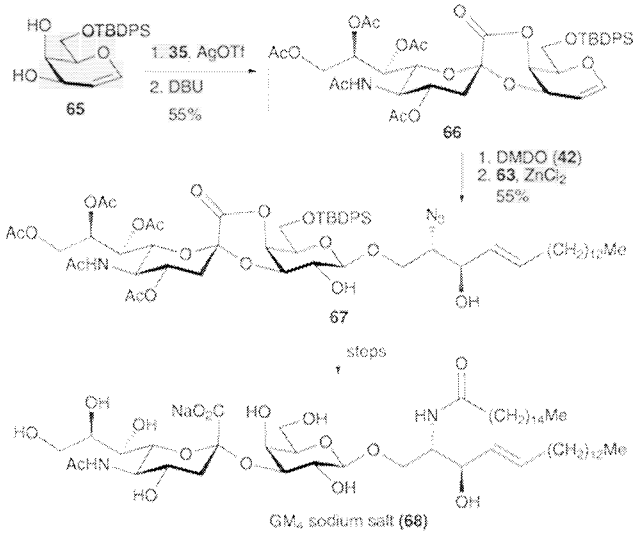
The uniquely generated 2'-hydroxyl group arising from opening of the 1,2-epoxide donors has also been exploited in the synthesis of β-mannosides via the oxidation/reduction protocol (**Scheme 15**).[46] Thus, oxidation of **54a** with acetic anhydride and DMSO followed by reduction of the unpurified product with $NaBH_4$ and acetylation provided selectively the β-mannoside **58** in 89% yield.



Scheme 16. Direct formation of α-linked glucose linkages.



Scheme 17. Studies towards the synthesis of GM_4.



Scheme 18. Synthesis of GM_4.

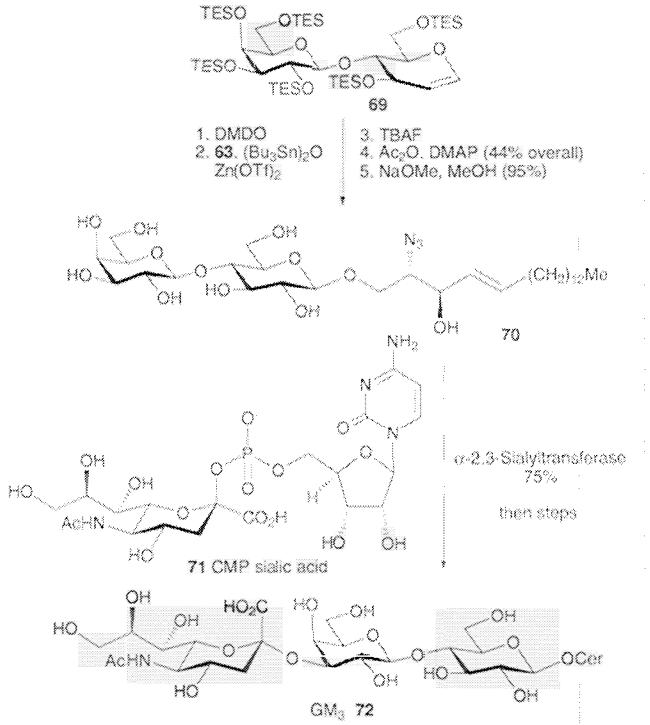
In addition, in certain cases an α-glucoside can be obtained directly from a glucal epoxide (**Scheme 16**).[47] The $AgBF_4$-promoted reaction of epoxide **43** with stannyl ether **59**, followed by acetylation, afforded α-glycoside **60**. The process was readily reiterated to provide trisaccharide **61**. This method is presently limited to primary hydroxyl acceptors and certainly does not constitute a comprehensive solution to the challenging problem of generating α-glycosides.

The possibility of using glycal epoxides in the construction of gangliosides has been examined.[48,49] An important advance involved the use of galactal-derived epoxide **62** (**Scheme 17**). Hitherto, in many cases, galactal-derived epoxides were not functioning well as stereospecific β-galactoside donors. The use of a cyclic carbonate that engages the C-3 and C-4 oxygens (see structure **62**) has had a most useful consequence in favoring β-galactosylation in a variety of situations. Reaction of construct **63** with **62** resulted in a high degree of selectivity for β-glycoside formation at the primary alcohol. Cleavage of the carbonate gave rise to tetraol **64**. *Contrary to many apparent precedents,* **64** *underwent sialylation at the C-2 rather than the C-3 hydroxyl.*

Fortunately, a straightforward solution was found by directly submitting glycal **65** to sialylation with **35** (**Scheme 18**). Coupling occurred smoothly at the allylic alcohol, generating a 3-sialylated galactal derivative which, upon treatment with DBU, provided the 3,4-spirolactone glycal **66**. Epoxidation with dimethyldioxirane and glycosylation with ceramide precursor **63** produced glycoside **67**, which was converted to the pure sodium salt of GM_4 (**68**). A slightly modified route was employed in the eventual synthesis of GM_4.

A combination of chemical and biological means was used to achieve a particularly straightforward synthesis of the important ganglioside GM_3 (**72**) (**Scheme 19**).[48]

Thus far, we have focused on the use of glycal epoxides in the synthesis of β-glycosides. It is also possible to convert such epoxides to other glycosylating agents (**Scheme 20**).[50] For instance, compound **43** was converted to thiophenyl glycoside **73**, pentenyl glycoside **74**,



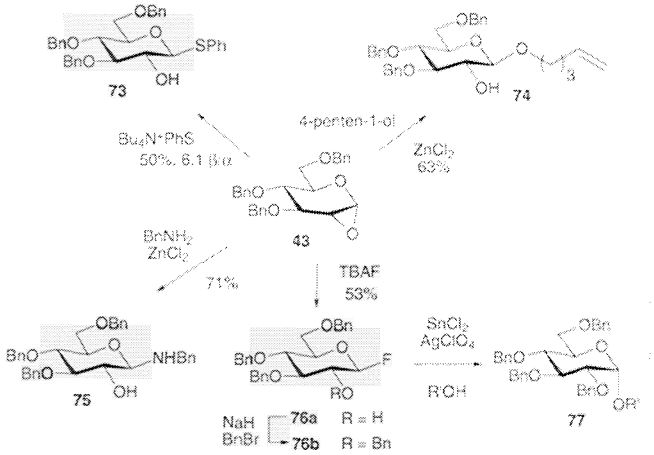
Scheme 19. Synthesis of GM_3.

benzylaminoglucoside **75**, and fluoroglycoside **76**. Compound **76a**, upon benzylation of the uniquely free C-2 hydroxyl group, gave rise to **76b** which served as a glycosyl donor in a conventional Mukaiyama reaction[51] to produce α-glycoside **77**.

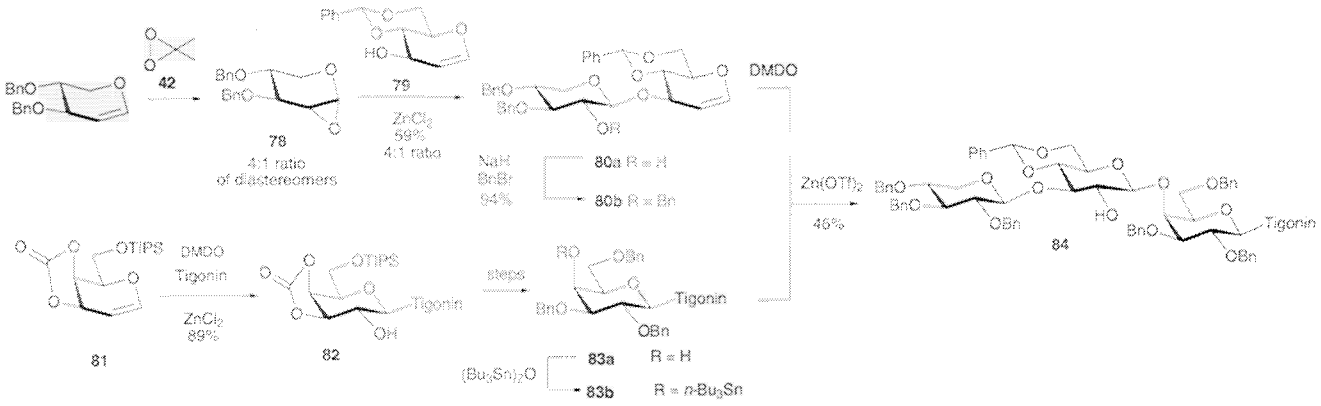
An advance in the emergence of glycal assembly logic was achieved in our synthesis of the complex saponin, desgalactotigonin (**Schemes 21** and **22**).[52,53] In particular, we focused on the branched glucose ring in the carbohydrate sector, which is β-linked to the C-4 axial hydroxyl of galactose. Particularly intriguing was the branching of this glucose in that its C-2 hydroxyl is β-linked to another glucose while at C-3 it is β-linked to a xylose. The introduction of this central glucose ring in the form of glycal derivative **79** brought forth major simplifications in protecting group strategy. The free hydroxyl at C-3 served as an acceptor toward the xylal-derived epoxide **78** to afford, after benzylation, **80b**. The acceptor for coupling to this new donor (**80b**) was fashioned from galactal cyclic carbonate derivative **81**. Epoxidation of **81** followed by coupling to the tigonin aglycone afforded **83** in several steps. Once again (cf. **62** in **Scheme 17**) this type of epoxide had served us very well as a β-galactosylating agent. Several reaction steps were carried out on intermediate **82** to: (i) cleave the cyclic carbonate, (ii) engage the 4- and 6-hydroxyls as a benzylidene derivative, (iii) effect a benzylation at C-2 and C-3, (iv) cleave the benzylidene linkage, (v) re-benzylate at C-6, and (vi) effect a stannylation at C-4 to produce glycosyl acceptor **83b**. Zinc triflate-mediated coupling of **83b** with the epoxide of **80b** afforded, albeit in only 46% yield, the steroidal trisaccharide **84**. The glycal epoxide coupling method had accomplished the identification of a unique hydroxyl group at C-2 of the central glucose for branching.

At this stage, however, the free hydroxyl group in **84**, flanked as it was by glycosidic bonds at C-1 and C-3, could not, in our hands, be glycosylated with epoxide donors (cf. **43**, **Scheme 22**). However, we were readily able to fashion a competent donor from **43**. Thus, epoxide ring opening with fluoride[27] afforded **85** which was converted to its benzoate **86**. The latter functioned with apparent α-face participation to favor heavily β-glycoside formation. Indeed, coupling of **86** with **84** was smoothly accomplished, and was followed by deprotection to provide desgalactotigonin (**87**).

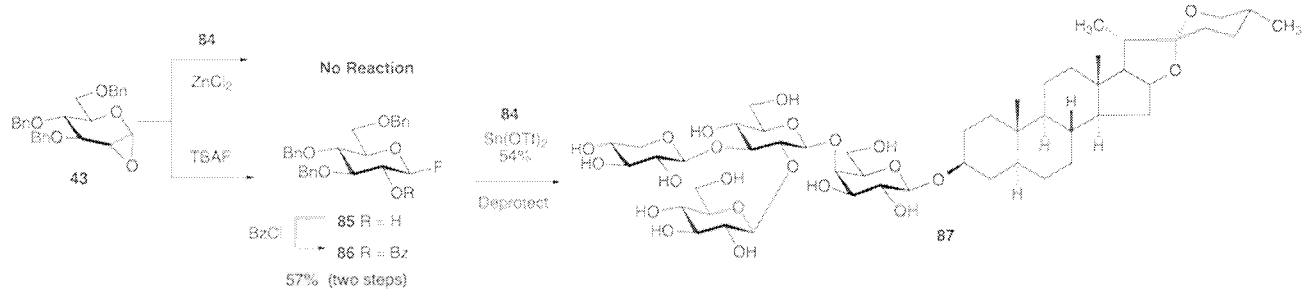
In summary, the logic of glycal assembly had allowed for a high degree of convergence in assembling the complex branched target system. Glycal epoxide opening had been used to expose a unique hydroxyl group to function as a glycoside acceptor (see compound **86**)



Scheme 20. Conversion of anhydrosugars to other donors.



Scheme 21. Synthesis of desgalactotigonin precursor.



Scheme 22. Synthesis of desgalactotigonin.

and to install a participating neighboring group in a regiospecific fashion. The participating group directed the fluoroglycosyl donor toward β-glycoside formation (en route to **87**).

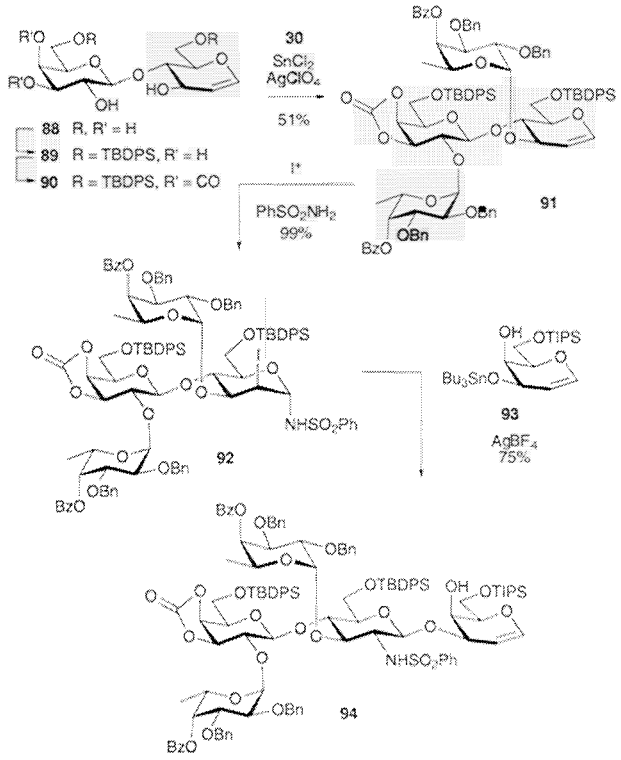
4. Application of the Glycal Assembly Method to the Synthesis of Lewis Determinants, Blood Group Determinants, and Tumor Antigens

The glycal assembly logic was next applied to the synthesis of Lewis and blood group determinants. In so doing one would be drawing from glycal epoxides and halosulfonamides in the same synthesis. The glycal epoxide methodology would be used to install β-glycosidic linkages and the azaglycosylation methodology would be used to incorporate the *N*-acetyl glucosamine substructure. The first goal in this regard was the Le^y determinant.[54,55] The objective here was not only that of synthesizing the carbohydrate sector of the determinant but also its conjugation to a carrier protein such that it would approximate more closely the realities in biological systems. The Le^y determinant was of particular interest to us because it had been previously identified as an important epitope for eliciting antibodies against colon and liver adenocarcinoma cell lines.[56] *It has recently been implicated as a marker in metastatic prostate cancer.*[57] We hoped to simulate this capacity with fully synthetically derived antigen.

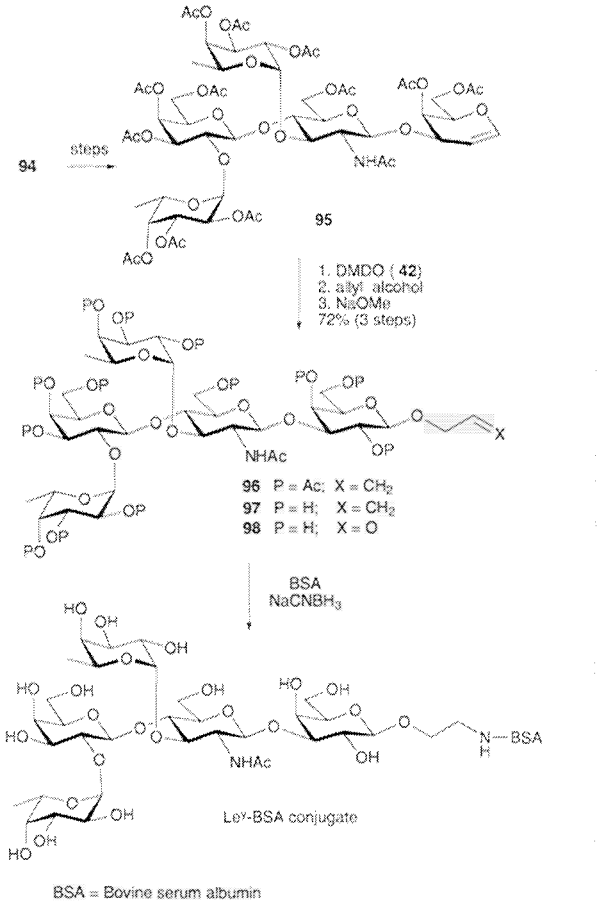
Inspection of the Le^y structure points toward the possibility of building from a central lactose core for this purpose. Given our preference for exploring the chemistry of glycals, lactal (**88**) was identified as the lactose equivalent (**Scheme 23**). The two primary positions of lactal were silylated to produce the di-TBDPS derivative **89**. The *cis* hydroxyl substituents at C-3' and C-4' of **89** were engaged in a cyclic carbonate to give compound **90**. In this way, the required two hydroxyl groups at C-3 and C-2' of the galactose moiety were readily identified *in two steps* as glycosyl acceptor sites. Fluorosugar **30** was employed as the glycosyl donor. It bears a nonparticipatory benzyl ether at C-2 and a potentially participating benzoate at C-4. In any event, treatment of **90** with **30** under suitable conditions resulted in clean incorporation of two fucose residues with formation of compound **91**. The glycal double bond was then subjected to iodosulfonamidation under the usual conditions to give rise to **92**. The latter functioned as a masked azaglycosyl donor. Reaction of **92** was conducted with mono-TIPS stannylated galactal derivative **93**. This critical coupling gave rise to a 75% yield of the bisfucosylated compound **94**. Thus, the tetrasaccharide determinant was efficiently constructed such that it still contained an exploitable double bond.

Before proceeding to the final glycosylation it was strategically useful to convert the benzenesulfonamide function to an acetamido group as well as to regularize all of the protecting groups as acetates (**Scheme 24**). This goal was accomplished and led to compound **95** which was subjected to the action of dimethyldioxirane. The epoxide thus produced functioned as a competent donor with allyl alcohol as the acceptor to provide **96**. Total deprotection of all acetate groups, affording **97**, was accomplished by the action of sodium methoxide. We were then ready for the conjugation phase using the reductive amination method.[58] Amino acid and carbohydrate analysis of the pseudoglycoprotein indicated the incorporation of approximately 15 pentasaccharide units into the theoretically available 38 lysine residues. Immunization studies of conjugates of **98** in mice are currently in progress, and the results are not without promise.

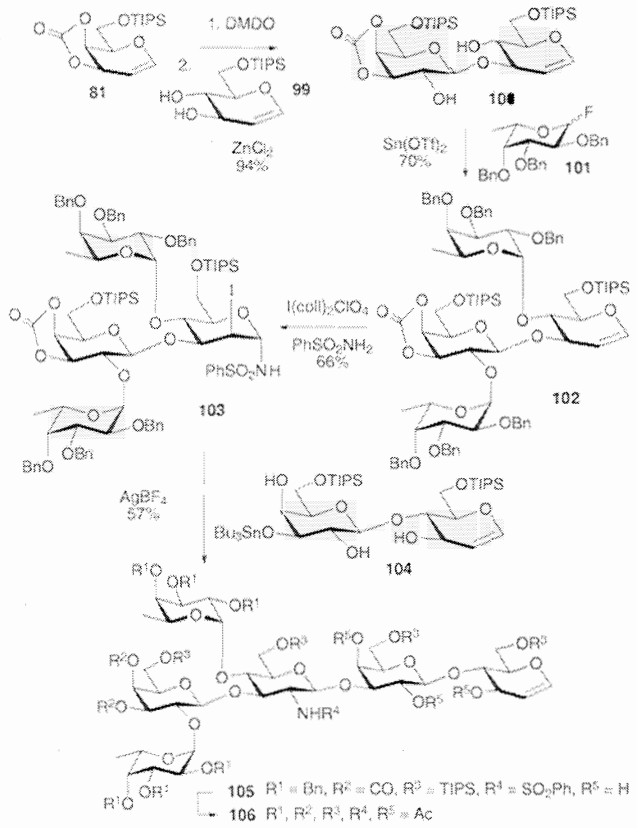
The synthesis of the Le^b determinant in a form that can be bioconjugated was also accomplished.[55,59] This determinant is more



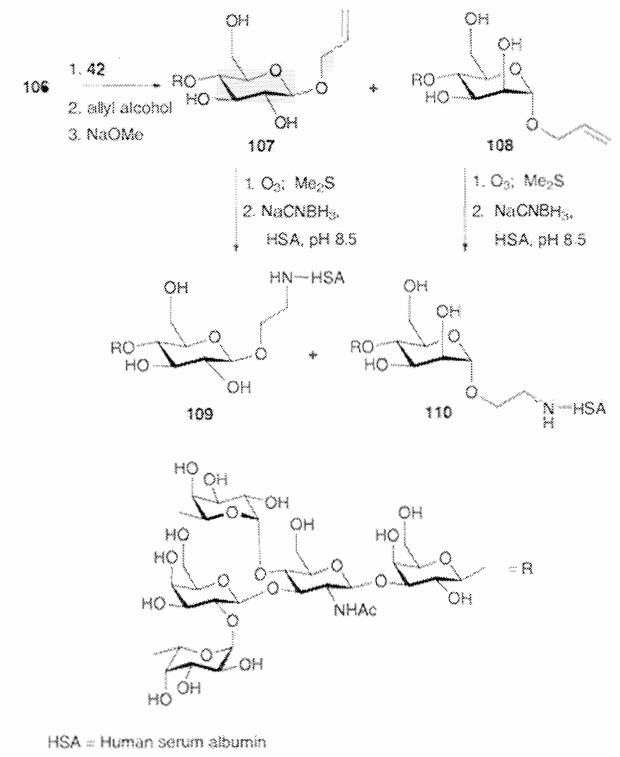
Scheme 23. Synthesis of an Le^y glycal.



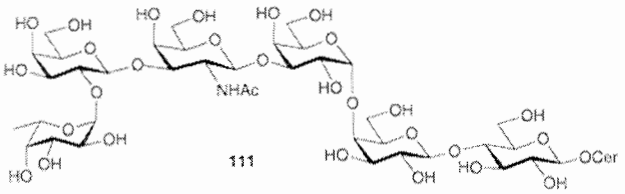
Scheme 24. Conjugation of Le^y to a protein carrier.



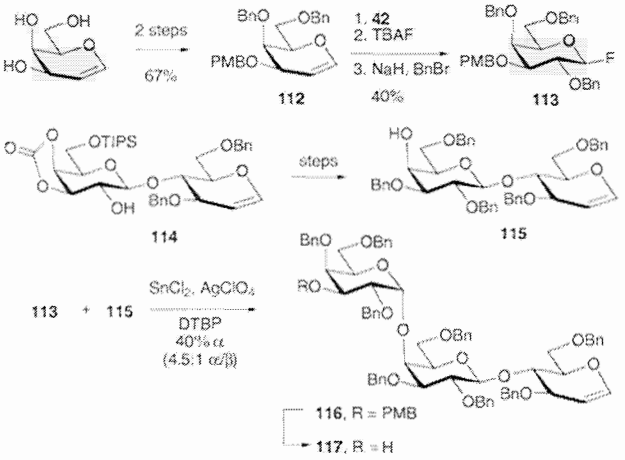
Scheme 25. Synthesis of a Le^b glycal.



Scheme 26. Conjugation of Le^b to a carrier protein.



Scheme 27. Structure of the MBr1 carbohydrate antigen.



Scheme 28. Synthesis of a trisaccharide acceptor.

the synthetic standpoint than is the Le^y target in that lactal **90**, trivially available from lactose, cannot serve as a starting material. The synthesis was achieved as outlined in **Scheme 25**.

In compound **106**, the critical tetrasaccharide recognition domain of the Le^b determinant had been assembled in a highly convergent fashion and insulated, through a disaccharide spacer, from the implement to be used in bioconjugation.

Cleavage of all acetate groups gave rise to **107** and **108**. These oligosaccharides were separately ozonolyzed, and the resultant glycolic aldehyde products were reductively coupled to HSA[58] to provide adducts **109** and **110** (**Scheme 26**).

This construct is of particular interest because it incorporates the recognition domain which has been implicated in the binding of *Helicobacter pylori* to gastric epithelial cells.[60] *This form of infection is claimed to be one of the major causative elements of gastric ulcer and, possibly, gastric cancer.* The possibility of synthesizing soluble binding agents for *H. pylori* constitutes an exciting goal for the glycal assembly methodology. The chemistry described above can readily be accommodated into a synthesis of an H-type I structure as well as an H-type II structure.[55]

The glycal assembly method has culminated in the synthesis of a hexasaccharide glycosphingolipid, which is a breast tumor associated antigen of potential clinical importance. Structure **111** (**Scheme 27**) was isolated from breast cancer cell line MCF-7 and was immunocharacterized by the monoclonal antibody MBr1.[61]

The synthesis involved the construction of two trisaccharide domains which were then brought together to provide the hexasaccharide structure.[62] Galactal **112** was converted into the fluorosugar **113** (**Scheme 28**). The desired acceptor **115** was fashioned from disaccharide

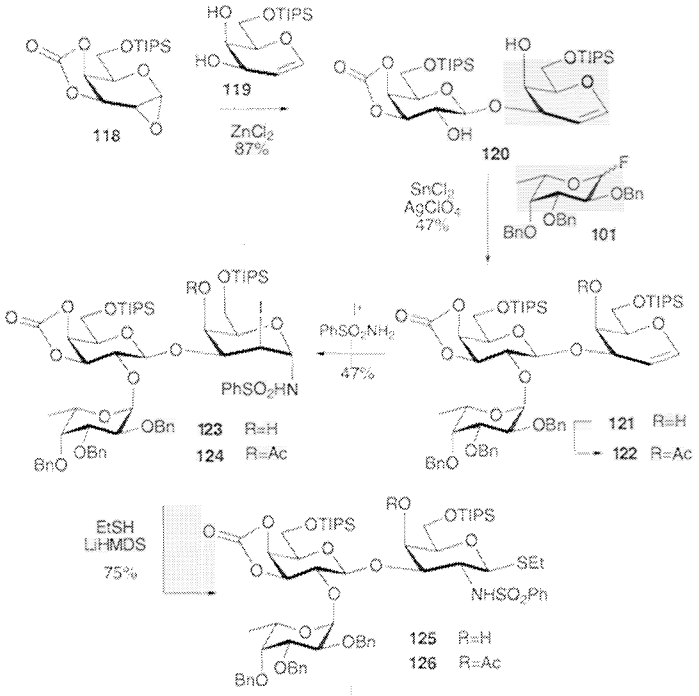
114 (itself derived from glycal coupling) after protecting group manipulations. Coupling of **113** and **115** afforded trisaccharide **116**. Deprotection of the PMB ether provided **117**, setting the stage for merger with a suitable trisaccharide donor.

Construction of the donor began with **118** which was glycosylated with acceptor **119** to afford disaccharide **120** with excellent regio- and stereoselectivity (**Scheme 29**). Regioselective fucosylation of the equatorial hydroxyl of **120** with donor **101** provided trisaccharide **121**. This trisaccharide was acetylated to produce **122**, which was transformed into iodosulfonamide **124**.

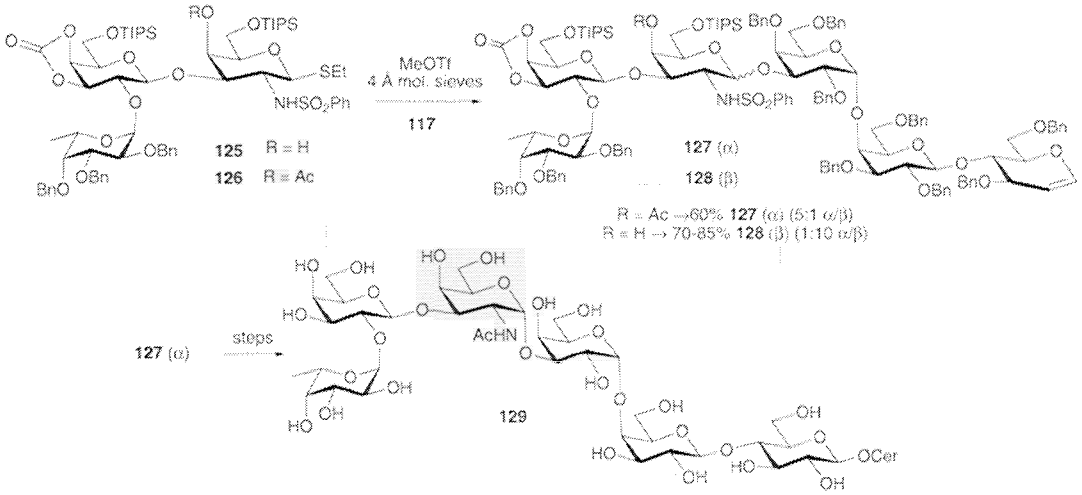
Unfortunately, iodosulfonamide donors of this type were not competent in the desired direct coupling reaction (see **Scheme 9**) with various trisaccharide acceptors. A large excess of difficultly available acceptor would be necessary and this requirement is certainly not appropriate. We therefore examined the conversion of **124** to thioglycoside donors (see earlier precedent in **Scheme 9**). Treatment of iodosulfonamide **124** with lithium ethanethiolate indeed afforded exclusively the β-ethyl thioglycoside **126**. Such systems, under promotion by methyl triflate, function as azaglycyl donors in coupling reactions even with complex acceptors.

Precedent established in our program had suggested that, in coupling reactions, donors of this type would give the β-product, presumably due to sulfonamide participation.[63] When donor **126** was reacted with the acceptor **117**, a hexasaccharide was obtained which was advanced through the remaining manipulations in the synthesis (**Scheme 30**). However the spectral properties of the ultimate product **129** did not correspond to those reported by Hakomori for the natural antigen assumed to be properly represented by structure **111**. On this basis, and on the basis of self-consistent spectral analysis, it was concluded that the material obtained from the coupling of the two trisaccharides had arisen from selective formation of the unexpected (and undesired) α-linked product **127**.

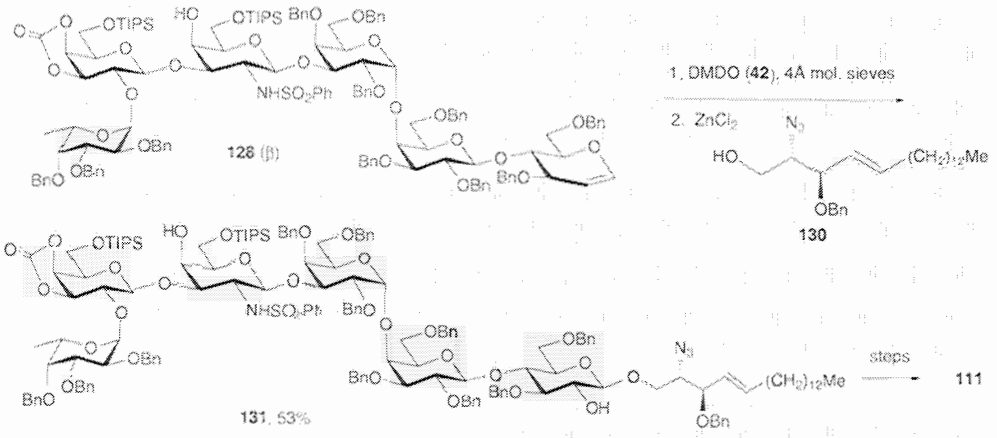
We subsequently found that when the trisaccharide donor **125** (obtained by the sequence **121** → **123** → **125**) was employed in the key coupling reaction, the desired β-product **128** was indeed obtained with high selectivity. Thus, there may be an unsuspected electronic or participatory effect which biases the system towards the α-product when the 4-hydroxyl is substituted. Alternatively, there may be a positive β-directing effect exerted by the 4-hydroxyl group of the donor. We emphasize that the occurrence of α-glycosylation and the remarkable turnover in selectivity has not yet been fully generalized though it has been observed in several other cases. It does serve to underline once again the subtle nature of the problem of stereochemistry of glycosylation. The outcome is not only a function of the type of donor and reaction conditions employed, for in



Scheme 29. Synthesis of a trisaccharide donor.



Scheme 30. Synthesis of the hexasaccharide glycal.



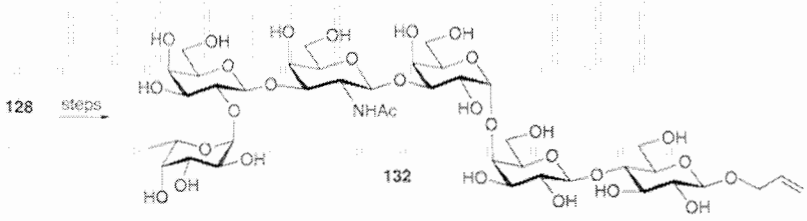
Scheme 31. Completion of the synthesis of the MBr1 antigen.

complicated cases it can be much influenced by specific molecular interactions between donor and acceptor.

The properly configured hexasaccharide **128** was epoxidized and coupled with ceramide precursor **130** to provide **131** (**Scheme 31**). This ceramide attachment can be conducted more efficiently on trisaccharide **117**.

Compound **131** was elaborated and deprotected to afford the natural material **111**. The fully synthetic antigen **111** has been shown to bind to monoclonal antibody MBr1 in ELISA and immune thin-layer chromatography assays while the unnatural isomer **129** exhibits very weak binding in the same assays. Also, MBr1 is strongly reactive with human breast cancer cell line MCF-7 by flow cytometry. Preincubation of MBr1 with glycosphingolipid **111** completely inhibits this reactivity with MCF-7.

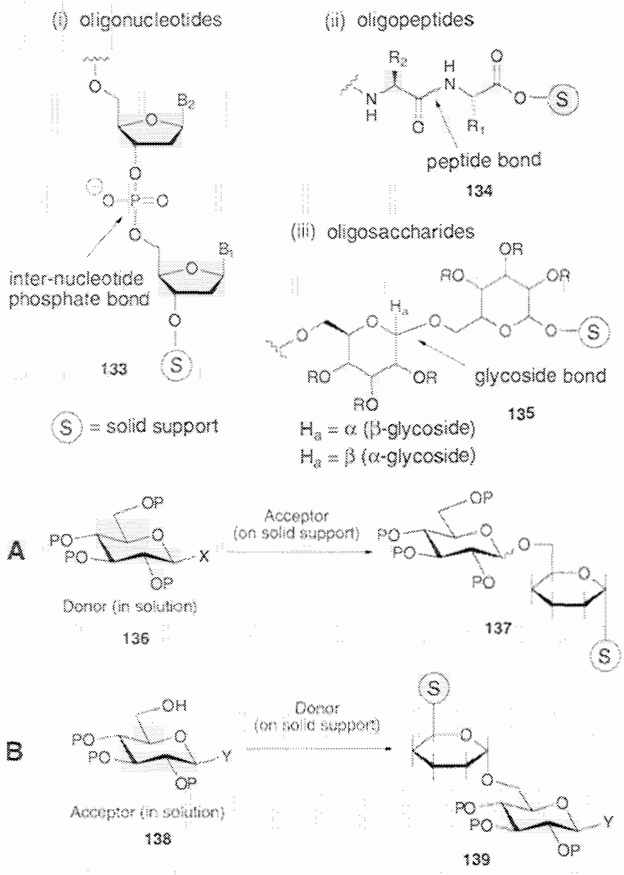
Hexasaccharide **128** was also converted to the corresponding allyl glycoside **132** and, through it, was converted to protein conjugates as presented above for Le^b and Le^y (**Scheme 32**). *Early studies indicate that our synthetic constructs are immunogenic in vivo.* The usefulness of the antibodies thus produced against cancer cells is currently being evaluated. The ultimate goal is their development as agents for vaccinelike applications in cancer treatment.



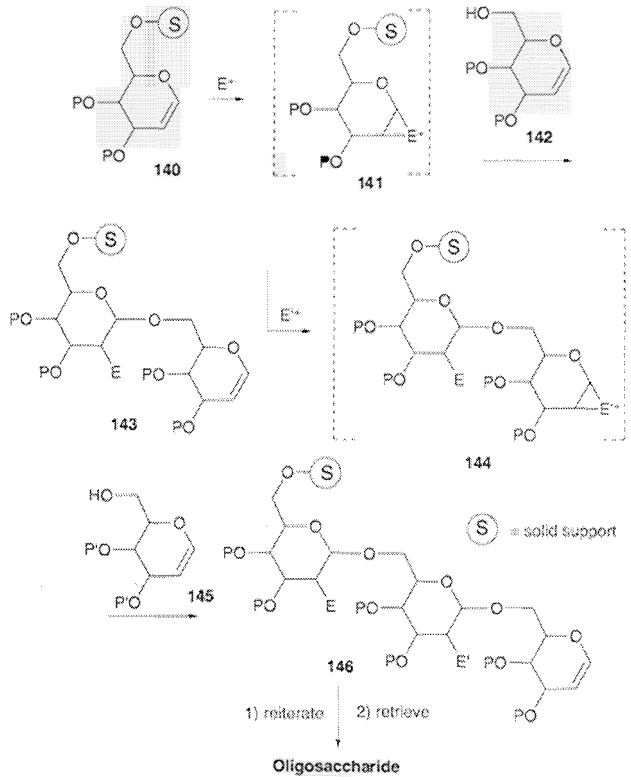
Scheme 32. Formation of an MBr1 allyl glycoside for protein conjugation.

5. Solid-Phase Synthesis of Oligosaccharides and Glycopeptides

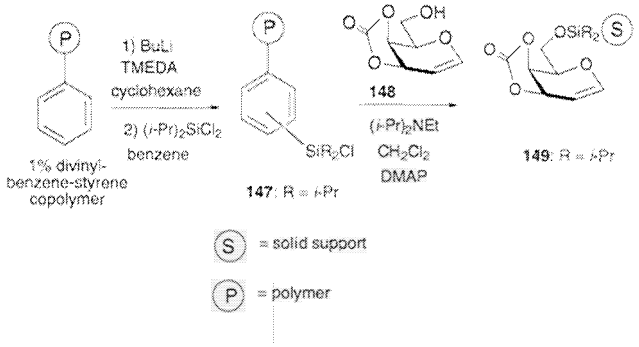
While progress in the synthesis of oligosaccharides and glycoconjugates by the solution-based methodology described above was certainly reassuring, the importance of the field is such that these advances served as a prod to seek still greater levels of simplicity and efficiency. It was instructive to think about this problem in the broader context of biooligomer synthesis, thus inviting analogies between oligosaccharide synthesis and the synthesis of oligonucleotides and peptides. Of course, impressive advances had been registered in the solution-phase synthesis of these latter biooligomers. However, it is clear that the major upsurge in the synthesis of these substances arose only after solution-based coupling methods were adapted to the solid phase. While polymer-supported synthesis of oligopeptides[64] and oligonucleotides[65] is not a panacea, it has certainly been of enormous benefit in terms of yield improvement, procedural simplification and relief from the need for purification at each stage. The chemistry of the various reiterations



Scheme 33. Solid-phase synthesis of biopolymers.



Scheme 34. Solid-phase carbohydrate synthesis employing glycals.



Scheme 35. Preparation of a polymer-linked glycal.

must be of such a quality that the single purification is practical in producing a product of the required homogeneity.

In polypeptide and oligonucleotide synthesis, it is the high yields in the individual coupling steps which seem to render the final-stage purification strategy viable. Excellent yields arise from the inherent quality of the coupling steps and are further "amplified" by the capacity to employ an excess of the solution-based coupling partner which is then removed from the solid phase by filtration.

In contrast, the science of assembling oligosaccharides on a solid phase is in a much less developed state.[66] It thereby reflects the fact that oligosaccharide synthesis is intrinsically far more complicated than the synthesis of oligonucleotides and oligopeptides (**Scheme 33**).

Consider the synthesis of oligonucleotides, particularly 2-deoxyoligonucleotides. Assuming the availability of the individual oligonucleosides, each elongation involves the fashioning of an internucleotide bond. For this purpose, it is necessary to distinguish the 5' and 3' hydroxyl groups and to discover a high-yielding coupling step. *The fashioning of the internucleotide bond does not carry with it the development of further chirality.* Similarly, the fashioning of the repeating bond of a peptide involves the need to distinguish α-amino and α-carboxyl groups from any such or related functionality (cf. thiol and hydroxyl) present on various side chains. A high-yielding amide-bond formation is necessary. *Once again, no new chirality is being fashioned in the elongation of the oligopeptide.* When applied to the solid phase, the logic of the elongations is implied in structures **133** and **134**, respectively. Clearly, in contemplating the synthesis of an oligosaccharide on solid support (cf. **135**) the complexity level rises markedly.

Thus, in fashioning the repeating units from an aldohexose one must distinguish the anomeric region of one of the components to serve as the donor region (see **136**). In the case of combining hexose units, one must also differentiate one of five rather closely related hydroxyls to serve as the glycosyl acceptor center (see **138**). Most demanding is the need to control the stereochemistry at each newly emerging glycosidic bond. *Unlike the case with its companion biooligomers, the formation of each glycoside bond constitutes a transaction of serious stereochemical moment.*

In contemplating the syntheses of oligosaccharides on a solid support, two overall strategies can be entertained. In one instance (Case A, **Scheme 33**), a glycosyl acceptor is mounted into a support, and the solution-based donor (**136**) as well as the promoter are administered for the coupling step. Glycoside **137** is produced. To reiterate the process, a new acceptor must be fashioned on the support. This would generally involve cleavage of a specific protecting group (P) to generate a new acceptor center with positional definition.

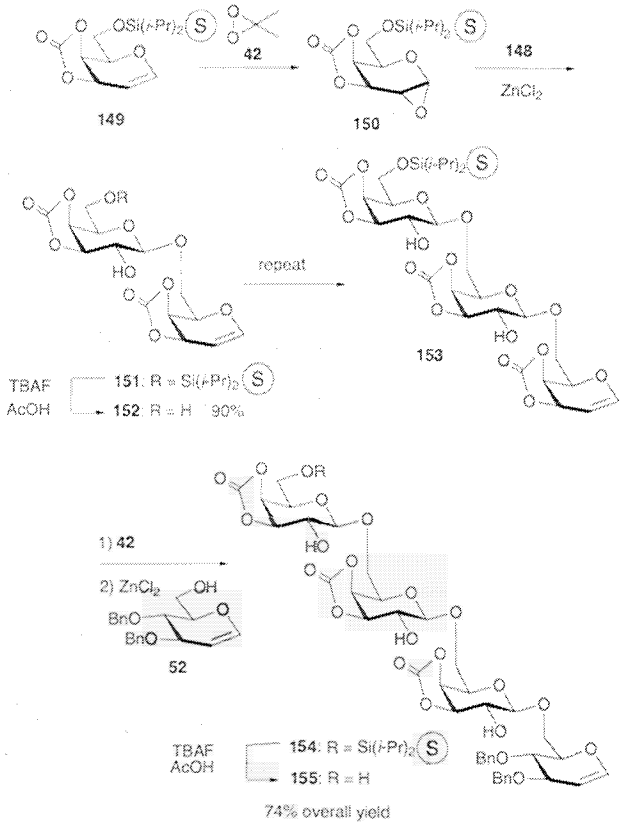
The alternative strategy (Case B) involves recourse to polymer-based glycosyl donor reacting with solution-based acceptor (**138**). For reiteration, the donor functionality must be unveiled from the terminal anomeric functionality (Y) on the solid-phase-bound structure (**139**). Also, positionally defined glycosyl acceptors must be synthesized for each iteration such that the acceptor character is manifested at a particular hydroxyl center and the donor character can be fashioned at the anomeric center of the product.

It was in dealing with the problem of solid-phase carbohydrate synthesis that we felt that glycal-based constructions might prove to be particularly valuable.[67,68] The guiding paradigm was that shown in **Scheme 34**. Polymer-bound glycal **140** would be synthesized by attaching the requisite glycal to a suitable solid support. The system would be activated by an unspecified electrophile E^+ to furnish polymer-bound donor **141**. In principle, **141** can be a substoichiometric mechanistic intermediate (cf. iodoglycosylation) or a characterizable chemical entity (cf. 1,2-epoxide). Coupling of **141** with solution-based glycal acceptor **142** would give rise to the elongated polymer-bound glycal **143**. Reiteration of the process generates **146** via new polymer-bound donor **144** and solution-based acceptor **145** (which may or may not be identical to **142**).

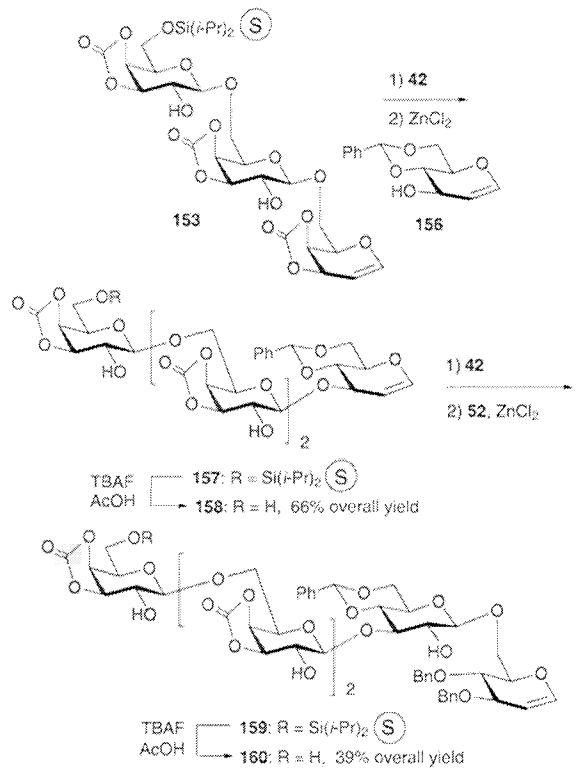
We selected a silicon-based linker and a commercially available polystyrene (cross-linked with 1% divinyl benzene) support. Metallation of the polymer leads to formation of the aryllithium species. When exchange is followed by silylation with a difunctional silane of the type R_2SiCl_2, a silyl chloride functionalized resin is obtained (**Scheme 35**).[69]

We turned to diisopropyldichlorosilane as the silylating agent. This led us to **149** as our support-bound donor of choice. The loading of carbohydrate was determined to be in excess of 0.9 mmol of **148** per gram of solid support. The activation method we developed at first was that of glycal epoxidation using 3,3-dimethyldioxirane as the oxidant.

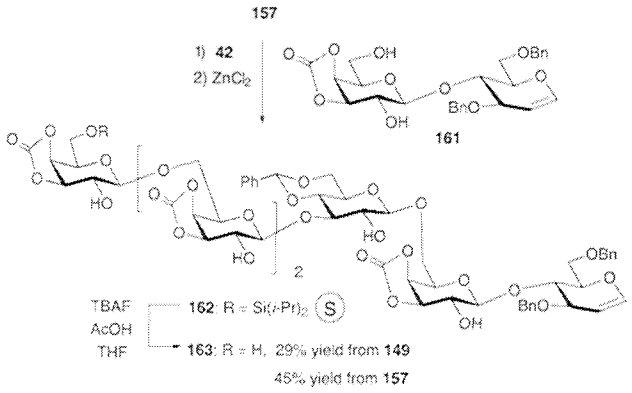
Reaction of **150** with glycal acceptor **148** under mediation by zinc chloride afforded **151** (**Scheme 36**). We established the presence of



Scheme 36. Solid-phase synthesis of 1,6-linked polysaccharide residues.



Scheme 37. Solid-phase synthesis of a pentasaccharide.



Scheme 38. Solid-phase synthesis of a hexasaccharide.

151 following treatment with tetra-*n*-butylammonium fluoride (TBAF) which resulted in the isolation of **152** in ca. 90% yield. Reiteration of the sequence, twice more, using acceptors **148** and **52** in sequence, followed by removal from the polymer with TBAF, led to tetrasaccharide **155** in 74% overall yield (ca. 90% average yield per coupling step).

Several features of the method should be emphasized. First, the polymer-bound donors where the C-3 and C-4 hydroxyl groups are engaged as a cyclic carbonate are, in fact, highly stereoselective galactosylating agents. Single purification at the tetrasaccharide stage was a straightforward matter. Another feature was the "self-policing" nature of failed couplings. While the average coupling yields are only ca. 90%, the uncoupled epoxide is apparently destroyed by hydrolysis. Thus, we do not encounter entities with deletions in the interior of the chain.

Secondary-alcohol glycosyl acceptors are also accommodated by this method (**Scheme 37**). Compound **153**, following epoxidation with **42**, reacted with D-glucal derivative **156** to give **157**. Tetrasaccharide **158** was retrieved from the support by the action of TBAF in a 66% overall yield based on **149**. Assuming 90% yield per coupling stage in the synthesis of **153**, glycosidation of **156** had occurred in ca. 80% yield.

Compound **157** was oxidized with **42** to give a polymer-bound glucosyl donor. This epoxide reacted with a tetrahydrofuran solution of **52** and $ZnCl_2$ to provide **159**, from which pentasaccharide **160** was obtained in 39% overall yield from **149**. This glycosidation, which had been achieved in approximately 60% yield based upon **157**, also occurred with a high degree of stereoselectivity. However, in this particular case, a minor component, believed to be the α-product, was detected in the ^1H NMR spectrum.

The scheme can be rendered more convergent through recourse to disaccharide and even higher oligomer acceptors (**Scheme 38**). Thus, epoxidation of polymer-bound tetrasaccharide glycal **157** followed by zinc chloride mediated coupling with disaccharide acceptor glycal **161** and retrieval from the support using TBAF afforded a 58% overall yield of **163** (29% overall from **149**, 45% yield from **157**).

The method is also applicable to the synthesis of branched structures through the logic of glycal assembly as demonstrated in the assembly of a partial Lewis b glycal. Branching at the C-2 hydroxyl was achieved in a growing chain by exploiting the hydroxyl group unveiled in the epoxide donor-based glycosylation (**Scheme 39**).

Another of our goals has been that of building upon the capabilities which have been attained in glycal assembly to synthesize glycopeptides.

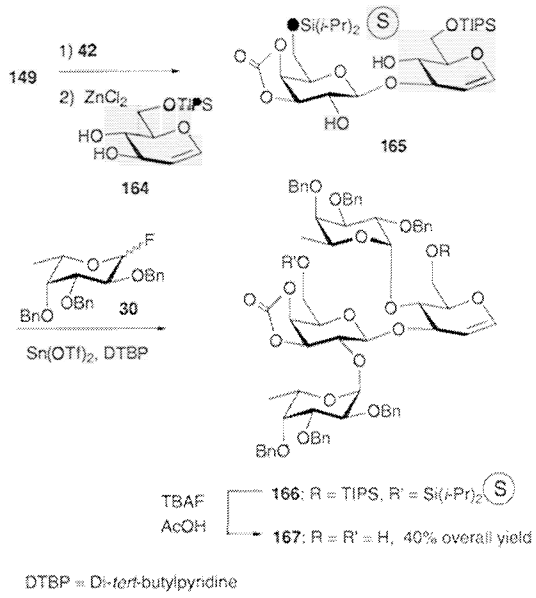
Our first objective was that of reaching asparagine-linked glycopeptides. Brilliant advances in glycopeptide synthesis have been achieved by many researchers,[70] including notably, Paulsen, Kunz, Meldal, and Lansbury. The strategy we hoped to implement would be radically different and maximally convergent.

It was envisioned that a terminal glycal of a synthetic oligosaccharide domain would be subjected to iodosulfonamidation. As demonstrated earlier in a simpler model, treatment of such an intermediate with azide resulted in the formation of a β-anomeric azide following suprafacial movement of the α-sulfonamide from C-1 to C-2. Reduction of the azide and acylation of the resultant anomerically pure β-amino functionality provided a protected glycopeptide. Fortunately, this capability was transferable to the solid phase.

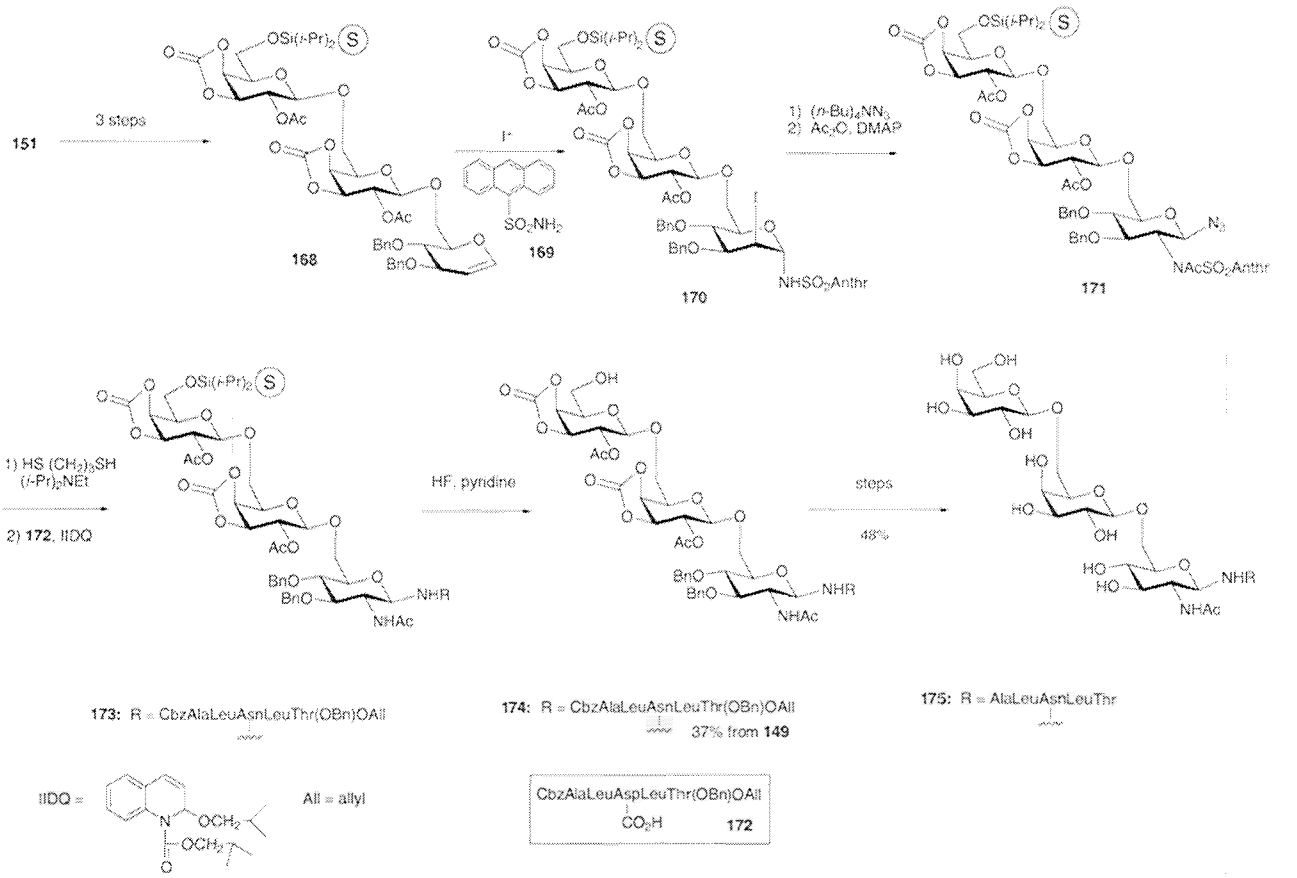
While the synthesis of glycopeptide ensembles is a complex undertaking, the most difficult part of the enterprise may actually be the final maneuvers required to produce the fully deprotected entity since the *N*-asparagine-linked glycopeptide can be a rather vulnerable construct.

The method developed for the synthesis of glycopeptides on a solid support was based upon methodology developed for solution-phase synthesis.[71,72] In synthesizing the carbohydrate domain we focused on a target structure which could be reached by the most straightforward methodology we had developed. For this purpose, support-bound trisaccharide **168** was prepared (**Scheme 40**). This set the stage for functionalization of the glycal linkage with a view to glycopeptide formation.

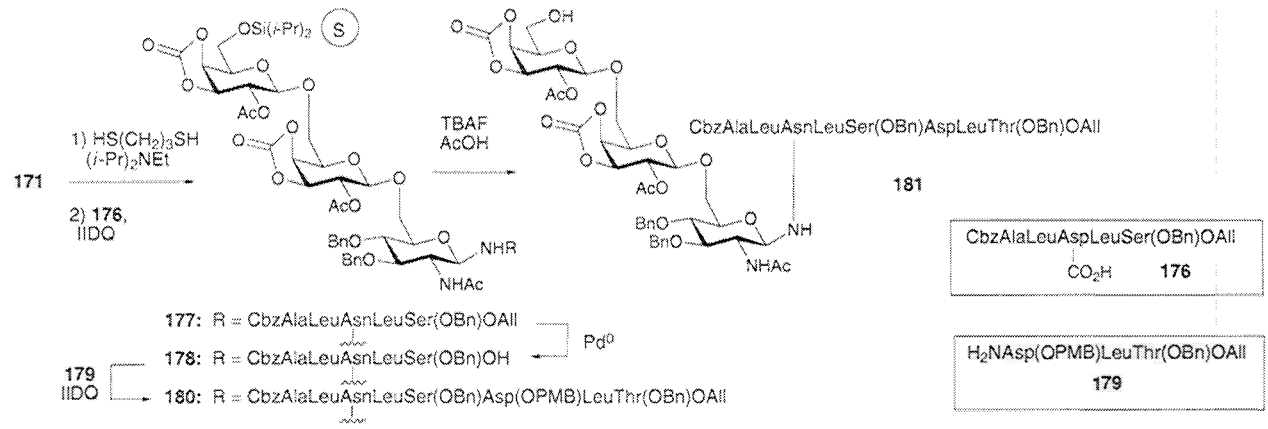
Treatment of **168** with 9-anthracenylsulfonamide (**169**) and di(*sym*) collidine iodonium perchlorate gave rise to **170**. Reaction of the latter with tetra-*n*-butylammonium azide triggered the expected relocation of the sulfonamide.



Scheme 39. Solid-phase synthesis of branched sugars.



Scheme 40. Solid-phase synthesis of *N*-linked glycopeptides.



Scheme 41. Solid-phase synthesis of *N*-linked glycopeptides.

The principal advantage in using the anthracenesulfonamide linkage is that it can be cleaved by a variety of mild methods. These protocols are compatible with synthesis on solid supports. Thus, treatment of **171** with 1,3-propanedithiol and $(i\text{-Pr})_2$NEt effected both the reduction of the azide and removal of the sulfonamide. The resulting amine was coupled with pentapeptide **172** in the presence of IIDQ to afford the protected glycopeptide **173**. Removal from the solid support with HF•pyridine provided the glycopeptide **174** in 37% overall yield. *In the latter case this constitutes an average yield of ca. 90% per step over the ten steps from polymer-bound glycal* ***149*** Chromatography on a short column of reversed-phase silica (C-18) was sufficient to obtain these compounds in pure form. This ready purification capability arises from the previously described "self-policing" feature of the solid-phase glycal assembly method and illustrates the efficiency in the conversion of the terminal glycal to the terminal glucosylamine.

The remaining protecting groups of **174** were cleaved under standard conditions to provide the completely deblocked glycopeptide **175** in 48% overall yield from **174**. Structural characterization by NMR spectroscopy confirmed the β configuration of all the anomeric linkages.

The presence of orthogonal protecting groups on the *C*- and *N*-termini of the peptide provides the opportunity to extend the peptide chain while the ensemble is bound to the solid support. Alternatively, after removal from the support, the liberated peptide terminus may provide a functionality for linking to a carrier molecule to generate other glycoconjugates. ***Scheme 41*** *shows how the peptide portion of the glycopeptide was extended while still bound to the polymer support.* Solid-phase-bound trisaccharide pentapeptide **177** was assembled as above from **171** employing pentapeptide **176** in the coupling reaction.

The *C*-terminus of **177** was deprotected to give the acid **178**. Solid-support-bound **178** was then coupled to tripeptide **179** (with a free *N*-terminus) to give glycopeptide **180**. Retrieval from the solid support afforded trisaccharide-octapeptide **181** in an 18% overall yield from polymer-bound galactal carbonate.

The assembly strategy shown here is, in principle, totally general in that it does not require the existence of the transferases and the availability of nucleoside activated hexoses. It can also accommodate the inclusion of unnatural (artificial) sugars in the construction. Such building blocks are available from the Lewis acid catalyzed diene-aldehyde cyclocondensation reaction. All workable approaches, whether purely chemical or chemo-enzymatic, are complementary for reaching the common goal of carefully designed, fully synthetic glycopeptides.

6. Conclusions

In this review we have shown, by example, the power of glycal assembly. Ours is only one of several laboratories attacking the forefront problems of complex oligosaccharide assembly. We lay no claim to indispensability on behalf of our methods. All of the targets we reached in this paper could probably have been reached by other coupling methods or assembly strategies. A fair number of the syntheses shown here, have been in fact attained through more conventional carbohydrate chemistry. We do, however, feel that glycal assembly may offer large advantages in synthetic conciseness. The strategies discussed above may bring relief from many of the onerous burdens of protecting group manipulations which have dominated this field. Glycal assembly has stimulated the development of new coupling technologies, and the methods are improving.

We are confident that solid-phase methodology will be expanded, and that substantial progress in this regard is in the offering. We expect major new advances in glycopeptide synthesis to be realized by our methods, by other chemical methods, and, indeed, by enzymatically assisted methods.

Ultimately, the test of the success of the field at the chemical level will be whether complex oligosaccharide and glycoconjugate synthesis can effectively be practiced by even nonspecialized laboratories eager to take on new problems as they arise. The work described here notwithstanding, such is yet far from being the case. Thus, there is much need for progress.

In the past chemists have lavished a great deal of time and much needed energy in developing a host of glycosylation methods and strategies. These advances have spawned a new and very serious challenge, i.e., conceptualization of valuable targets. Though much more needs to be achieved at the chemical level as we go forward, the time is already at hand to prepare and evaluate new constructs to test important possibilities in structural biology, immunology, and medicine. In our case, it has only been in the last two years that our methodology has produced ample amounts of material for clinical evaluation. No one can, at this time, safely predict the full impact of such carbohydrate-protein constructs on either the diagnosis or the treatment of cancer. *Thus, the largest challenges may now lie in guessing what should be made and in marshaling the multidisciplinary resources necessary for the systematic evaluation of the products of such efforts.*

Acknowledgments

The research reviewed in this paper was possible only through the dedication, enthusiasm and creativity of scores of co-workers whose names are acknowledged in the cited publications from our laboratory. It is to *all* our associates on these papers, and to other members of the laboratory, that the program is lastingly indebted.

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Crisscross Cycloaddition Reactions

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Abstract

Reaction of aromatic aldazines with some olefins or acetylenes proceeds via a so-called "crisscross" pathway. The same reaction pathway has been identified for the reaction of hexafluoroacetone azine with electron-rich terminal olefins or acetylenes. Known examples of the intramolecular crisscross cycloaddition are also reviewed.

Introduction

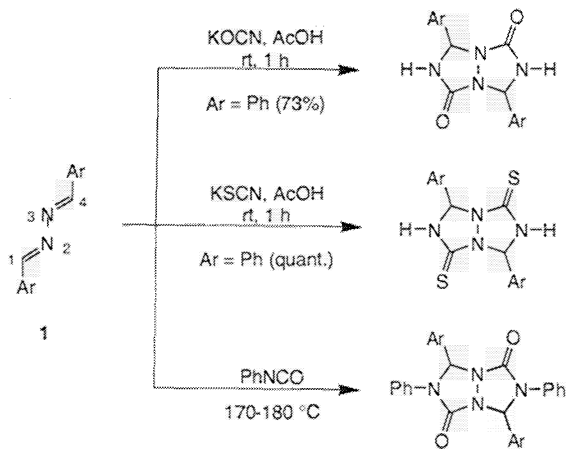
There are many "hot" subjects in organic synthesis that are periodically reviewed in leading journals. In contrast, there are some "orphan" topics that are rarely mentioned in surveys.[1] This review deals with one such topic, the so-called "crisscross" cycloaddition—a bis[3+2] cycloaddition—and covers the literature until the end of 1996.

In 1917, Bailey et al.[2,3] reported a new reaction of aromatic aldazines **1** with two equivalents of cyanic acid, thiocyanic acid (both formed *in situ* from potassium cyanate and potassium thiocyanate, respectively) and isocyanates, leading to unexpected products (**Scheme 1**). Although these aromatic aldazines are 2,3-diaza analogs of 1,4-diaryl-1,3-butadienes, the addition reaction took place at the 1,3- and 2,4-positions rather than the 1,4- or 1,2-positions of the conjugated double bonds. Because of this reactivity pattern the reaction has been dubbed a "crisscross" addition.

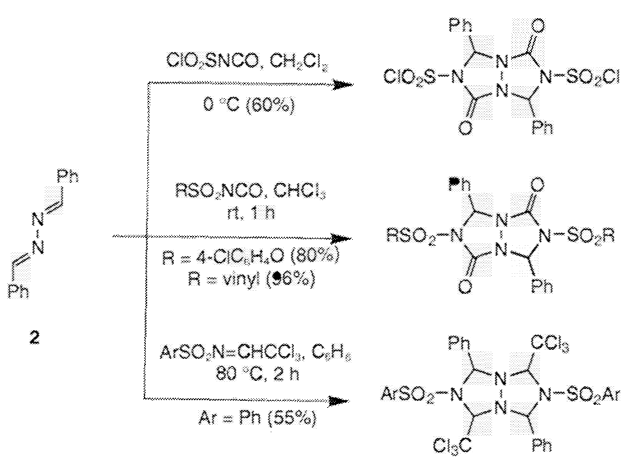
Intermolecular Cycloadditions

Many examples of the reaction leading to the 1,2,4-triazolo[1,2-*a*][1,2,4]triazole moiety are found in the literature. In most, benzaldazine (**2**) or substituted benzaldazines are used as aromatic aldazines; only occasionally are heteroaromatic aldazines used. Examples of the reaction of benzaldazine (**2**) with chlorosulfonyl isocyanate,[4] arylsulfonyl isocyanates,[5,6] vinylsulfonyl isocyanates,[5] and arylsulfonyl imines[7,8] are given in **Scheme 2.**

Further work has shown that this crisscross addition is general for the reaction of azines of aromatic aldehydes with various electron-deficient olefins in which the double bond is terminal (e.g., alkyl acrylates, acrylonitrile)[9,10] or in which allylic substituents do not sterically hinder the reaction (e.g., maleic anhydride[9,11] or sulfolene)[12] (**Scheme 3**). Most papers on the crisscross addition do not mention the formation of possible isomers. However, Shimizu[10] described the formation of both *cis-cis* and *cis-trans* isomers in yields of 5 and 20%, respectively, in the crisscross addition of methyl acrylate to benzaldazine (**2**). Similarly, Kovacs et al. isolated a very minor stereoisomer alongside the main product from the reaction of maleic anhydride and benzaldazine.[13]



Scheme 1

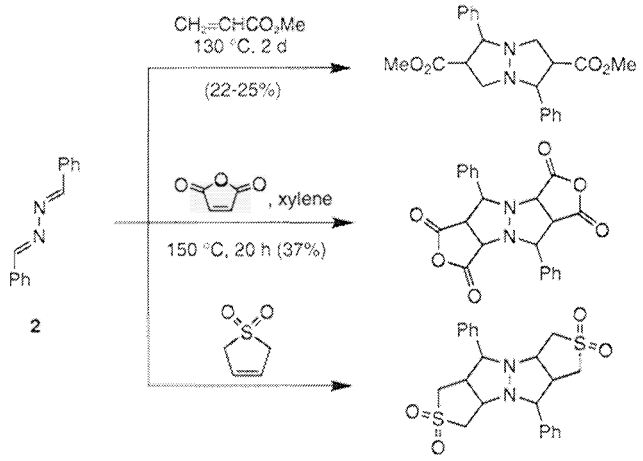


Scheme 2

Aliphatic and mixed aromatic-aliphatic aldazines do not usually produce crisscross products. Reaction of aldazine **3** with ketene **4** is a rare example of such a reaction (**eq 1**). However, compound **3** does not react with the agents usually used in the crisscross additions, namely isocyanates and isothiocyanates.[14]

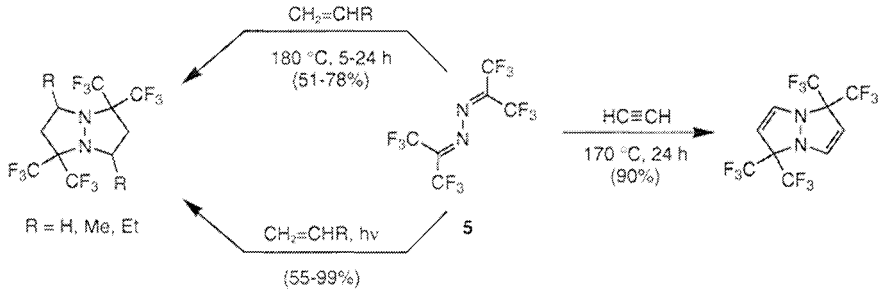
Hexafluoroacetone azine (**5**), an electron-deficient azine, reacts with electron-rich terminal olefins and acetylenes under thermal (160-180 °C) and photochemical conditions, to give the corresponding 2:1 crisscross adducts in yields often higher than 80% (**Scheme 4**).[15,16]

In contrast, enol ethers yield only small amounts of the crisscross products, and enamines do not provide this type of product at all.[17] Electron-deficient olefins and acetylenes do not usually react under comparable conditions, and *cis* and *trans* nonterminal olefins afford different products formally derived from the intermediate bis(trifluoromethyl)carbene.[18] The only type of electron-deficient olefins reported to react with **5** are alkyl acrylates, which produce mixtures of both *trans* and *cis* isomers **6** and **7**, together with the *trans* isomer **8** as shown in equation 2.[19]



Scheme 3

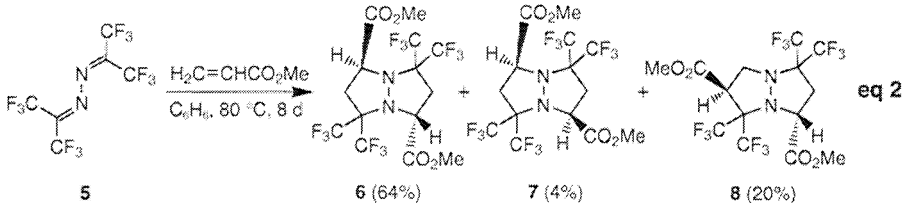
Burger and co-workers isolated the stable zwitterionic intermediate **9** in 85% yield from the intermolecular cycloaddition of one equivalent of 2-methylpropene onto azine **5**, and determined its structure by X-ray analysis.[20-23] Similar zwitterionic intermediates, such as **10**, were also isolated from reactions of several acetylenes with hexafluoroacetone azine (**5**).[24] This fact opened the way to a new variant, called *mixed crisscross addition.* Since the intermediates **9** and **10** also react with electron-deficient species, many different derivatives are available by this route as outlined in **Schemes 5** and **6**. If unsymmetrical olefins or acetylenes are used, mixtures of both possible regioisomers are usually obtained.[23-25] The second step of the mixed crisscross cycloaddition reaction is in fact an example of a 1,3-dipolar cycloaddition reaction, a subject beyond the scope of this article. 1,3-Dipolar cycloaddition reactions leading to bicyclic compounds containing two bridgehead nitrogen atoms have been reviewed recently.[26]



Scheme 4

Intramolecular Cycloadditions

Theoretically, two different possibilities of intramolecular crisscross addition exist, as shown in **Scheme 7**. Apparently, the distance between the azine group and the multiple bond, as well as the thermodynamic stability of the cyclic product, determines whether a "lateral"- or "central"-type cyclization is preferred.[27]



It is interesting to note that two different examples of intramolecular crisscross addition have been reported. Thermal cyclization of *O*-propargyl derivatives **11** produce only the corresponding "lateral" products **12**, in low to moderate yields (**eq 3**). The *O*-allyl analog of **11** (R = H) produces only the corresponding Claisen rearrangement product. Though the thermal cyclization of the azine derived from *O*-allyl aldehyde **13** yields only very low yields of the crisscross product **14**, treatment of the aldehyde with hydrazine hydrochloride, followed by addition of triethylamine, provides a high yield of **14** (**eq 4**).[10,17,28]

Heating of **15** produces **16**, a product of "central" cyclization, in nearly quantitative yield (**eq 5**).[27] The reaction is of interest, being the first intramolecular crisscross cycloaddition leading to a central-type cyclization product. This reaction is also one of the rare examples of the crisscross reaction involving non-fluorine-containing aliphatic azines.

A slight variant of the crisscross reaction is illustrated by the examples in equations 6 and 7. Heating of benzaldazine (**2**) with 2,3-epoxypropyl phenyl ether in the presence of stannic chloride provides a low yield (less than 20%) of **17**, a product of crisscross addition.[29,30] Similarly, thioglycolic acid reacts with benzaldazine (**2**) in concentrated benzene solutions to produce a mixture containing, along with two other compounds, **18**—a product of crisscross addition.[31] In a series of substituted benzaldazines yields of the respective final products are greatly influenced by the nature of the ring substituents.

In addition, the same reaction performed in dilute benzene solutions produces mixtures that do not contain the crisscross reaction product.[32]

Conclusions

Most of the crisscross cycloaddition products mentioned in this review have not been prepared by other means, and often other similarly simple ways of preparing them are hardly possible (for a recent review on bicyclic systems with two nitrogen atoms at the ring junction, see ref. 26). However, so far only a limited number of such products has been described, and none of them has a practical application. I hope that this survey would bring the crisscross cycloaddition reaction to the attention of readers. I believe that this reaction, especially in its mixed and intramolecular versions, has the potential to become a source of interesting new compounds. Consequently, the resulting product diversity could lead to the discovery of practical applications for some of these new products.

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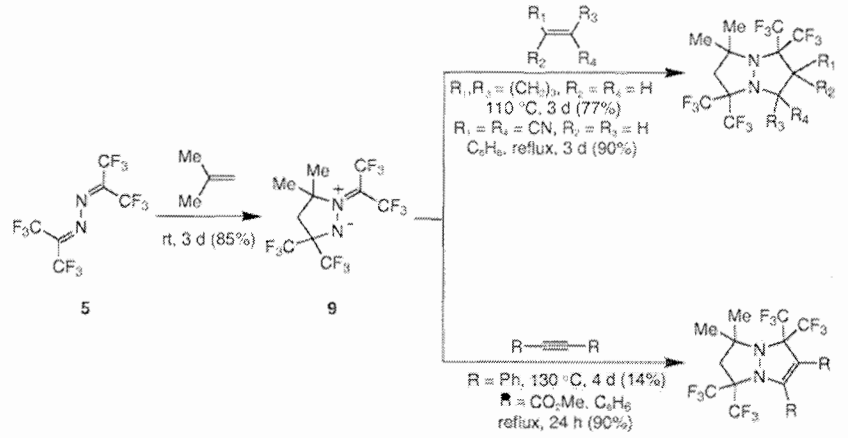
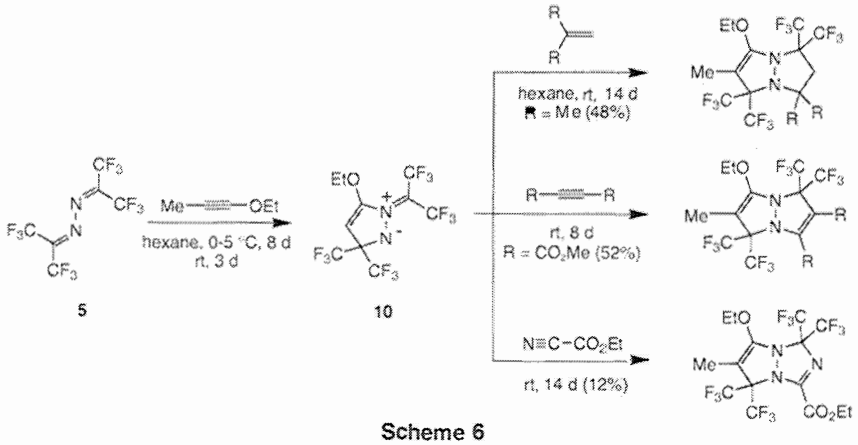
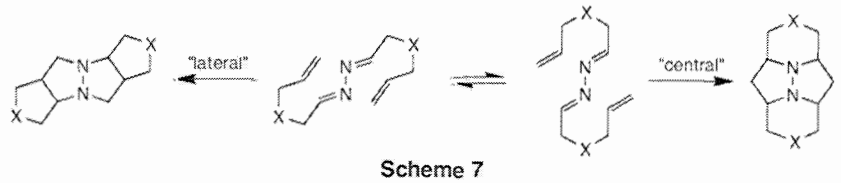


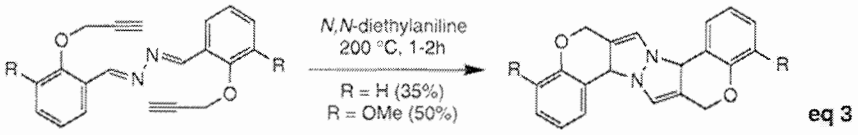
Scheme 5



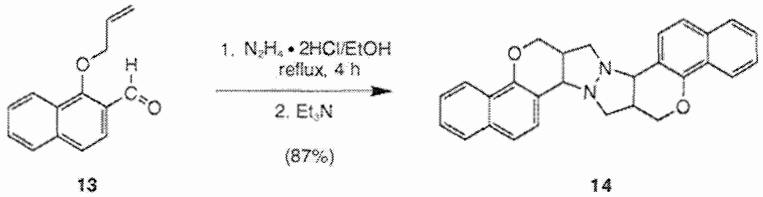
Scheme 6



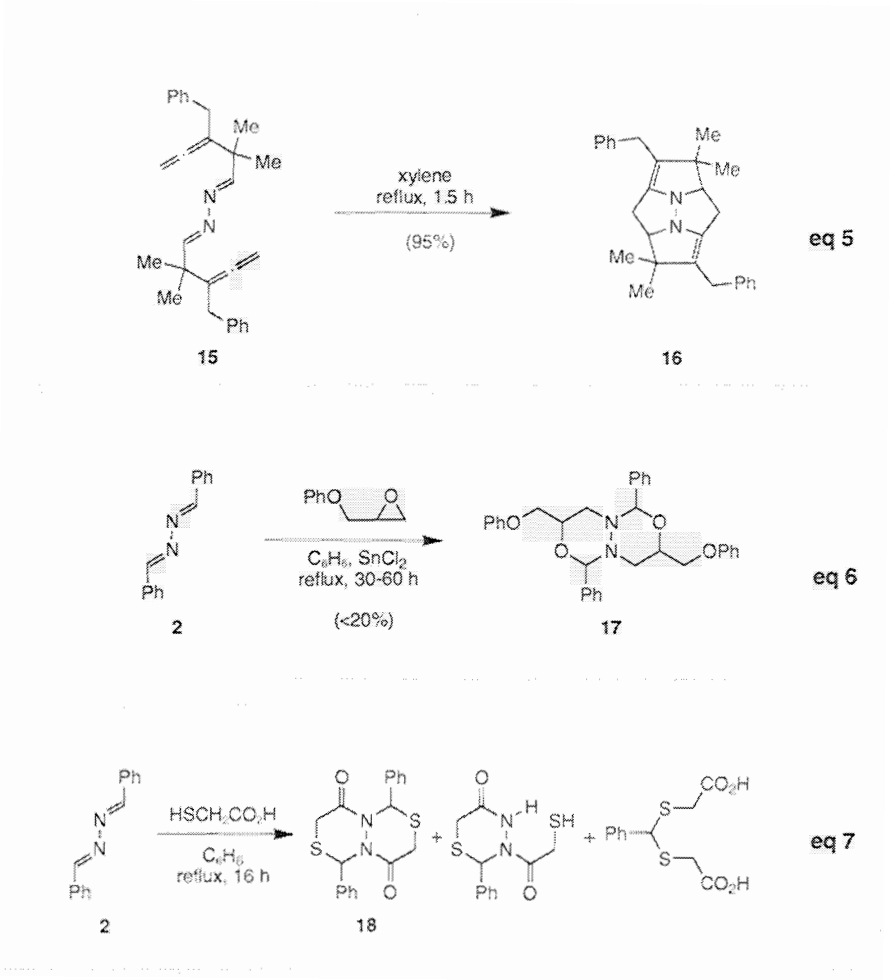
Scheme 7



eq 3



eq 4



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About our Cover

The Simon Vouet (1590–1649) painting on our cover, *The Muses Urania and Calliope* (oil on wood 31⅛ x 49⅜ in.), depicts two allegorical female figures reclining in front of a classical portico. On the left is the Muse of Astronomy, Urania, robed in celestial blue, wearing a diadem of six stars, and supported by an astral globe. She is accompanied by one of her eight sisters, Calliope, the Muse of Epic Poetry. Calliope holds a bound volume of Homer's *Odyssey*, one of the best known epic poems she inspired.

In all probability, this tranquil scene is part of a series executed by Vouet for a wealthy Parisian patron in the 1630s. The entire ensemble does not seem to have survived, but four other remaining works suggest that the picture's original context was a decorative scheme illustrating all nine Muses and the god of intellect, Apollo, whom they served. The picture's compositional elegance, figural equilibrium, and delicate color harmonies provided the perfect setting for *salon* life during Louis XIII's reign.

The device of incorporating the Muses in room decor appeared in late fifteenth-century Italy and continued to enjoy popularity in seventeenth-century France. By implication, the presence of the nine goddesses transformed a given architectural space into a Temple of the Muses or *Mouseion*—from which our word *museum* has evolved.

This painting is part of the Samuel H. Kress collection at the National Gallery of Art.

Lab Notes

Clean and Efficient Procedure for the Complete Removal of Reddish, Colloidal Selenium from Reaction Mixtures

The complete removal of selenium byproducts (notably H_2SeO_3)[1] from a reaction mixture is a nuisance well-known to synthetic chemists using selenium dioxide (SeO_2). Recently, we have engaged in synthesizing some formylpyridine derivatives utilizing SeO_2, and we have been troubled by the same problem. In our case, it is largely worsened by the coordination of SeO_2 and/or its secondary derivatives with the pyridine nitrogen (observed by NMR).

Though one communication was published in 1978 in your journal dealing with the removal of selenium from a reaction mixture (by briefly heating the mixture in DMF to cause the black tar formed to precipitate out of the solution),[2] the method does not work well in our experiments, even with extensive silica gel column chromatography.

We wish to report a safe, clean, and efficient procedure for the complete removal of reddish, colloidal selenium by simply stirring the reaction mixture (usually in dioxane) with anhydrous $NaHCO_3$ powder (to remove selenic acid), anhydrous $MgSO_4$ (to remove H_2O), then filtering through a thin pad of a 1:1 mixture of Florisil® and Celite® (both are available from Aldrich Chemical Co.), and rinsing the paste with a suitable solvent such as dichloromethane, ethyl acetate, or acetone. The filtrate usually gives no indication of the existence of selenium species.

(1) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp 992-993. (2) Milstein, S.R.; Coats, E.A. *Aldrichimica Acta* **1978**, *11*, 10.

Rex X-F. Ren, Ph.D., and
Koji Nakanishi, Ph.D.
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Celite is a registered trademark of Celite Corp. Florisil is a registered trademark of U.S. Silica Co.

Rapid Dissolution of Starch in Water

Many of our chemistry labs require a large amount of starch indicator on hand. Preparing starch solutions for chemistry or biology labs by suspending the starch in cold water, and then slowly bringing the suspension to a boil to dissolve the starch is a time-consuming process. A good way to speed the preparation of starch solution is first to bring water for the solution to a boil. While heating, mix the starch into a column of cold water representing about 10% of the intended starch solution. Simply dump the small volume of cold starch suspension into the boiling water. The starch will go into solution instantly. Allow to cool before use.

Leo V. Carr, Lab Manager
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Editor's Note: For a discussion of the issues surrounding the dissolution of starch in water, the reader should consult, among others, the following two references: (1) Mitchell, W.A. *J. Chem. Educ.* **1977**, *54*, 132, and (2) Green, M.M.; Blankenhorn, G.; Hart, H. *ibid.* **1975**, *52*, 729.

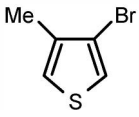
Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to Aldrich (attn: Lab Notes, *Aldrichimica Acta*). For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. **Z15,000-2**). If we publish your *Lab Note*, you will also receive an Aldrich periodic table turbo mouse pad (Cat. No. **Z24,409-0**). It is Teflon®-coated, 8½ x 11in., with a full-color periodic table on the front. We reserve the right to retain all entries for future consideration.

Teflon is a registered trademark of E.I. du Pont de Nemours & Co., Inc.

"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President



Professor Mario Leclerc at the Université de Montreal kindly suggested that we offer this thiophene. It has been used to prepare conducting and chromic regioregular polythiophenes.[1,2]

(1) Faïd, K.; Leclerc, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2761. (2) Lévesque, I.; Leclerc, M. *Chem. Mater.* **1996**, *8*, 2843.

47,499-1 3-Bromo-4-methylthiophene, 95%

Naturally, we made this useful compound. It was no bother at all, just a pleasure to be able to help.

It is interesting how customers see us and our commitment to service; for example, we recently received the following e-mail:

I am in receipt of Volume 30, Number 1, 1997 of your *Aldrichimica Acta* magazine.

This issue's cover, Sir Edwin Henry Landseer's "Attachment", struck me as particularly interesting. The picture depicts a "faithful terrier's long vigil beside the lifeless body." This cover generated a lot of interest in our laboratory.

My question to you is this: Does the cover have a secondary meaning?

One of the most interesting possibilities might be that the faithful terrier's vigil could be interpreted as Aldrich's long-standing commitment to its customers.

What do you think?

I look forward to more interesting choices of fine artwork on the covers of your publications.

Michael L. Valentine
Washington College
Chestertown, MD

Asymmetric Synthesis Using Rhodium-Stabilized Vinylcarbenoid Intermediates

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Abstract

Rhodium(II) carboxylate-catalyzed decomposition of 2-diazobutenoates in the presence of alkenes or dienes results in highly diastereoselective cyclopropanations. Furthermore, these cyclopropanations occur with high asymmetric induction when using either α-hydroxy esters as chiral auxiliaries on the carbenoid, or chiral catalysts containing N-arylsulfonylprolinate ligands. These transformations can be used in general methods for the asymmetric synthesis of vinylcyclopropanes, cyclopropaneamino acids, 4,4-diarylbutanoates, cycloheptadienes, bicyclo[3.2.1]octadienes, 8-oxabicyclo[3.2.1]octan-3-ones, tropanes and other polycyclic compounds.

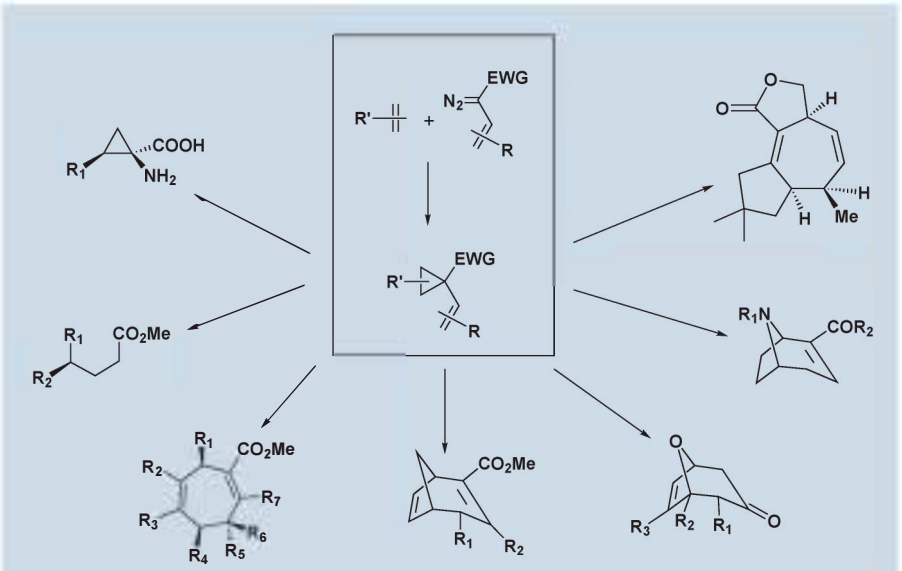
Introduction

Enantiomerically pure cyclopropanes are very useful chiral building blocks since they may be converted to a variety of acyclic and cyclic products through stereochemically well-defined ring-opening reactions or rearrangements.[1] This article focuses on a new method for the highly diastereoselective and enantioselective synthesis of vinylcyclopropanes, and the utilization of these in the asymmetric synthesis of many types of ring systems as illustrated in **Scheme 1**.

A number of methods have been developed for the asymmetric synthesis of cyclopropanes. One of the most efficient methods has been the metal-catalyzed decomposition of diazoacetate derivatives in the presence of alkenes (**eq 1**).[2] In the last few years, a series of highly effective C-2 symmetric copper,[3] ruthenium[4] and rhodium(II) amide catalysts[5] has been developed for this reaction. However, the reaction scope remains limited since diazoacetate cyclopropanations generally occur with poor control of diastereoselectivity unless very bulky ester groups are used;[6] furthermore, these catalysts do not necessarily exhibit great utility in reactions with other types of carbenoids.[7]

The focus of our research program has been on the cyclopropanation chemistry of 2-diazobutenoate derivatives.[8] Prior to our studies, the chemistry of metal-stabilized vinylcarbenoids had met with fairly limited success.[9] Intermolecular cyclopropanations occurred in poor to moderate yield and stereoselectivity (**eq 2** and **3**).[9a-c] One notable early example was reported by Corey and involved an intramolecular cyclopropanation that was used in the synthesis of sirenin (**eq 4**),[9f,g] and has since been achieved asymmetrically using a chiral copper catalyst.[10] In general, not only are the vinylcarbenoid transformations ineffective, but the vinyldiazomethane precursors are difficult to handle as they are prone to rearrangement to 3*H*-pyrazoles.[11]

When we initiated our program on vinylcarbenoid chemistry, we discovered that vinyldiazomethane **1a** was indefinitely stable at ambient temperature but underwent



Scheme 1

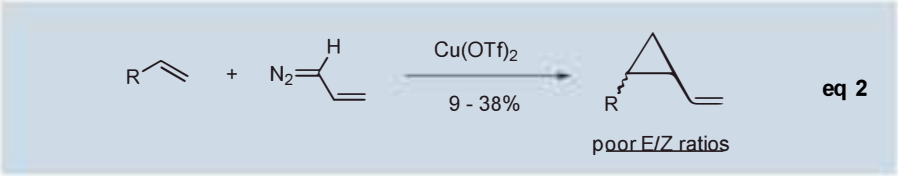
rhodium(II) acetate catalyzed decomposition in the presence of cyclopentadiene to give the endo product **3a** exclusively in 98% yield (**eq 5**).[12] This remarkable stereochemical result was considered to be due to a two-step reaction process, a cyclopropanation followed by a Cope rearrangement of the divinylcyclopropane intermediate. This mechanistic hypothesis was confirmed by using the bulkier vinyldiazomethane **1b**. With this substrate, divinylcyclopropane **2b** was isolated and its slow rearrangement to **3b** was followed.

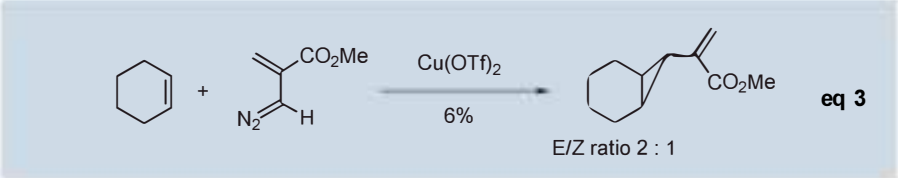
The formation of **3a** in such high yield meant that the vinylcarbenoid cyclopropanation with **1a** had proceeded with very high diastereoselectivity, as only cis divinylcyclopropanes would be expected to undergo a Cope rearrangement under moderate conditions.[14] This was confirmed in the model cyclopropanation reaction with styrene (**Scheme 2**) in which the diastereoselectivity seen with vinyldiazomethane **4** (>20 : 1)[13] was in stark contrast to the low levels observed with the traditional diazoacetate system **5** (1.6 : 1).[14]

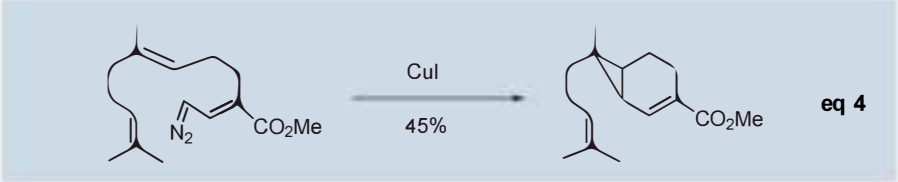
The ability of vinylcarbenoids to generate vinylcyclopropanes of defined stereochemistry offers numerous synthetic opportunities. This review will first describe the range of vinyldiazomethanes that may be used in this chemistry. This will be followed by an account of two methods for the asymmetric synthesis of the vinylcyclopropanes. The final section will describe the elaboration of the highly enantioenriched cyclopropanes into a variety of other ring systems.

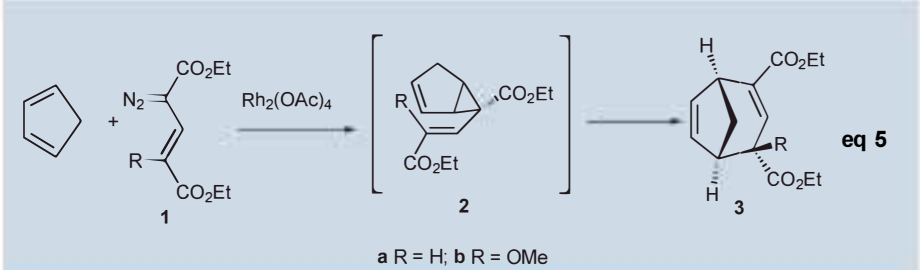
Synthesis of Vinyldiazomethanes

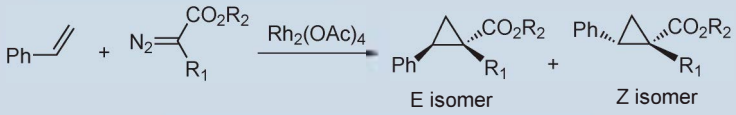
The vinyldiazomethanes that have been commonly used in our studies contain an electron-withdrawing group adjacent to the diazo functionality.[8] This electron-withdrawing functionality not only inhibits the tendency of vinyldiazomethanes to rearrange to 3*H*-pyrazoles, but is also necessary to achieve highly diastereoselective cyclopropanations. The types of vinyldiazomethanes that have been successfully used are shown in **Figure 1**. A range of functionality can be tolerated in the vinyl portion, including electron-withdrawing and electron-donating groups, and even cyclic systems. The major limitation for the vinylcarbenoid structure is the presence of excessive bulk around the carbenoid site. Bulky electron-withdrawing groups can cause the vinylogous portion of the vinylcarbenoid to become the active electrophilic site, but usually the use of nonpolar solvents can minimize this type of reactivity.[15] If bulky functionality is flanking both sides of the











Diazo	R_1	R_2	E/Z ratio
4	CH=CHPh	Me	>20
5	H	Et	1.6

Scheme 2

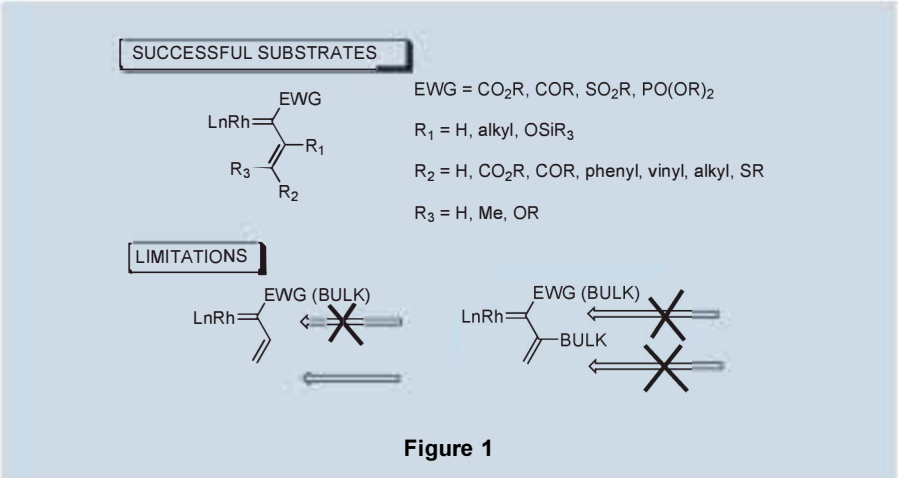


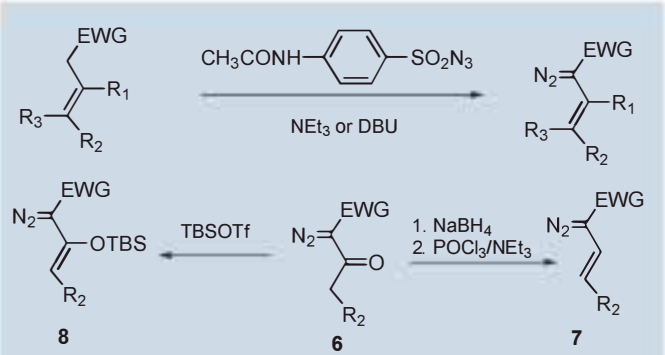
Figure 1

carbenoid, intermolecular reactivity can be seriously inhibited and the vinylcarbenoid will simply rearrange to a cyclopropene.[16]

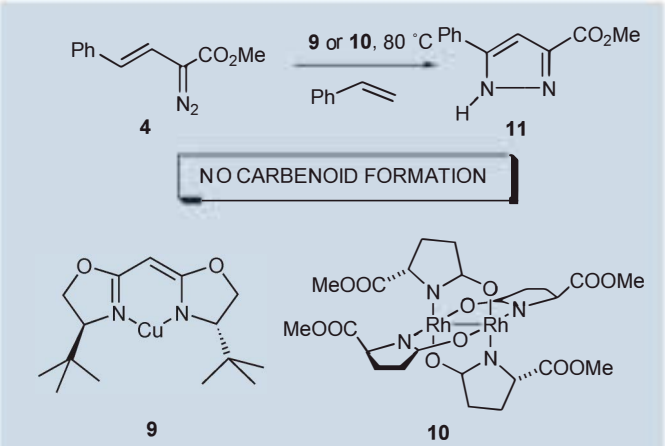
Vinyldiazomethanes with two electron-withdrawing groups are readily prepared by diazo transfer reactions using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and triethylamine as the base (**Scheme 3**).[17] Vinyldiazomethanes with a single electron-withdrawing group may be prepared by a diazo transfer reaction using DBU as the base. Alternatively, vinyldiazomethanes with a single electron-withdrawing group may be prepared from diazoacetoacetate **6** either by reduction followed by dehydration to form **7**,[18] or by *O*-silylation to form **8**.[19] Vinyldiazomethanes with two electron-withdrawing groups tend to be indefinitely stable at ambient temperature, while most vinyldiazomethanes containing a single electron-withdrawing group may be stored for weeks in solution at -20 °C.

Asymmetric Vinylcarbenoid Cyclopropanations

Considering the range of chiral catalysts that are available for diazoacetate decomposition, the development of reaction conditions for asymmetric vinylcarbenoid cyclopropanations had initially been considered to be relatively straightforward. Unfortunately, this was not the case because vinyldiazomethanes require a kinetically active catalyst such as rhodium(II) carboxylates to avoid their competing rearrangement to 3*H*-pyrazoles. As can be seen in **Scheme 4**, Masamune's copper complex **9**[3a,b] or Doyle's rhodium(II) amide complex **10**[5] failed to catalyze carbene formation from vinyldiazomethane **4** at room temperature.[2b] Under more forcing conditions, **4** rearranged to pyrazole **11**. Consequently, two alternative strategies were developed to achieve asymmetric cyclopropanations by vinylcarbenoids. The first utilizes α-hydroxy esters as chiral auxiliaries on the vinylcarbenoid, while the second is based on a chiral rhodium(II) carboxylate catalyst.



Scheme 3



Scheme 4

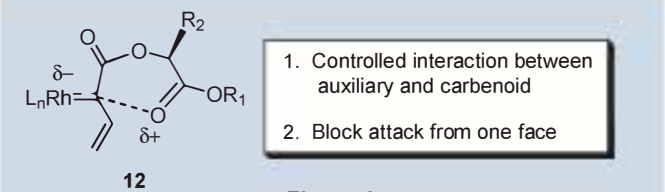
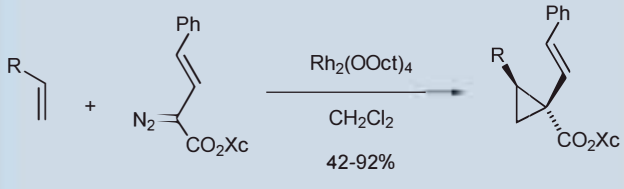


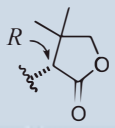
Figure 2

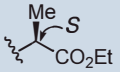
A. α-Hydroxy Esters as Chiral Auxiliaries on the Vinylcarbenoid

From preliminary studies, it became abundantly clear that traditional strategies for designing chiral auxiliaries such as the use of menthol or borneol derivatives[21] would not be practical for intermolecular vinylcarbenoid transformations. Any auxiliary that would have been effective at blocking one face of the carbenoid was also likely to react with the highly reactive carbenoid. Therefore, an alternate approach was explored in which a deliberate interaction between the carbenoid and auxiliary was employed as illustrated in **Figure 2**.[2b] The extent of the neighboring group participation would be limited, allowing structure **12** still to exhibit carbenoid rather than ylide reactivity,[22] while the rigid arrangement would permit the chiral influence to dictate which face of the carbenoid would be accessible. This led to the development of (*R*)-pantolactone and (*S*)-lactate as viable chiral auxiliaries for vinylcarbenoid cyclopropanations (**Table 1**).[2b] Rhodium(II) octanoate catalyzed decomposition of (*R*)-pantolactone derivative **13a** in the presence of alkenes resulted in cyclopropanation with up to 97% de. Alternatively, cyclopropanation with the (*S*)-lactate derivative **13b** occurred in 67% de.

Table 1. Asymmetric cyclopropanation using chiral auxiliaries.



a: Xc = 

b: Xc = 

R	Diazo	Temp, °C	de, %	Abs. config.
Ph	**13a**	25	89	(1*R*,2*R*)
Ph	**13a**	0	97	(1*R*,2*R*)
$pClC_6H_4$	**13a**	0	>95	(1*R*,2*R*)
$pMeOC_6H_4$	**13a**	0	>95	(1*R*,2*R*)
AcO	**13a**	0	90	
EtO	**13a**	0	92	
Ph	**13b**	25	67	(1*S*,2*S*)

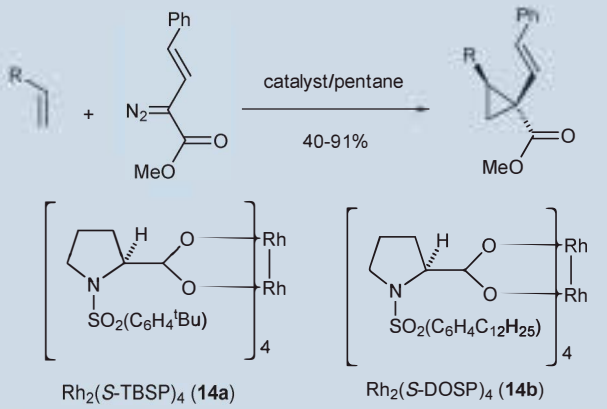
B. Rhodium(II) Prolinates as Chiral Catalysts

Even though the chiral auxiliary method resulted in cyclopropanation with impressive levels of diastereoselectivity, still it was felt that the optimum method for asymmetric vinylcarbenoid cyclopropanations would use an appropriate chiral catalyst instead. Rhodium(II) carboxylates are kinetically very active at decomposing diazo compounds, but the literature precedence for asymmetric intermolecular cyclopropanations using rhodium(II) carboxylates was not encouraging.[23] However, both McKervey[24] and Ikegami[25] had achieved notable successes in asymmetric intramolecular C-H insertions using proline and phenylalanine derivatives as chiral ligands.

Even though rhodium(II) prolinate derivatives are not effective at asymmetric cyclopropanation using the traditional diazoacetates as substrates, these catalysts give spectacular results with the vinyldiazomethane system. The optimum catalysts are the (*S*)-*N*-(4-*tert*-butylphenylsulfonyl)prolinate derivative, Rh_2(*S*-TBSP)$_4$ (**14a**), and the (*S*)-*N*-(4-dodecylphenylsulfonyl)prolinate derivative, Rh_2(*S*-DOSP)$_4$ (**14b**), since the highest enantioselectivity occurred in hydrocarbon solvents in which these catalysts are soluble. Examples of the asymmetric intermolecular cyclopropanation are shown in **Table 2**.[26] The catalysts are so active that when the reactions are carried out at -78 °C virtually all substrates result in cyclopropanations with greater than 90% ee. The reaction is applicable to 1-substituted, 1,1-disubstituted, and *cis*-1,2-disubstituted alkenes. *trans*-1,2-Disubstituted alkenes, however, do not react intermolecularly with vinylcarbenoids.

The combination of an electron-withdrawing (EWG) and an electron-donating substituent (EDG) on the carbenoid appears to be the crucial requirement for high diastereoselectivity and enantioselectivity when the rhodium(II) prolinate system is used. Carbenoids containing only an EWG, only an EDG, or two EWG's result in cyclopropanations with very poor diastereo- and enantioselectivities.[27] This has led to the discovery of methyl phenyldiazoacetate **15** as an excellent substrate for asymmetric cyclopropanation.[27] A range of alkene substrates can be used and the results are summarized in **Table 3**.[27,28] Doyle has compared the efficiency of Rh_2(*S*-TBSP)$_4$ with some of the chiral rhodium amide and copper catalysts and found that Rh_2(*S*-TBSP)$_4$ is by far the superior catalyst for asymmetric induction in the phenyldiazoacetate system.[28]

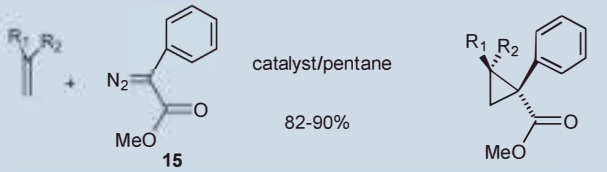
Table 2. Asymmetric cyclopropanation using chiral catalysts.



Rh_2(*S*-TBSP)$_4$ (**14a**) Rh_2(*S*-DOSP)$_4$ (**14b**)

R	ee, % at 25 °C (with Rh_2(*S*-TBSP)$_4$)	ee, % at -78 °C (with Rh_2(*S*-DOSP)$_4$)
Ph	90	98
$pClC_6H_4$	89	>97
$pMeOC_6H_4$	83	90
AcO	76	95
EtO	59	93
nBu	>90	-
Et	>95	-
iPr	95	-

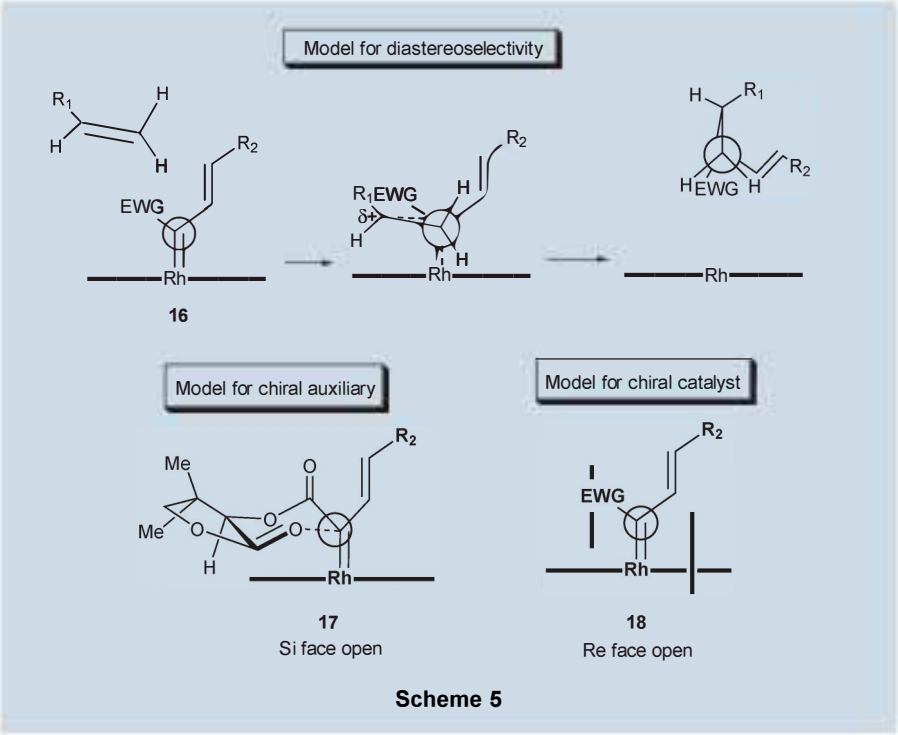
Table 3. Asymmetric cyclopropanation using methyl phenyldiazoacetate.



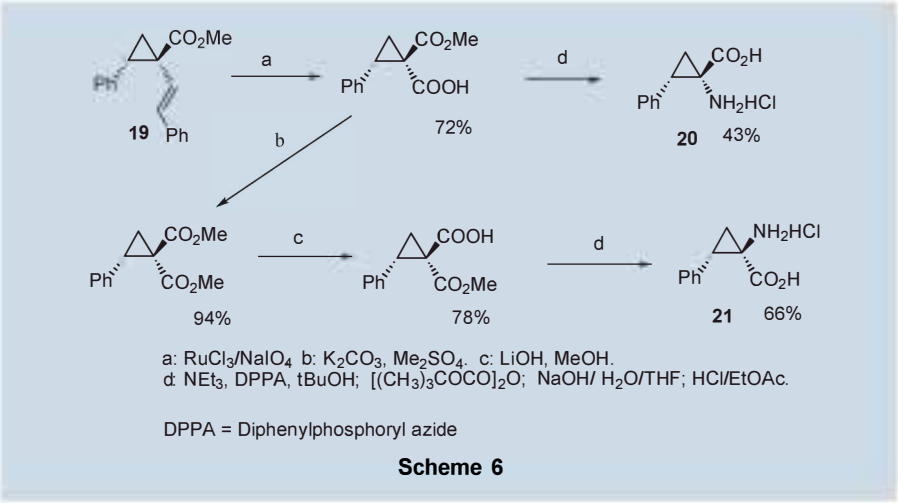
R_1	R_2	Catalyst	ee of *Z*, % at 25 °C
Ph	H	Rh_2(*S*-TBSP)$_4$[27]	87
$pClC_6H_4$	H	Rh_2(*S*-TBSP)$_4$[27]	85
$pMeOC_6H_4$	H	Rh_2(*S*-TBSP)$_4$[27]	88
EtO	H	Rh_2(*S*-DOSP)$_4$[27]	66
nBuO	H	Rh_2(*S*-DOSP)$_4$[27]	64
nBu	H	Rh_2(*S*-DOSP)$_4$[27]	77
Ph	Ph	Rh_2(*S*-TBSP)$_4$[28]	97
Ph	Me	Rh_2(*S*-TBSP)$_4$[28]	85(*E*), 81 (*Z*)

Models for Vinylcarbenoid Stereoselectivity

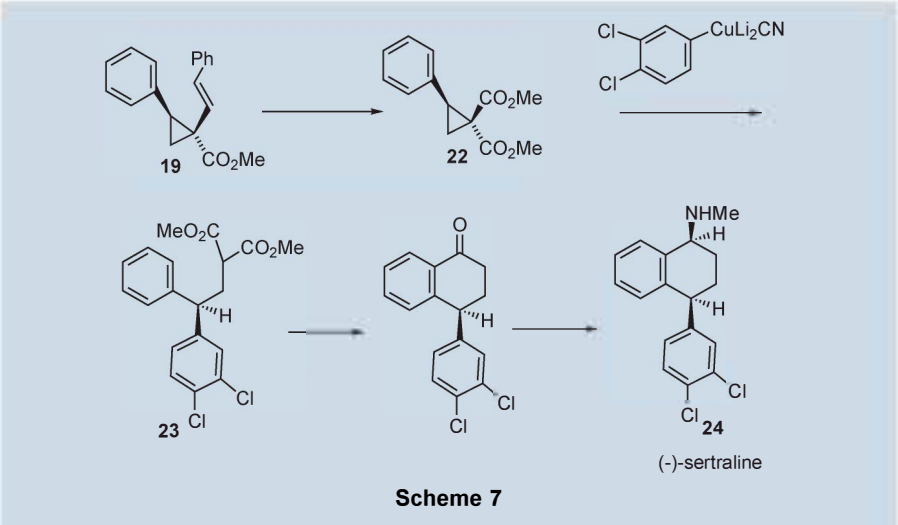
Reasonable models to explain the stereoselectivity in these reactions are shown in **Scheme 5**.[22,26] Model **16** accounts for the remarkable *E/Z* stereoselectivity exhibited in vinylcarbenoid cyclopropanations: Due to the fact that vinylcarbenoids do not react with *trans* alkenes, the alkene is considered to approach the carbenoid in a side-on mode with bulky substituents pointing away from the "wall" of the catalyst. The cyclopropanation is believed to be nonsynchronous with the alkene approaching preferentially on the side of the EWG. This general model is very similar to that proposed by Doyle for the stereoselectivity of diazoacetate cyclopropanations.[14] Structure **17** represents the model for the asymmetric induction using the (*R*)-pantolactone auxiliary.[29] The lactone carbonyl preferentially blocks the Si face of the carbenoid as this would limit unfavorable steric interactions between the auxiliary and the wall of the catalyst. Using the same trajectory for the alkene approach to the carbenoid as was considered above, structure **17** would lead to the preferential formation of the (1*R*,2*R*)-cyclopropane. Structure **18** represents the working hypothesis for the asymmetric induction using the prolinate catalysts.[26] In this predictive model, the catalyst behaves as if it had D_2 symmetry with the arylsulfonyl groups (marked as a thickened line) aligned in an "up-down-up-down" arrangement. Due to the D_2 symmetry, only one face of the catalyst needs to be considered. As can be seen in structure **18**, assuming a similar alkene approach as in structure **16**, the Re face of the carbenoid is blocked, leading to the formation of the (1*S*,2*S*)-cyclopropane.



Scheme 5



Scheme 6



Scheme 7

Applications

Vinylcyclopropanes with up to three stereogenic centers are readily formed in the reaction between vinylcarbenoids and alkenes.[7] The vinyl functionality that exists in the resulting cyclopropane offers numerous opportunities for further transformations. A generally useful application of vinylcyclopropanes is as chirons for the stereoselective synthesis of cyclopropaneamino acids as illustrated for **19** (**Scheme 6**).[26] By an appropriate sequence of oxidative alkene cleavage followed by a Curtius rearrangement either diastereomer of phenylcyclopropaneamino acid (**20** and **21**) can be formed in enantiomerically pure form.

Vinylcyclopropane **19** is readily converted to diester **22** by oxidative cleavage followed by esterification.[2b,26,29] Corey has demonstrated that **22**, on aryl cuprate induced ring opening, readily forms **23** with complete inversion of stereochemistry (**Scheme 7**).[29] This methodology was elegantly applied to the asymmetric synthesis of the 5-HT reuptake inhibitor (–)-sertraline (**24**).

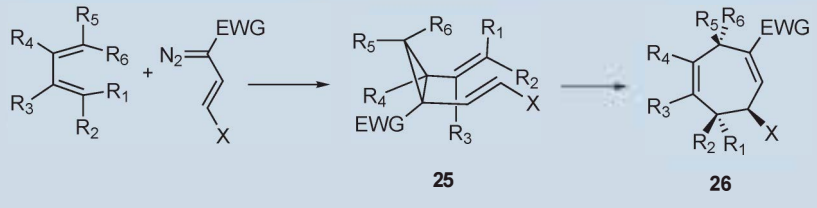
The extension of the asymmetric vinylcarbenoid cyclopropanation to dienes results in an extremely general method for the construction of seven-membered rings (**26**) with excellent control of stereochemistry (**Scheme 8**).[3b] The stereoselectivity that occurs in these vinylcarbenoid cyclopropanations results in a strong preference for the formation of *cis*-divinylcyclopropanes **25**. Furthermore, the Cope rearrangement of the divinylcyclopropane takes place through a boat transition state such that seven-membered rings with up to three stereocenters (e.g, **26**) are formed in a predictable manner.

The stereocontrol that is possible with this type of chemistry is illustrated in the case of *cis*- and *trans*-piperylene (**Scheme 9**).[3b] Decomposition of **4** in the presence of *cis*-piperylene at room temperature results in the stereocontrolled formation of *trans*-cycloheptadiene **27** in 90% ee (96% ee at -78 °C).[31] Alternatively, the reaction with *trans*-piperylene results in the formation of *cis*-cycloheptadiene **28** in 90% ee (99% ee at -78 °C).[31]

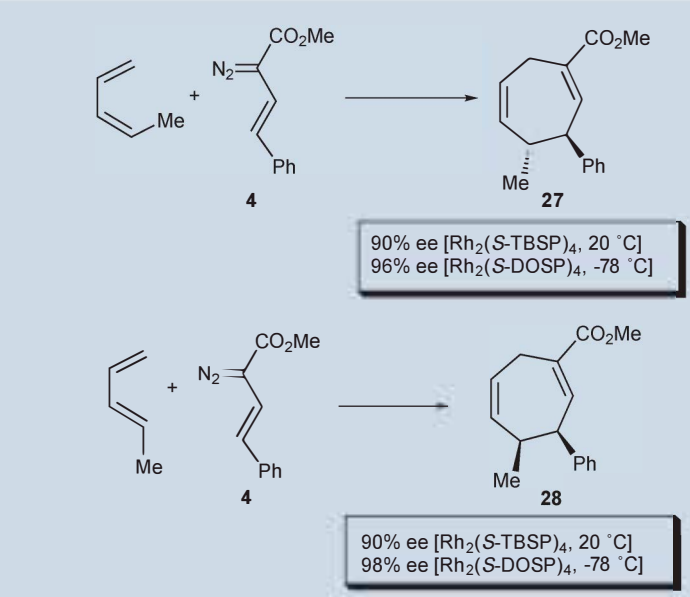
The reaction between cyclopentadiene and a series of vinylcarbenoids illustrates the range of functionality that can be accommodated on the carbenoid while maintaining a high degree of asymmetric induction (**Table 4**).[3b,31] Bicyclo[3.2.1]octadienes **29** are formed with complete control of relative stereochemistry. The ideal vinylcarbenoid substrates for asymmetric induction contain either an alkyl, vinyl, or phenyl group at the vinyl terminus, while the presence of an electron-deficient group at this position or

a large substituent at the central carbon is detrimental to the asymmetric induction.

The reaction between vinylcarbenoids and furans is an efficient method for the asymmetric synthesis of 8-oxabicyclo[3.2.1]octan-3-ones (**Scheme 10**).[32] These oxabicyclic systems are very versatile intermediates in organic synthesis and have been prepared typically in racemic form by the [3 + 4] annulation between allyl cations and furans.[33] The chiral auxiliary approach is best suited for high asymmetric induction with the siloxyvinyldiazomethane **30**. The reaction of **30** with furans generates 8-oxabicyclo[3.2.1]-octadienes **31** in good yield and diastereoselectivity (75-95% de).[32] The utility of this methodology was demonstrated by the synthesis of oxabicycles **32-34**, which had been previously used in racemic form as crucial building blocks in diastereoselective syntheses.



Scheme 8

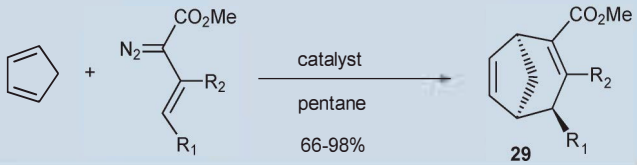


Scheme 9

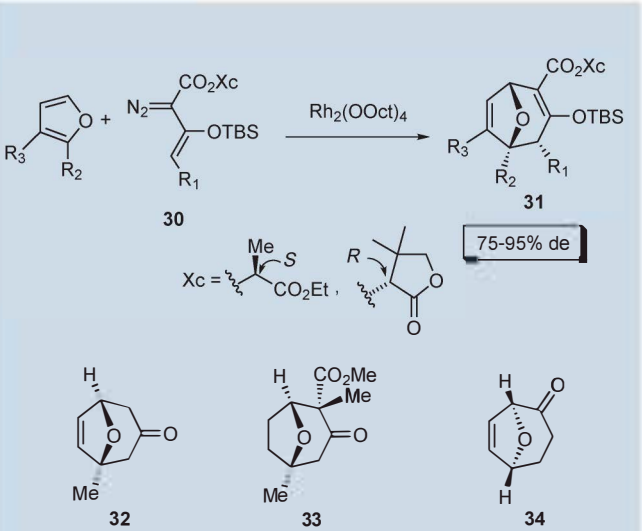
The reaction between vinylcarbenoids and pyrroles is a general method for the stereoselective construction of tropanes (**Table 5**).[34,35] Asymmetric induction using the rhodium prolinate catalyst is not effective in this case because the pyrrole is too electron rich and leads to products derived from zwitterionic intermediates.[35] On the other hand, the subtle advantage of the chiral auxiliary approach is demonstrated in the tropane series because the neighboring group interaction between the auxiliary and the carbenoid not only results in diastereocontrol but also enhances the chemoselectivity of the carbenoid.[36] Using the reactions of the *S*-lactate derivatives **35** with *N*-BOC-pyrroles, the asymmetric synthesis of tropanes **36** was achieved in respectable yields and diastereoselectivity.[35] The utility of this methodology has been demonstrated by the synthesis of a series of 2β-acyl-3β-aryltropanes **37**.[37] These compounds are of considerable current interest because they are useful as molecular probes and potential medications for the treatment of cocaine addiction.

In principle, the asymmetric reaction between vinylcarbenoids and dienes has very broad applications. An illustration of this

Table 4. Asymmetric synthesis of bicyclo[3.2.1]octadienes.

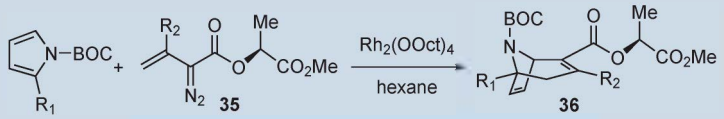


R_1	R_2	ee at 25 °C, % [with Rh_2(*S*-TBSP)$_4$]	ee at -78 °C, % [with Rh_2(*S*-DOSP)$_4$]
Ph	H	75	93
Me	H	83	92
CH=CH$_2$	H	91	93
H	H	63	-
CO_2Et	H	10	-
H	Me	64	-
H	OTBS	42	-

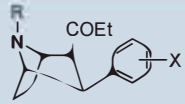


Scheme 10

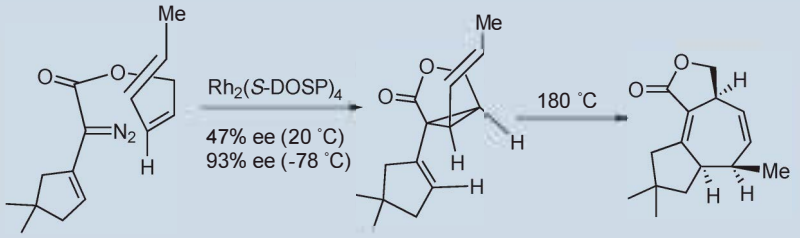
Table 5. Asymmetric synthesis of tropanes.



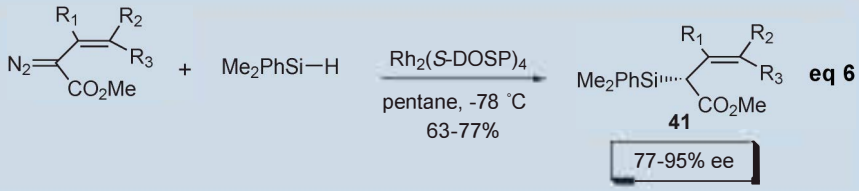
R_1	R_2	Yield, %	de, %
H	H	82	66
Me	H	54	59
Ph	H	64	53
CH_2OTBS	H	62	70
Ac	H	30	67
H	OTBS	64	66
Me	OTBS	55	58
Ph	OTBS	74	52
Ac	OTBS	58	79



37



Scheme 11



point is seen in the intramolecular reaction used in the synthesis of 5-epitremulenolide (**Scheme 11**).[38] Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of vinyldiazomethane **38** at -78 °C resulted in the formation of *trans*-divinylcyclopropane **39** in 65% yield. Under forcing conditions, **39** underwent a Cope rearrangement to form the tricyclic product **40** (absolute stereochemistry has not been determined) in 85% yield and 93% ee with full control of the relative stereochemistry at the three stereogenic centers.

The focus of this account has been on the asymmetric cyclopropanation chemistry of vinylcarbenoids, but in principle other asymmetric vinylcarbenoid transformations should be equally feasible. An illustration of this point is the asymmetric Si-H insertion reaction (**eq 6**).[39] A series of allyl silanes **41** was prepared with high enantioselectivity using Rh_2(*S*-DOSP)$_4$ as catalyst at -78 °C.

Conclusion

In summary, the cyclopropanation reaction of rhodium-stabilized vinylcarbenoids has great utility since it is highly diastereoselective, and the resulting vinylcyclopropanes are versatile synthetic intermediates. In combination with the two complementary methods that have been developed for asymmetric vinylcarbenoid cyclopropanations, the chemistry is applicable to the enantioselective synthesis of a wide variety of acyclic, cyclic, and polycyclic systems.

Acknowledgment

The author thanks the members of his group, both past and present, who have contributed to much of the work described in this report. These studies were generously supported by the National Science Foundation (CHE 9024248 and CHE 9421649) and by PHS grants DA-06301 and DA-06634.

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Dimethyl tricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3,4-dicarboxylate: A Versatile Ambident Dienophile

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Outline

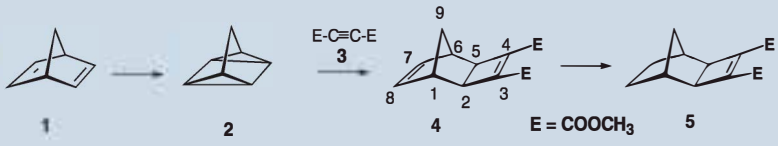
1. Introduction

Our interest in the title compound, dimethyl tricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3,4-dicarboxylate (Smith's diene) **(4, Scheme 1)**, commenced in the early 1980s and stemmed from the fact that it was an easily obtained cyclobutene which we required as a transfer reagent[1-3] for cyclobutene-1,2-diester. It became more important, however, when we realized its potential for preparing spacer molecules. Indeed, diene **4** was the starting point in our original report on the synthesis of binanes (Section 3.1.1)[4] as typified by the production of 6σ-binane **8** from the reaction of quadricyclane **2** with diene **4** (**Scheme 2**).

As part of our program for building rigid alicyclic architectures,[5] we have used Smith's diene (**4**) as a model system for evaluating cycloaddition reagent reactivities as well as site- and stereoselectivities. This role played by Smith's diene (**4**) is the theme of this review.

2. Preparation of Smith's Diene and its 7,8-Dihydro Derivative

Dimethyl tricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3,4-dicarboxylate (**4**) was first described by Claibourne D. Smith in 1966.[6] Referred to as Smith's diene by our research group (and in this review), **4** is made by the bishomo Diels-Alder cycloaddition of dimethyl acetylenedicarboxylate (DMAD,**3**) with quadricyclane (**2**) (**Scheme 1**). As quadricyclane (**2**) is produced[7] by the photoinduced [2π + 2π] intramolecular cycloaddition of norbornadiene **1**—itself a Diels-Alder product of acetylene and cyclopentadiene[8]—so the strong Diels-Alder influence commenced from the very beginning of **4**.

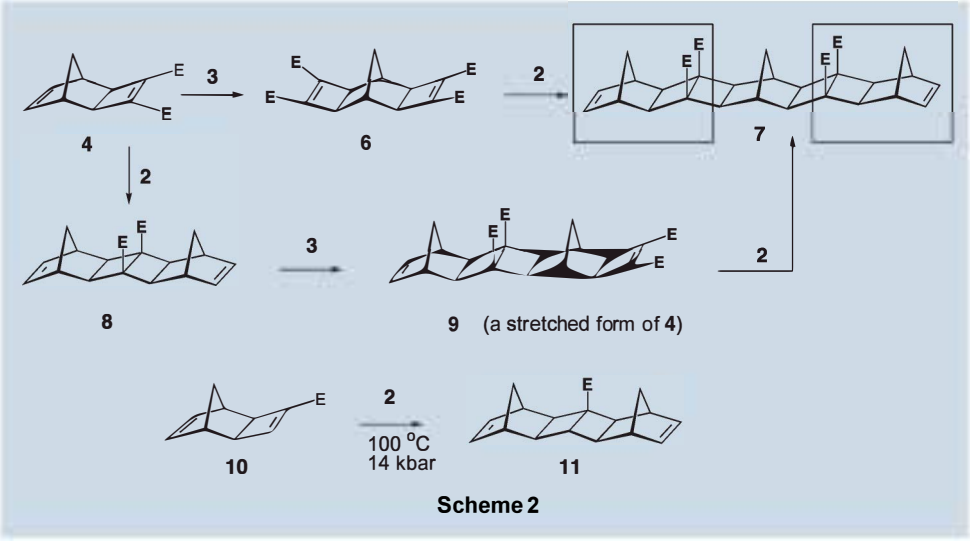


Scheme 1

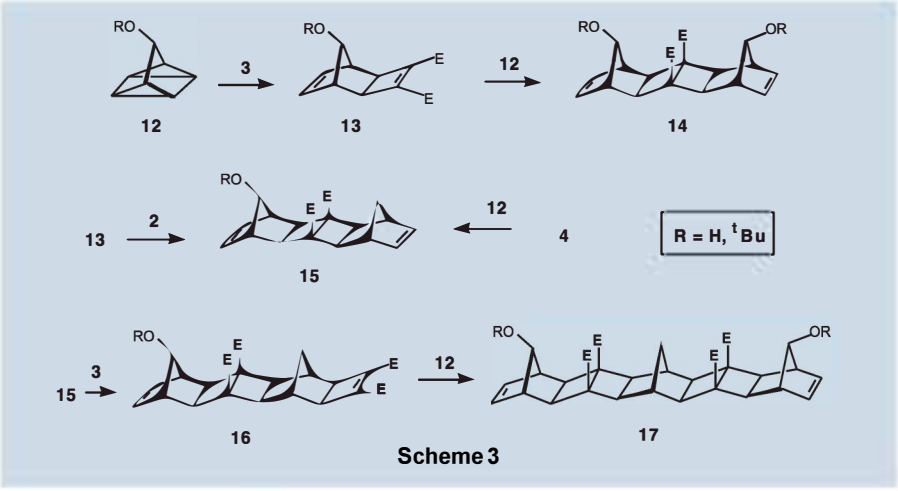
Preparation of Dimethyl (1α,2β,5β,6α)-tricyclo[4.2.1.0^{2,5}]-nona-3,7-diene-3,4-dicarboxylate "Smith's Diene" (4)[6]

A mixture of quadricyclane (**2**) (36.8 g, 0.40 mol) and dimethyl acetylene dicarboxylate (**3**) (56.8 g, 0.40 mol) in carbon tetrachloride (100 mL) was heated under reflux for 5 hours. The solvent was removed to give crude **4** as a yellow oil. Vacuum distillation afforded the product as a colorless, viscous liquid (77.5 g, 83%), bp 82-88 °C at 3 x 10^{-2} torr (lit. bp 94 °C at 5 x 10^{-1} torr).[6] ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 2H, H9a,b), 2.56 (s, 2H, H2, H5), 2.61 (m, 2H, H1, H6), 3.80 (s, 6H, 2 CH_3's), 6.18 (m, 2H, H7, H8). ^{13}C NMR ($CDCl_3$) δ 38.16, 39.45, 44.13, 51.69, 135.88, 144.94, 161.65.

The 7,8-dihydro derivative **5** serves as a model cyclobutene-1,2-diester in many cycloaddition reactions. It can be formed by controlled hydrogenation (Pd/C) of **4** in ethyl acetate at atmospheric pressure, or by ruthenium-catalyzed [2π+2π] addition of dimethyl acetylenedicarboxylate (DMAD) onto norbornene.[9] Cycloaddition results obtained with alkene **5** are a better guide to reactivity than those obtained from Smith's diene (**4**), as it is the dihydro subunit in **5** which is present in those other polyalicyclic systems produced by catalyzed cycloaddition of DMAD onto norbornene end groups (see later).



Scheme 2



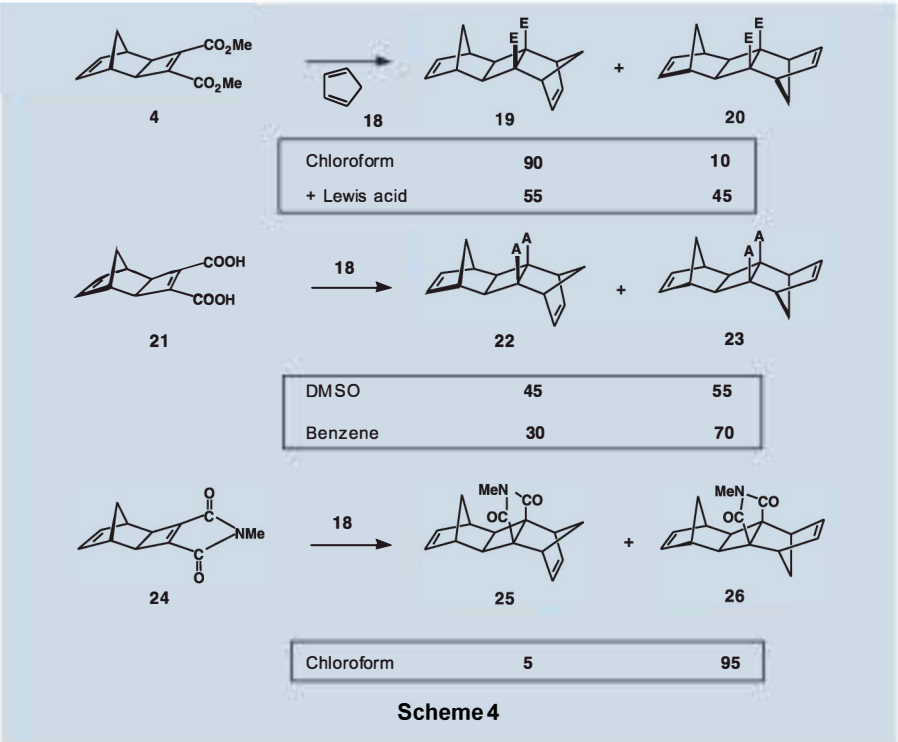
Scheme 3

3. Diels-Alder Cycloadditions

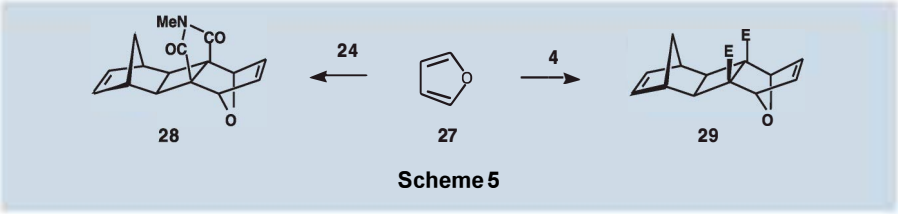
3.1. Reactions at the Cyclobutene-1,2-diester π-Bond

3.1.1. Quadricyclanes: Routes to Binanes and Molracs

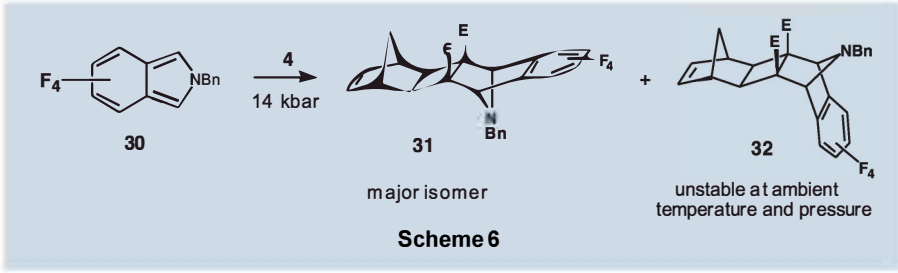
As mentioned in the introduction, we used Smith's diene (**4**) as the starting point for molrac construction. This happened as a result of our curiosity about why **4** didn't react further with quadricyclane in Smith's original reaction. Subsequent experiments revealed that the reaction did occur at higher temperatures. Quadricyclane (**2**) reacted at the cyclobutene-1,2-diester π-bond of **4** to form the hexacyclic molrac **8**,[4] in which high stereospecificity accompanied the cycloaddition process (**Scheme 2**). This observation was the first step in the development of a rigid polyalicyclic framework and became a driving force when it was coupled with the observations reported by Mitsudo and his group in Japan.[9] They had found some years earlier, that dimethyl acetylenedicarboxylate (DMAD) reacted with norbornenes under the influence of certain ruthenium catalysts to produce exo-fused cyclobutene-1,2-diesters. Application of these two reactions in tandem allowed the stereospecific



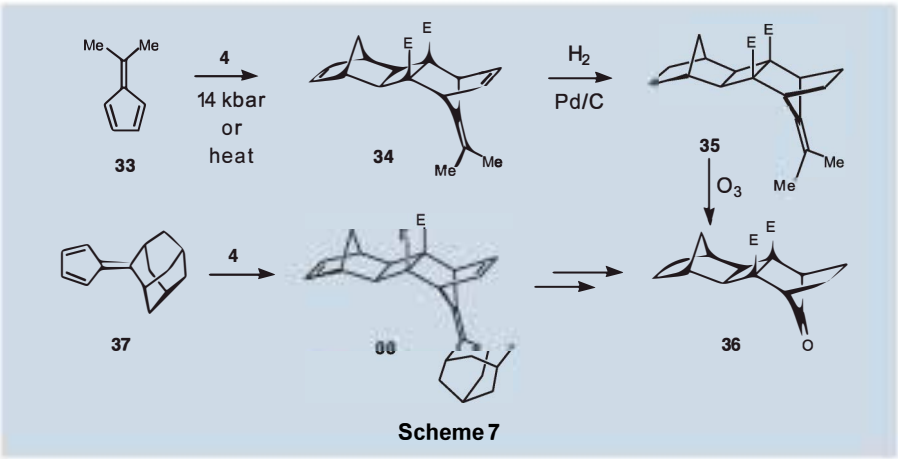
Scheme 4



Scheme 5



Scheme 6



Scheme 7

formation of extended molecular structures comprised entirely of fused norbornanes and cyclobutanes (**Scheme 2**). At that time they were termed binanes and are now recognized as a subclass of molecular racks (molracs)—renamed to accommodate a larger selection of alicyclic and aromatic fusion partners.

Reaction of quadricyclane with Smith's diene produces the hexacyclic structure **8**, while controlled Mitsudo cycloaddition of DMAD onto **8** can be used to form the heptacyclic system **9**. Since molracs of type **9** have both norbornene and cyclobutene-1,2-diester groups at the termini, they can be viewed as stretched Smith's dienes. Further reaction of quadricyclane with the cyclobutene-1,2-diester system of **9** produces the decacyclic system **7**, in which each terminus contains a 3,4-dihydro variant of Smith's diene (boxed).

More recently, Jenner[10] has shown that quadricyclane reacts with **10**, the monoester equivalent of Smith's diene, to produce the hexacyclic system **11**. In this case the reaction was achieved using a combination of heat (100 °C) and high pressure (14 kbar). We have found that only trace amounts of adduct are formed from the high pressure (10-15 kbar, several days) treatment of quadricyclane with Smith's diene when conducted at room temperature, leading to the conclusion that both heat and pressure are apparently required to effect quadricyclane cycloadditions in these systems.

This same construction method can be used to produce spacer molecules with built-in hydroxyl groups suitable for the attachment of functionality (**Scheme 3**). The substituted quadricyclane **12**, readily produced by photoisomerization of the corresponding norbornadiene, reacts with DMAD to produce the derivatized Smith's diene **13**.[11] Further reaction between **12** and **13** yields the symmetrical product **14** where the two alkoxy groups are outward-facing. These transformations are conducted on the *tert*-butyl ethers which can be transformed into the corresponding alcohols by treatment with trifluoroacetic acid.

Spacer molecule **17** is a stretched variant of **14** and is produced from the mixed cycloadduct **15**. Starting *bis*-alkene **15** can be prepared either by reaction of quadricyclane with functionalized Smith's diene **13**, or by reaction of substituted quadricyclane **12** with Smith's diene **4**. The alkoxy substituent in **15** has the syn configuration relative to the norbornene π-bond and protects it from exo attack. Consequently, ruthenium-catalyzed cycloaddition of DMAD onto **15** occurs only at the exposed norbornene π-center and provides monocyclobutene-1,2-diester **16** in high yield. Reaction of quadricyclane **12** with **16** produces the symmetrical product **17** in which each alkoxy group is outward-facing.

3.1.2. Cyclopentadiene, Furan, and Pyrroles

Smith's diene (**4**) is quite a reactive dienophile, reacting with cyclopentadiene (Cp, **18**) in refluxing chloroform to furnish a mixture of stereoisomeric adducts, **19** and **20**, by exclusive reaction at the β-face of the cyclobutene π-center (**Scheme 4**).[4] Adduct **19**, with a bent frame, is the dominant product, with only small amounts of the extended isomer **20** produced. The proportion of **20** can be improved by conducting the reaction in the presence of a Lewis acid (e.g., $AlCl_3$). The best way of producing **20**, however, is *via* cyclopentadiene addition to the dicarboxylic acid derivative **21** (formed by base hydrolysis of **4**) in benzene, yielding the extended adduct **23** as the major product (70%). Adduct **23** can be transformed into the diester **20** by controlled reaction with diazomethane (excess diazomethane yields a new cycloaddition adduct, see Section 4). The fused cyclobutenomaleimide **24**[12] is much more reactive than Smith's diene; it reacts with cyclopentadiene exothermically at room temperature to yield the extended isomer **26** as the major cycloaddition product.

While furan **27** reacted with the fused maleimide **24** at room temperature to form the extended stereoisomer **28** (**Scheme 5**), it reacted only sluggishly with Smith's diene (**4**) and only produced adduct **29** under the influence of a Lewis acid ($ZnCl_2$, $AlCl_3$, $LiClO_4$ are all effective) or high pressure; exclusive formation of the extended isomer was observed in all cases.

N-substituted pyrroles are much less reactive than the other 5-membered 1,3-dienes; no reaction was observed between *N*-(trimethylsilyl)pyrrole or *N*-benzylpyrrole with Smith's diene (**4**) under thermal or high pressure (4 days at 14 kbar) conditions, even in the presence of Lewis acids.[13]

Isoindoles, however, do react with **4** under high-pressure conditions; for example, *N*-benzyltetrafluoroisoindole **30** forms a mixture comprised of the extended adduct **31** and its bent isomer **32** (**Scheme 6**). The bent isomer is not stable, however, and reverts to the starting materials soon after exposing it to ambient temperature and pressure.[13]

3.1.3. Fulvenes: Carriers of Functionality

Fulvenes react with Smith's diene (**4**) under thermal conditions; typically, 6,6-dimethylfulvene **33** yields the extended isomer **34** as the exclusive product (**Scheme 7**).[14] X-ray

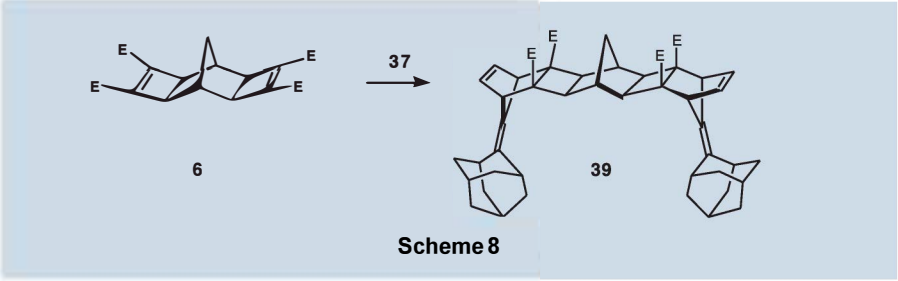
structural data obtained for **34** established conclusively the stereoselectivity of the reaction.[15] Using adamantylidenylfulvene (**37**), a similar adduct, **38**, was obtained where the adamantyl group is positioned rigidly onto the molecular framework by virtue of the olefinic linkage originating from the fulvene. Conversion of **34** and **38** (hydrogenation/ozonolysis) to the common ketone **36** confirmed the stereochemistry of **38** (**Scheme 7**).[14]

These reactions, which are improved by conducting the experiments under high-pressure conditions, can be extended to the formation of bisadducts by using the biscyclobutene **6**; e.g., adamantylidenylfulvene **37** affords the symmetrical product **39** as outlined in **Scheme 8**.[14]

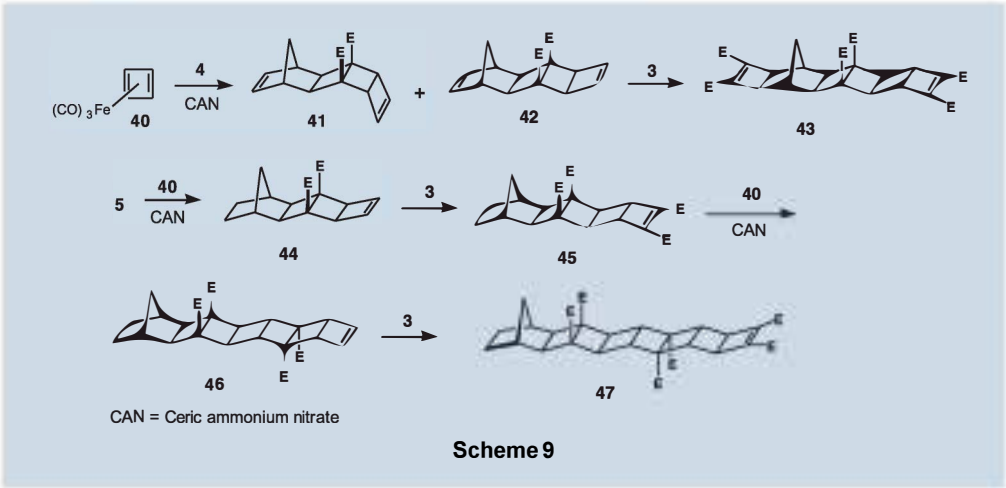
3.1.4. Cyclobutadiene: Entry to [n]Ladderanes

Smith's diene (**4**) reacts efficiently with cyclobutadiene (liberated from its iron tricarbonyl complex **40** with CAN) to form Diels-Alder adducts **41** and **42** by selective reaction at the cyclobutene π-bond of **4** (**Scheme 9**). The extended isomer **42** dominates 10:1 over the bent isomer **41**. Both π-bonds in **42** react with DMAD in the presence of a Ru-catalyst to produce bisadduct **43**; this is the first example of a cyclobutene π-bond reacting in this fashion. This process has been developed into an [*n*]ladderane synthesis by starting with the dihydro derivative **5** of Smith's diene and working in tandem.[16] In this way, the extended [*n*]ladderanes **46** and **47**, where n=6, 7, were reproduced (**Scheme 9**). This tandem process can be applied to other cyclobutenes and provides the most versatile route to [*n*]ladderanes currently available.

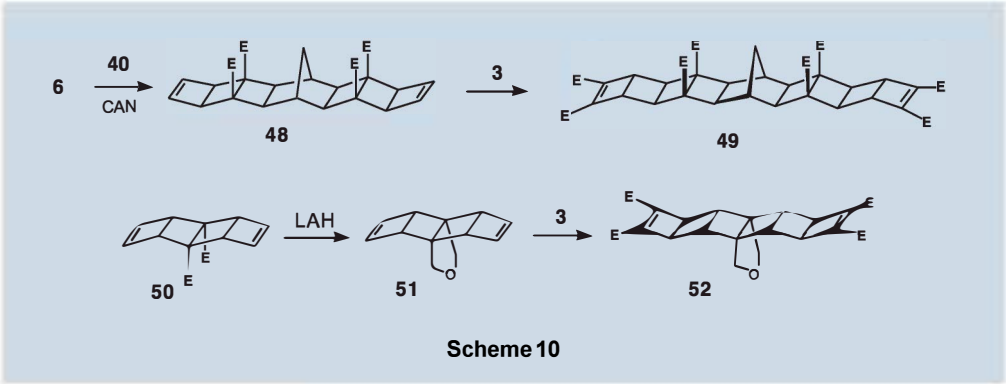
Bis(cyclobutene-1,2-diester) **6** reacted with two equivalents of cyclobutadiene to form the homo[8]ladderane **48** as the major bisadduct. This was shown to undergo further extension by treatment with DMAD/Ru-catalyst to produce the homo[10]-ladderane **49** (**Scheme 10**).[17] Such systems dwarf the pterodactylane **50**[18,19] and must



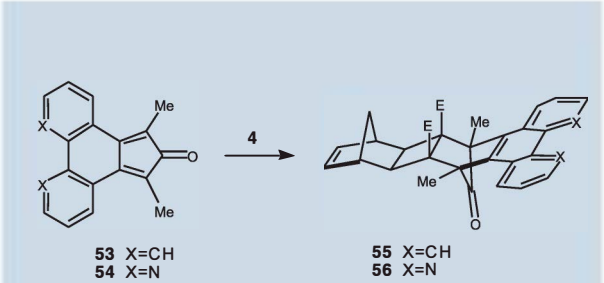
Scheme 8



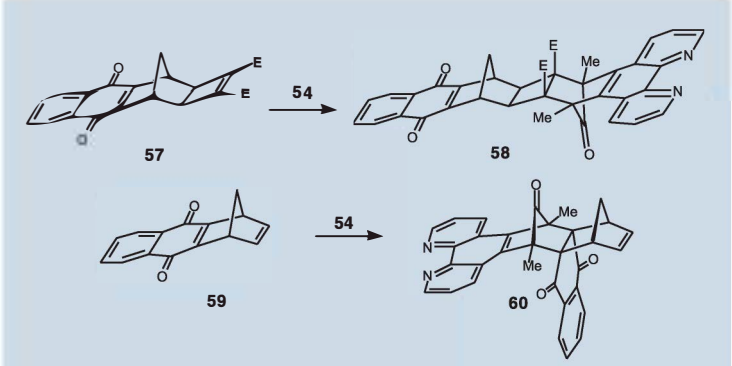
Scheme 9



Scheme 10



Scheme 11



Scheme 12

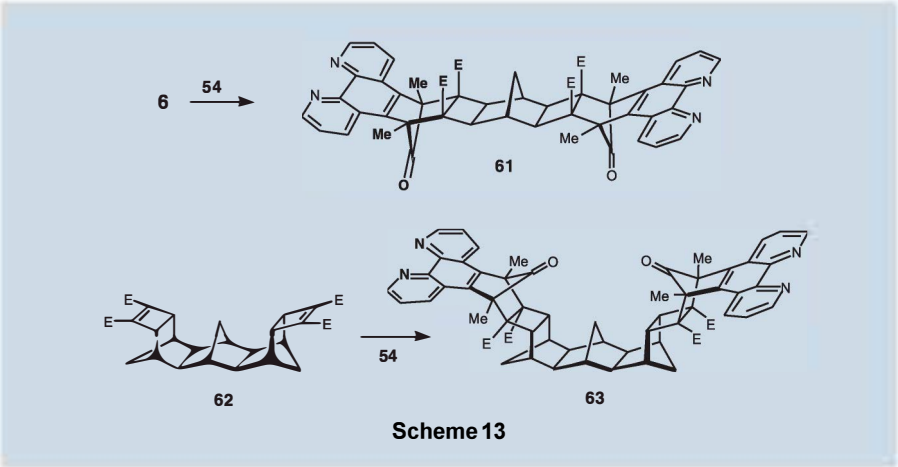
surely originate from the pterodactylane *grandis* species! Indeed, [6]ladderane **52** is a direct offspring of **50**. The reactions of substituted cyclobutadienes in this context have also been reported.[20]

3.1.5. Cyclones: Entry to Fused 1,10-Phenanthrolines

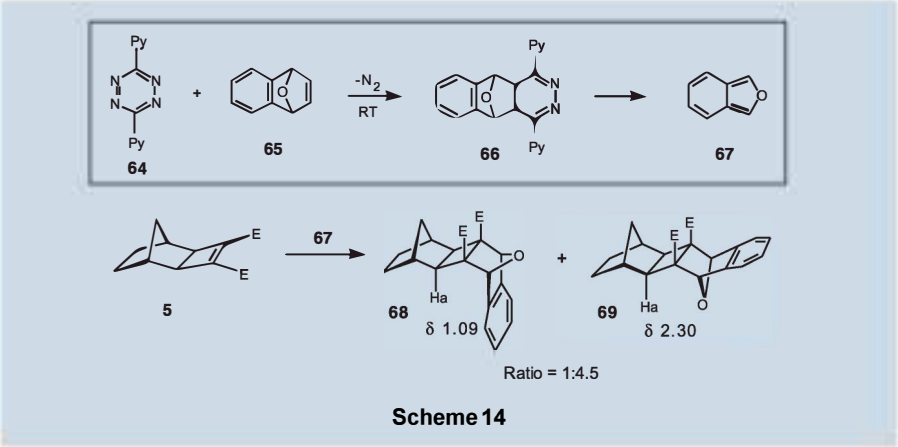
Cyclopentadienones (cyclones) readily react with Smith's diene (**4**) to form exclusively a single 1:1 adduct having the extended stereoisomeric structure; e.g., phencyclone **53** yielded adduct **55** (**Scheme 11**).[21] The specificity was conclusively established on the basis of ^{1}H NMR spectroscopy: the site selectivity by the retention of the norbornenyl resonances, and the stereospecificity by the upfield shift of the ester methyl resonances (δ 3.20).

The availability of diazaphencyclone (DAPC) **54** has allowed the cyclopentadienone methodology to be used for attaching the 1,10-phenanthroline ligand onto molracs.[22] Reaction of DAPC **54** with **4** again occurred stereoselectively at the cyclobutene-1,2-diester moiety to produce **56** (**Scheme 11**); this has opened up the stereospecific production of mono- and bisligands fused to rigid spacer systems.[23] Ambident dienophile **57** reacts with DAPC **54** at the cyclobutene π-bond to produce ligand **58**; in contrast, the related ambident dienophile **59** reacts with DAPC **54** at the naphthoquinone π-center to produce adduct **60** (lack of shielding of the methylene protons supports the stereochemical assignment) (**Scheme 12**).

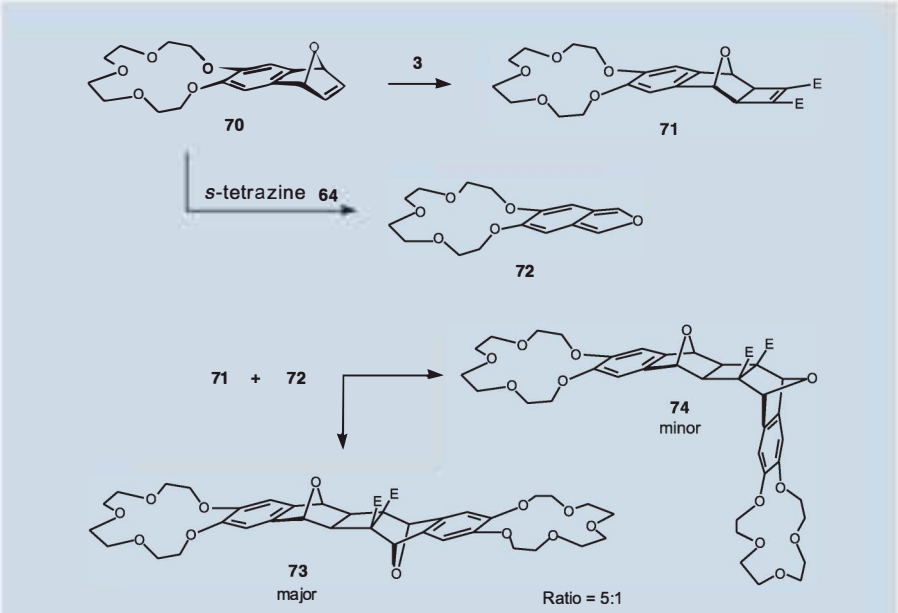
The presence of the dihydro-Smith subunit is exploited in the preparation of bisligand systems **61** and **63** by reaction of DAPC **54** with *bis*-alkene **6** or "U"-shaped **62,** respectively (**Scheme 13**).[24]



Scheme 13



Scheme 14



Scheme 15

3.1.6. Isobenzofurans and their Crown Ethers

A complex mixture of adducts arose from the reaction of isobenzofuran **67** with Smith's diene (**4**) as addition occurred nonstereospecifically at both π-centers of **4**. This mixture was examined by NMR spectroscopy, but individual components were not separated.[25] The stereospecificity of the reaction at the cyclobutene π-center was established using dihydro-Smith's alkene **5**, which was converted to adducts **68** and **69** (**Scheme 14**). Adducts **68** and **69** were easily distinguished by ^{1}H NMR spectroscopy using the ring-current effect of the aromatic ring: the norbornane protons Ha are shielded in **68** (δ=1.09) relative to **69** (δ=2.30), while the ester methyl groups in **69** (δ=3.54) are partially shielded relative to the corresponding ones in **68** (δ=3.80).[26]

Isobenzofuran **67** was generated in situ by reaction of 1,4-dihydro-1,4-epoxynaphthalene (**65**) with 3,6-di(2-pyridyl)-*s*-tetrazine (**64**) in chloroform solution.[27] The intermediate dihydropyridazine **66** can be isolated as a crystalline product if the reaction is performed in DMSO, and **66** can be used as a source of isobenzofuran in reactions where the substrate itself reacts with *s*-tetrazine **64**.

The use of isobenzofurans as delivery agents for the crown ether ionophore has formed a part of our host/guest study program.[28] Ruthenium-catalyzed addition of DMAD to the dihydroepoxynaphthalene **70**—having the

15-crown-5 subunit attached to the 6,7-position of the aromatic ring—gave oxa-Smith's derivative **71.** Compounds **70** and **71** are versatile starting materials for polycyclics containing crown ethers; their potential is illustrated by the generation of crown ether-isobenzofuran **72** by the *s*-tetrazine method, and its addition to the cyclobutene-1,2-diester component of **71** (**Scheme 15**). Two stereoisomeric adducts are observed: the extended product **73** and the bent isomer **74**; the former being the dominant one.

In the case of cavity bisalkene **75**, a single isomer was obtained with two equivalents of isobenzofuran **72**, each reacting stereospecifically with a cyclobutene-1,2-diester group to produce the symmetrical product **76** (**Scheme 16**). The "arms-outstretched" configuration of this product, together with the lining of the cavity's interior with bridging oxygen atoms, makes this material an enticing substrate for supramolecular studies.

3.1.7. Photochemical Cycloaddition Reactions

Eberbach reported that UV irradiation of Smith's diene (**4**) yielded the exo,antidimer **77** (**Scheme 17**) where cycloaddition occurred specifically at the cyclobutene-1,2-diester chromophores.[29] We have shown that the norbornene π-bonds in **77** reacted with azides to produce a diastereomeric pair of 2:1 adducts **79** that were converted photochemically to a single bisaziridine **80**. Formation of the oxygen analog **78** was achieved by direct mCPBA epoxidation of **77**.[3]

The value of products **78** and **80** was that they could be converted to a special type of rigid polyene structure (**Scheme 18**). Thus, thermally induced ring-opening of the cyclobutane rings was achieved under flash vacuum pyrolysis (FVP) conditions (500 °C, 5 x 10^{-3} torr), and led to the formation of rigid macrocyclic polyenes **81** and **82**, respectively. FVP of bisalkene **77** was also conducted, and produced the cyclic hexaene **83**. The lower yield (11%) of **83** reflects the operation of a competing retro Diels-Alder pathway open to **77**, where loss of cyclopentadiene yields cyclooctatetraene-1,2,5,6-tetraester **85**, possibly formed from intermediate **84.**

Mixed photocycloadditions have been conducted with norbornenes or cyclobutenes and, while Smith's diene (**4**) has not been involved in the study directly, the oxa-bridged relative **86** has (**Scheme 19**). Thus, irradiation of **86** with *N*-methyl-3,4-dibromomaleimide (**87**) produced a mixture of stereoisomeric cycloadducts **88** by exclusive reaction at the cyclobutene π-bond.[12]

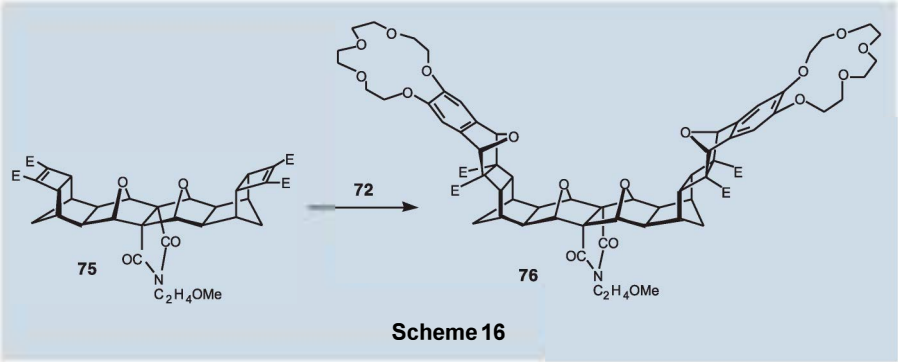
3.2. Reactions at the Norbornene π-Bond

Almost all the reactions discussed up to this point involve site-selective attack at the cyclobutene π-bond (at least initially). It would be remiss, however, to think that the norbornene π-bond was without its own character. Indeed, it is the preferred site of attack for many reagents, especially reverse-electron-demand dienes.

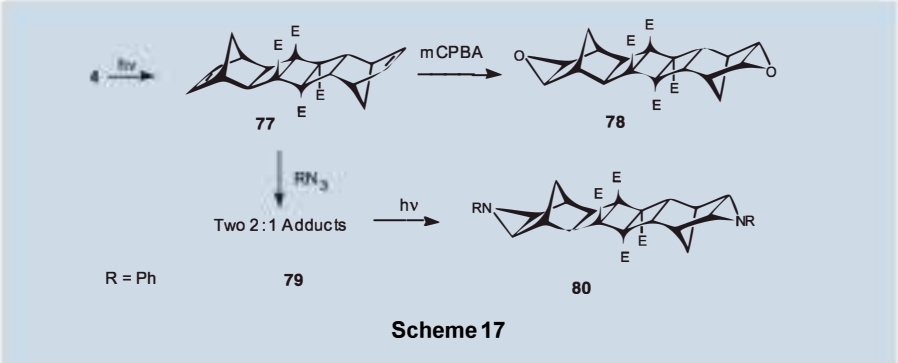
3.2.1. s-Tetrazines: Route to Fused DPP Ligands

Smith's diene (**4**) reacts with *s*-tetrazines at the norbornene π-bond to produce dihydropyridazines; e.g., 3,6-di(2-pyridyl)-*s*-tetrazine (**64**) reacts with **4** to furnish 4,5-dihydropyridazine **89** (**Scheme 20**).[30] This intermediate is moderately stable in the absence of acid, and either it, or its rearranged product, can be oxidized (DDQ) to the fused pyridazine **90**. The X-ray structure shows the conformation of each pyridine substituent almost coplanar with the pyridazine ring, and the nitrogen atom of each pyridine ring anti-related to an *N*-atom in the pyridazine ring.

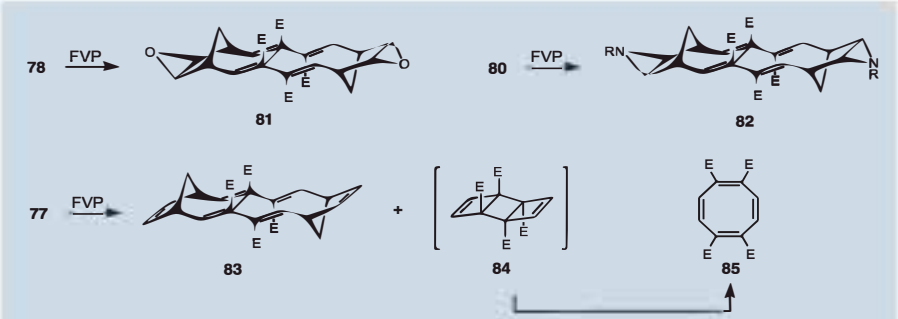
This reaction sequence of cycloaddition/DDQ dehydrogenation has been used to prepare a whole range of fused mono- and bisligands containing a fused 3,6-dipyridylpyridazine



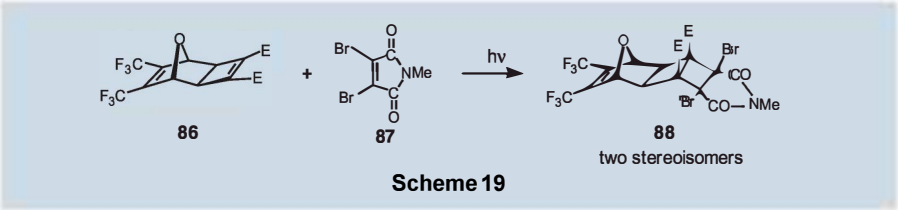
Scheme 16



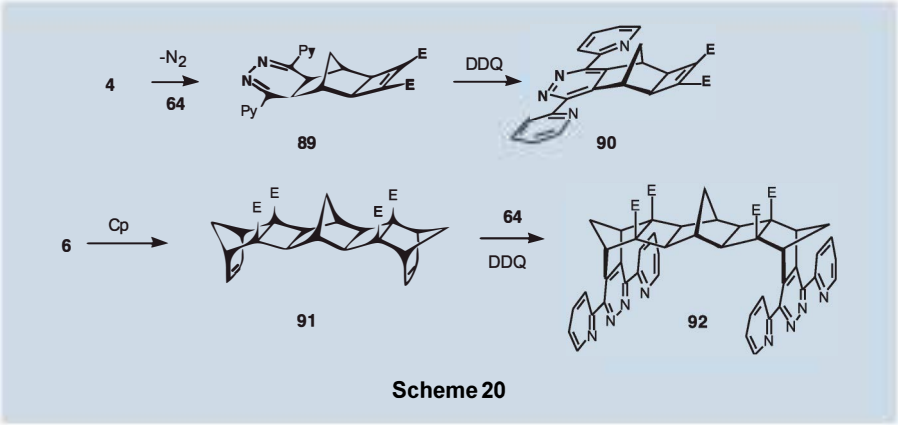
Scheme 17



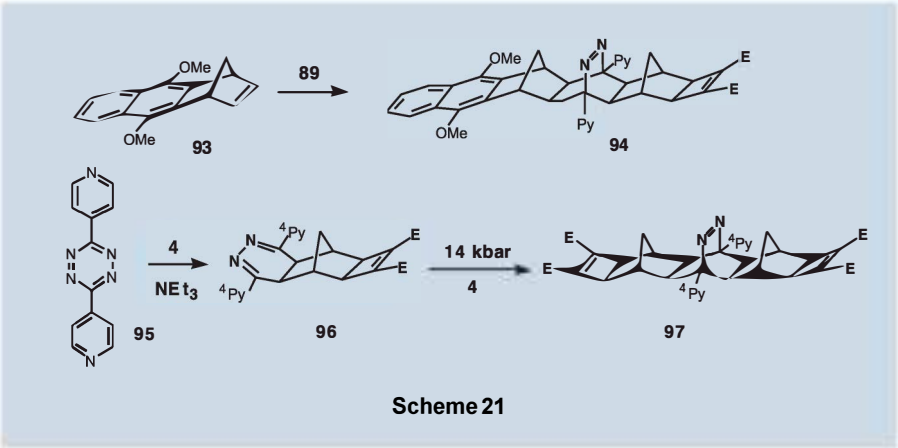
Scheme 18



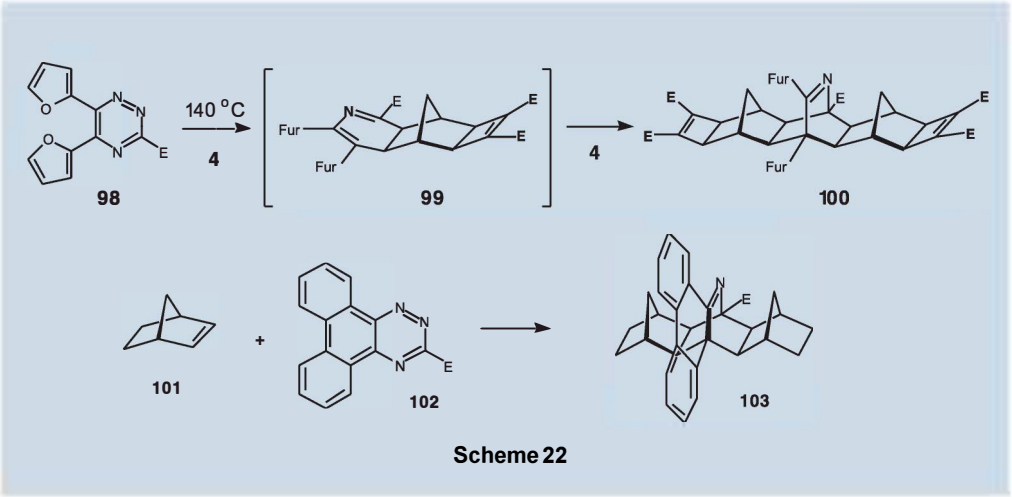
Scheme 19



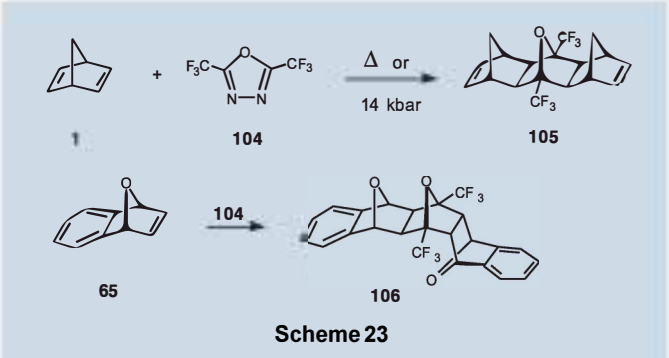
Scheme 20



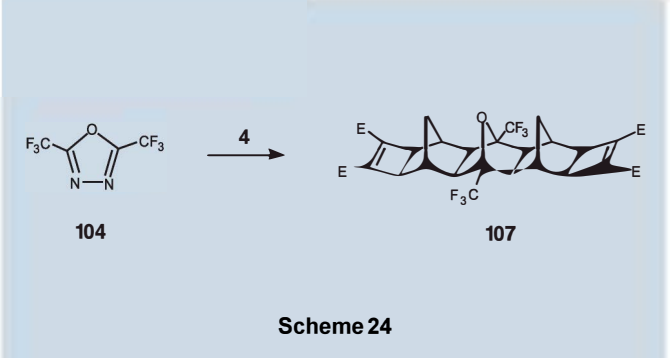
Scheme 21



Scheme 22



Scheme 23



Scheme 24

(dpp) component. Treatment of bisalkene **91**, readily obtained by cyclopentadiene addition to **6**, under these conditions produced the cavity-shaped system **92** containing two dpp subunits, where the ligand systems are roughly coplanar. Many other examples of such bisligands are reported in the original papers.[30,31]

The dihydropyridazines described above (e.g., **89**) are reactive 1,3-dienes and can be coupled with ring-strained dienophiles. Thus, reaction of **89** with naphthalenonorbornadiene **93** produces the coupled product **94** (**Scheme 21**). In a similar fashion, 3,6-di(4-pyridyl)-*s*-tetrazine **95** has been used to couple with Smith's diene (**4**) to produce the fully symmetrical aza-bridged product **97**; the intermediate dihydropyridazine **96** is not isolated, and the second step is achieved using high pressure (14 kbar).

3.2.2. 1,2,4-Triazines

1,2,4-Triazines are also active reverse-electron-demand dienes that react with ring-strained olefins to yield dihydropyridines. The triazine can be used as a carrier of functionality; thus, difuryltriazine **98** reacts with Smith's diene (**4**) exclusively at the norbornene π-bond to produce the 2:1 product **100** (**Scheme 22**). Dihydropyridine **99** is the presumed intermediate but is not isolated under the high-pressure conditions used to achieve coupling. In a similar fashion the fused triazine **102** can be used to couple norbornene to furnish the symmetrical product **103**.

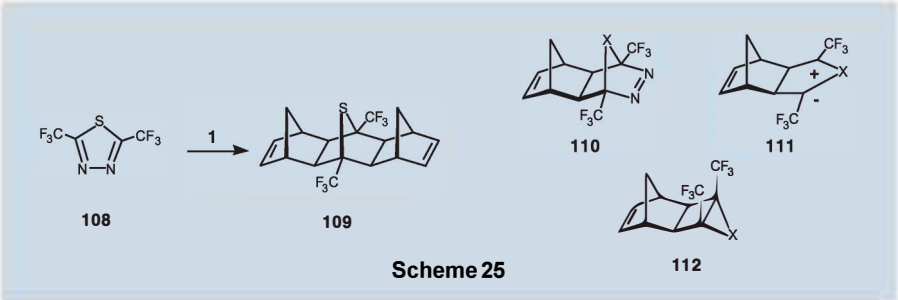
3.2.3. 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles

2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole (**104**) has been reported by several groups[32,33] to react with ring-strained alkenes under forcing thermal conditions to produce coupled products; e.g., norbornadiene produced the symmetrical tetracyclic system **105** (**Scheme 23**). More recently, we have found that similar conversions can be promoted by high pressure (8-14 kbar) even at room temperature. 1,4-Dihydro-1,4-epoxynaphthalene (**65**) can also be

coupled with oxadiazole **104**, although this time the coupled product **106** has a bent frame.[34]

Reaction of Smith's diene (**4**) with oxadiazole **104** yields the coupled product **107** (**Scheme 24**) in which two dihydro-Smith's units are fused stereospecifically to the central 7-oxanorbornane.

The corresponding 1,3,4-thiadiazole **108** produces the thia-bridged hexacycle **109** on treatment with norbornadiene **1** either thermally[35] or under high pressure[36] (**Scheme 25**). In this and the oxa-related cycloadditions (above), a diaza-alicycle related to **110** is considered to be an intermediate that decomposes to a 1,3-dipolar species **111**—the active intermediate for the second coupling step; other evidence rules out epoxide **112** (X=O) as an intermediate.

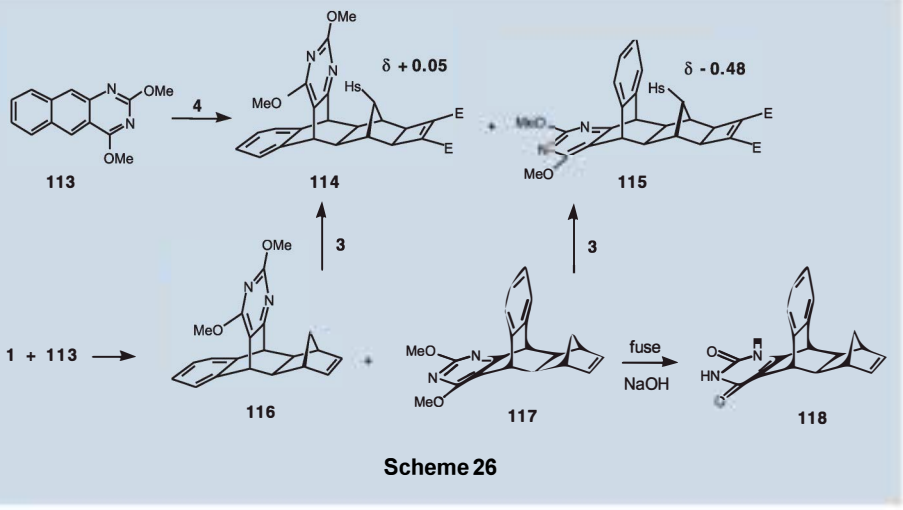


Scheme 25

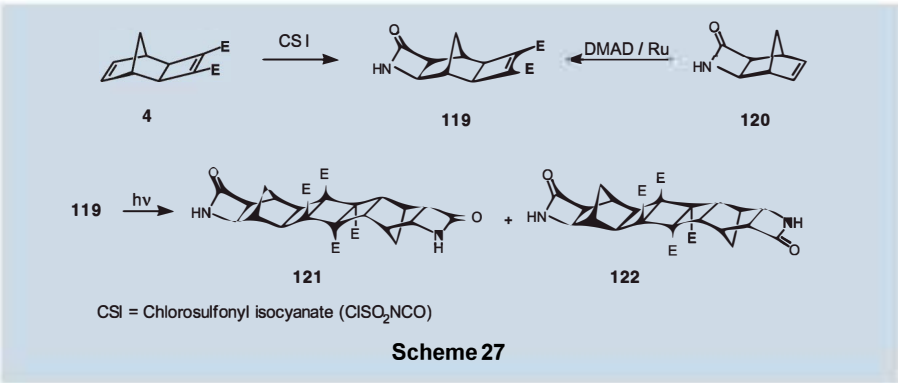
3.2.4. 1,3-Diazaanthracenes: Uracil Delivery Agents

The annellation of the pyrimidine ring onto alicyclic alkenes has been achieved using Diels-Alder chemistry. 2,4-Dimethoxy-1,3-diazaanthracene (DDA) (**113**) reacts with Smith's diene (**4**) under forcing thermal conditions (sealed tube at 180 °C) to form a mixture of stereoisomeric adducts **114** and **115** which can be separated by fractional crystallization (**Scheme 26**).[37] The stereochemical assignments are made on the basis of ^{1}H NMR chemical shift data where the benzenoid ring is more shielding than the pyrimidine ring, a fact reflected in the chemical shift of the proximate methylene bridge proton (Hs), which occurs at δ -0.48 and +0.05, respectively.

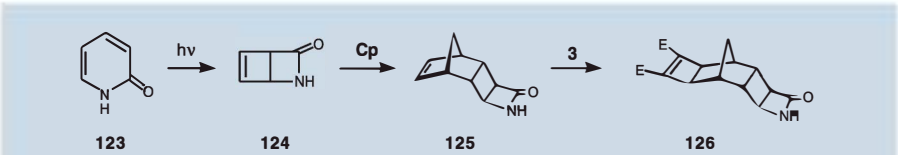
An alternative route to adducts **114** and **115** is the synthetically preferred method and involves cycloaddition of DDA (**113**) with norbornadiene **1** to produce a 2:3 ratio of adducts **116** and **117**, and in this respect follows on our earlier work[38] with anthracene (**Scheme 26**). These adducts, which can be separated by HPLC, are assigned their structures using the previously described shielding criteria. Ruthenium-catalyzed cycloaddition of DMAD onto **116** and **117** yields the corresponding cyclobutenes **114** and **115**. Conversion of this type of product to the uracil derivative is illustrated by the hydrolysis (NaOH fusion) of **117** to uracil **118**.



Scheme 26



Scheme 27



Scheme 28

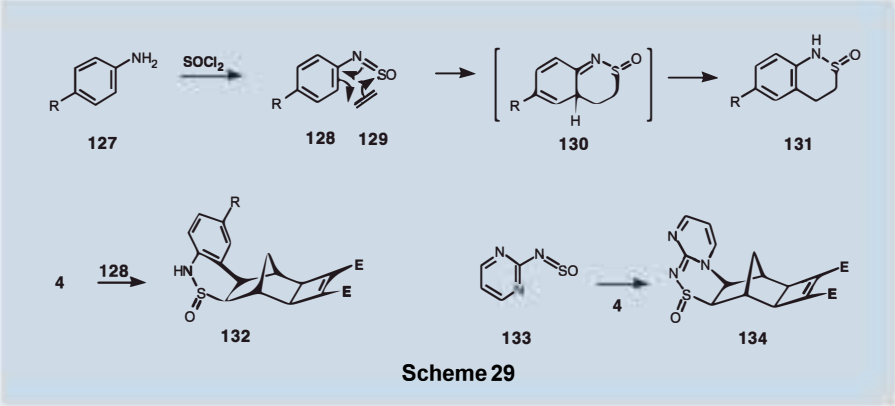
3.2.5. β-Lactam Products

β-Lactams fused to Smith's diene are available by chlorosulfonyl isocyanate cycloaddition.[39-42] Addition occurs site selectively at the norbornene π-bond to furnish the azahomo[4]ladderane **119** (also available by ruthenium-catalyzed cycloaddition of DMAD onto the lactam **120**). Photodimerization of **119** produced the bislactams **121** and **122** (**Scheme 27**). These diastereomers open the way for the production of space-separated β-amino acids by ring-opening of the β-lactam ring. Isomer **121** would produce a spacer where the peptides formed from the amino acids at its ends would extend in the same direction (i.e., syn), whereas from isomer **122** they would extend in opposite directions (i.e., anti) with respect to the vertical planes of the spacers.

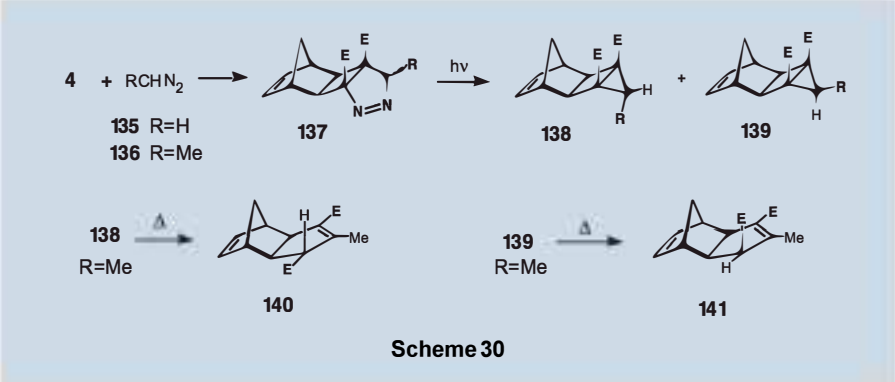
Formal fusion of a β-lactam component into the norbornene end of Smith's diene can also be achieved indirectly (**Scheme 28**). In this method, **124**, a photoisomer of **123**, is reacted with cyclopentadiene to yield exclusively **125**. Catalyzed addition of DMAD to the norbornene π-bond of **125** introduces the cyclobutene-1,2-diester component and completes production of the dihydro-Smith product **126**.[43]

3.2.6. Arylsulfinylamine Cycloadditions

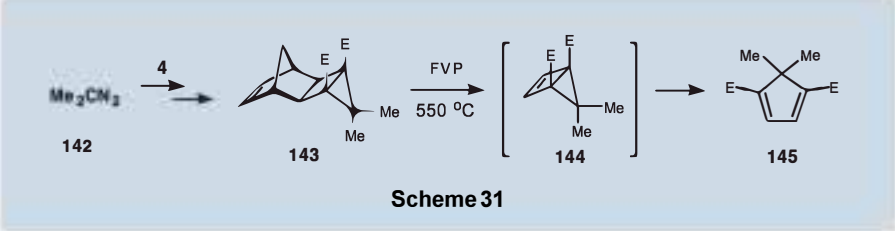
Arylsulfinylamines **128**, readily prepared by treatment of arylamines **127** with thionyl chloride, act as heterodienes with ring-strained dienophiles to form fused products **131** (**Scheme 29**).[44,45] We have exploited this characteristic to attach functionality to Smith's diene. Reaction of *N*-sulfinylanilines **128** with Smith's diene (**4**) occurred site selectively at the norbornene π-bond to produce the fused tetrahydro-1,2-azathianaphthalenes **132**. Extension of this procedure to *N*-sulfinylaminopyrimidine **133** provided access to the fused pyrimidine **134**.[46]



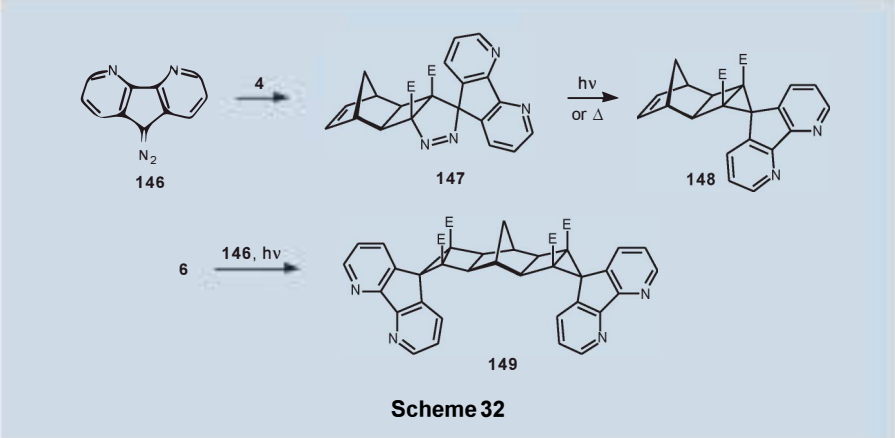
Scheme 29



Scheme 30



Scheme 31



Scheme 32

4. 1,3-Dipolar Cycloadditions

4.1. Diazoalkanes: Spiro-Fused Diazafluorene Ligands

Diazomethane **135** reacts rapidly with Smith's diene (**4**) to produce pyrazoline **137** (R = H) by exclusive reaction at the cyclobutene π-bond (**Scheme 30**); diazoethane **136** and 2-diazopropane **142** produce analogous products.[47] Photochemical ejection of dinitrogen yields the bicyclo[2.1.0] pentane derivatives **138**, **139**, and **143**, respectively. Since reaction occurs specifically at the cyclobutene π-bond, the opportunity to effect a retrodiene loss of cyclopentadiene becomes an option. However, it is again apparent that cyclopentadiene is a reluctant dienofuge since rearrangement of the strained bicyclo[2.1.0]pentane moiety occurs preferentially. In the case where diazoethane is involved, both cyclopropane stereoisomers **138** (R=Me) and **139** (R=Me) are available, allowing for the evaluation of the stereochemistry of the bicyclo[2.1.0]pentane rearrangement since **138** selectively forms **140** and **139** selectively forms **141**.

Flash vacuum pyrolysis of the dimethyldiazomethane adduct **143** caused fragmentation to cyclopentadiene and the substituted cyclopentadiene **145** (**Scheme 31**). In this example, no evidence for the intermediate bicyclopentene **144** was observed, and it might be that *direct* formation of the cyclopentadiene occurred as a result of the *cyclopropane* σ-bond participation in the fragmentation process.

Another ligand delivery reagent (see Section 3.1.6), this time for the introduction of the 1,8-diazafluorene ligand, has been developed using diazo chemistry (**Scheme 32**). Diazadiazofluorene[48] (DADAF) **146** is an active 1,3-dipolar reagent which reacted with Smith's diene (**4**) to produce the 1:1 cycloadduct **147** under the influence of heat (benzene at reflux) or high pressure (CH_2Cl_2, 14 kbar, room temperature). Ejection of dinitrogen thermally (toluene at reflux) or photochemically (350 nm) produced the spiro compound **148**. This opened the way for the preparation of molracs containing the 1,8-diazafluorene ligand.[23,49] In particular, the dual ligand **149** was produced in two steps from **6**.

4.2. Azides

Reaction of azides occurred preferentially at the norbornene π-center of Smith's diene to produce the corresponding triazoles **150** and subsequent photochemically induced loss of dinitrogen formed aziridines **151** (**Scheme 33**).[50] While there is evidence of dual adduct formation from continued reaction of monoadduct **150** with azides, no discrete products were isolated. With benzo-Smith's diene **152** as a substrate, reaction was achieved at the cyclobutene-1,2-diester π-bond to form

a triazoline adduct **153**, which was transformed to the aziridine **154** by UV irradiation.

4.3. Epoxycyclobutane-Alkene Cycloadditions

The cyclobutene-1,2-diester component of the 7,8-dihydro derivative of Smith's diene **5** can be epoxidized (MeLi, $^tBuO_2H$) to form epoxycyclobutane **155** (**Scheme 34**).[51] Heating **155** with norbornene **101** generates a single product **157** in a stereospecific cycloaddition involving ring-opening of the epoxide to the 1,3-dipolar intermediate **156**. Smith's diene forms a similar epoxide **158**, and it too undergoes similar cycloadditions.

This process can be employed as a coupling reaction for the production of large, rigid structures containing complex functionality (**Scheme 35**). This is illustrated using the methoxynaphthalene-functionalized epoxycyclobutane **160**, which is reacted with functionalized norbornenes **93**, **56**, and **148** to produce polyalicyclic structures **161-163**, respectively, as examples of space-separated bichromophoric systems.

5. Summary of Cycloadditions in Flow Sheet Form

Flow Sheet 1: Reactions at the cyclobutene-1,2-diester π-bond of Smith's diene (**4**).

Flow Sheet 2: Reactions at the norbornene π-bond of Smith's diene (**4**).

6. Acknowledgements

In concluding, it would be remiss not to mention the sterling contributions made by our many co-workers during the course of our love affair with Smith's diene. Much of this occurred in the course of preparing other targets, and it is only when combined in an account of this sort that one appreciates the central role Smith's diene has played in much of our research.

We thank the Australian Research Council and University Grant Schemes (ANU, Bond, CQU) for their generous support over the years that has made much of this research possible.

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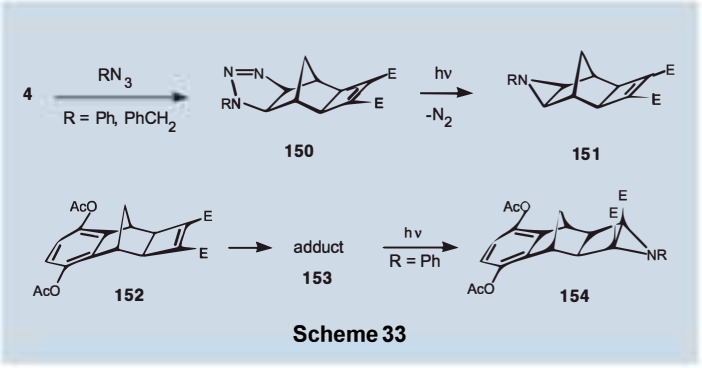
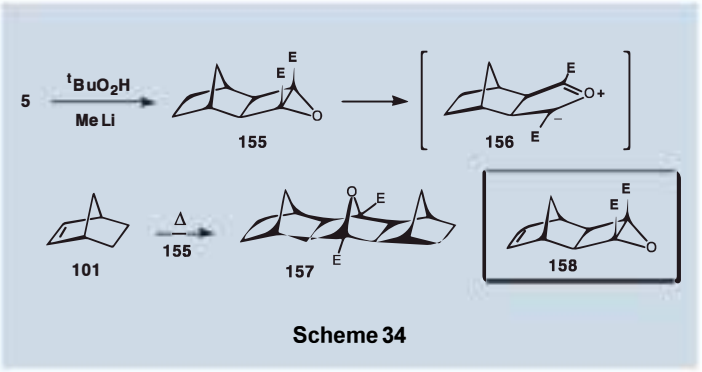
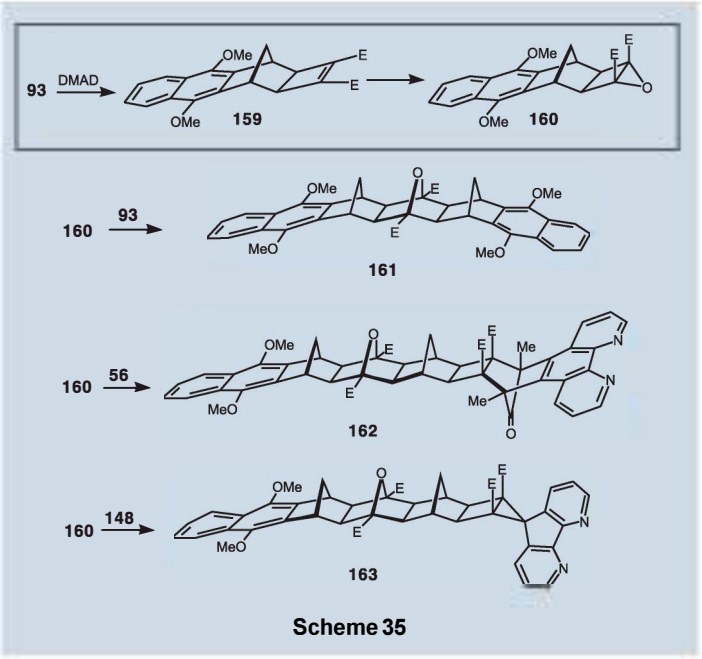


Scheme 33



Scheme 34



Scheme 35

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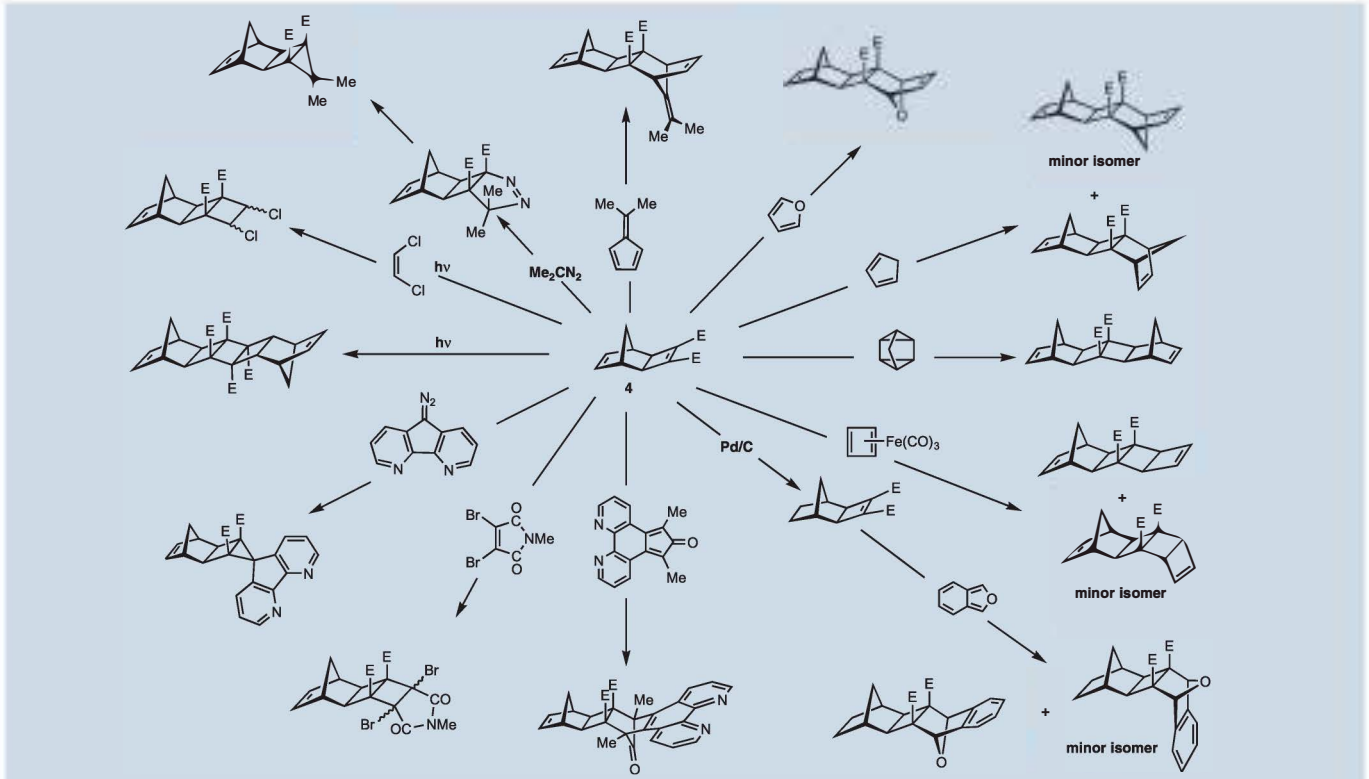
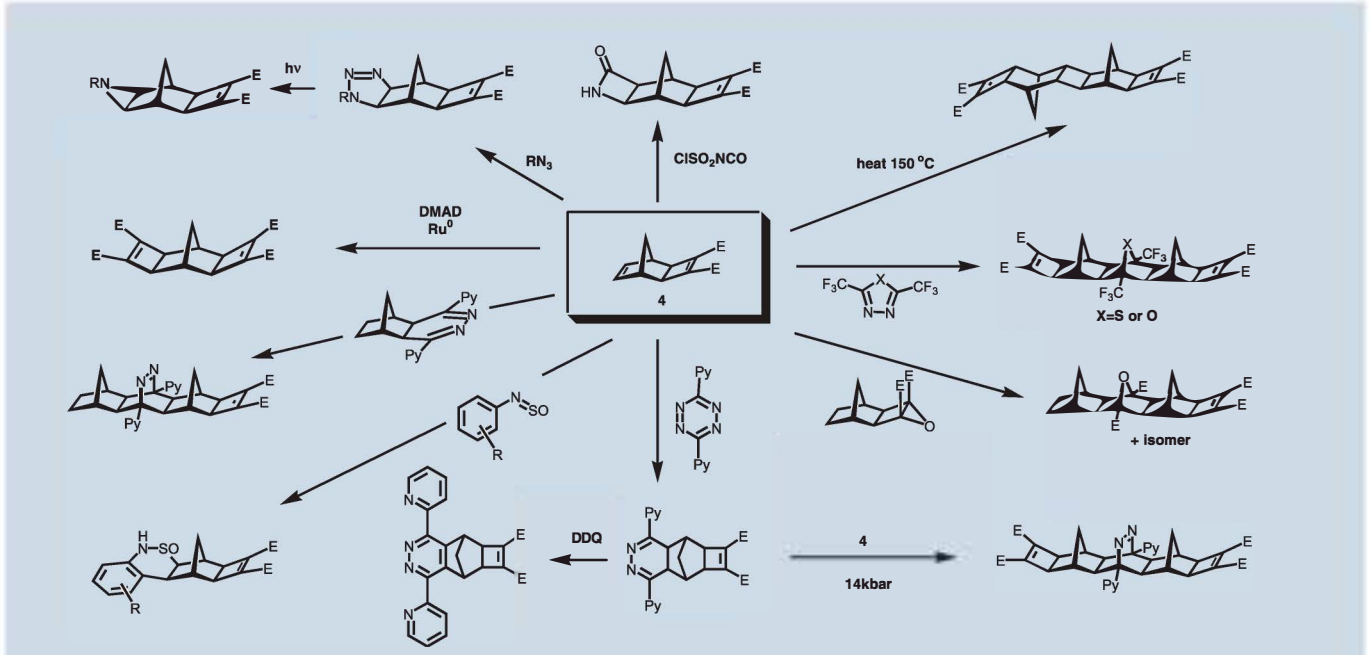


Sheet 1: Reactions at the cyclobutene-1,2-diester π-bond of Smith's diene (**4**).



Sheet 2: Reactions at the norbornene π-bond of Smith's diene (**4**).

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Ronald (Ron) N. Warrener studied chemistry at Sydney University (B.Sc., M.Sc.) and the University of New South Wales (Ph.D.). This was followed by a Postdoctoral Fellowship at Princeton (with E.C. Taylor), and academic appointments at the Australian National University (Professor and Head of Department 1979-1988), Bond University (Dean of Science and Technology 1988-1991), and Central Queensland University (Director, Centre for Molecular Architecture, 1992 to present). He has published extensively (200+ papers) in synthetic organic chemistry with special interest in photochemistry and cycloaddition chemistry. Also a noted researcher in Forensic Science, he directed centers in this specialty at ANU and Bond Universities. Since 1992 he has held an ARC Senior Research Fellowship, during which time he worked full-time in research and set up the CMA at Central Queensland University (details available at http://www.cqu.edu.au/research/cma/home.html). In 1996 he was awarded the RACI Medal in Organic Chemistry.

Douglas N. Butler was born in Melbourne, Australia in 1936 and received his primary and secondary schooling in New South Wales. He completed his B.Sc. (Hons.) degree at the University of New South Wales in 1958 and went on to the Victoria University of Manchester where his studies on the fungal pigment phomazarin led to the award of a Ph.D. in 1963 under the supervision of (the late) Professor Arthur J. Birch. After Postdoctoral positions at Harvard, Purdue and Toronto, he was appointed to the Chemistry Faculty at York University, Toronto where he stayed for 28 years.

He has recently joined his long-standing friend and collaborator, Ron Warrener, at the Centre for Molecular Architecture, Central Queensland University, Rockhampton as Deputy Director of that Centre.

His research interests have been in the areas of design and synthesis of systems bearing intramolecular proximity of functional groups, cycloadditions and 'molrac' constructions for the placement of desired functionalities bearing specific geometric and distance parameters.

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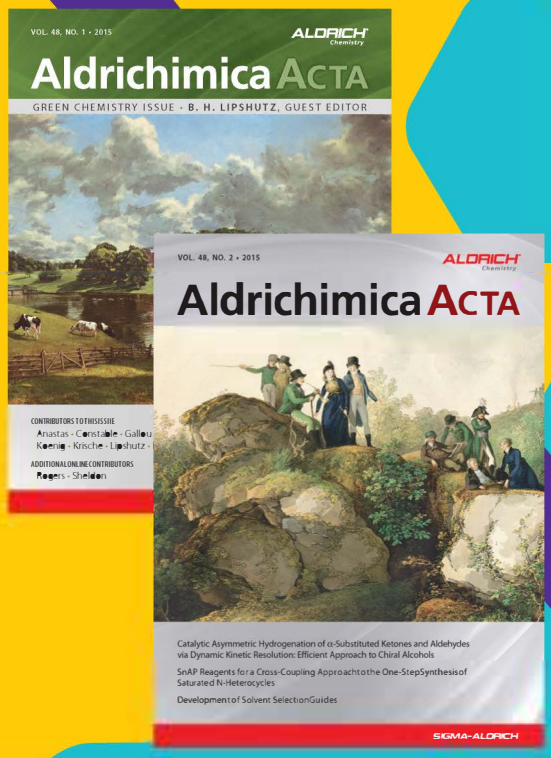

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