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Electrochemistry in Organic Synthesis

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About Our Cover:

This painting (oil on canvas, 17⅞ x 27⅜ in.) from the collection of The Saint Louis Art Museum is entitled *The Dovecote* and was painted in 1758 by the French artist Francois Boucher (1703-1770). Few artists were ever so completely in sympathy with the tastes and values of their patrons as Francois Boucher. A delightful landscape painted at the height of his career, this painting is just the sort of confection that made him the favorite of Louis XIV's mistress Madame de Pompadour and her fashionable circle. The dovecote tower and other elements of the composition are based perhaps on sketches made from life, but this is no record of a particular place. Instead, Boucher has conjured up an enchanted garden as charming as it is unreal. The idealized conception of country life expressed in this painting was shared by Boucher's patrons, who, to amuse themselves, would sometimes don rustic costumes and play at milking cows or tending sheep.

Color is a key ingredient in creating the painting's delectable illusion, from the deep blue-green foliage against the frosted blue sky to the touches of pale pink and bright coral. Boucher's masterful manipulation of light and shadow and the undulating curves that animate the sky, the trees, and even the rickety bridge bespeak the plausibility of this impossible world, so fluently rendered in short strokes of thickly applied paint.

Enthusiasm for charming yet highly artificial works like this one was not universal among Boucher's contemporaries. To the philosophers of the Enlightenment, such bonbons were symptomatic of the moral and intellectual flabbiness of the French ruling class.

Lab Notes

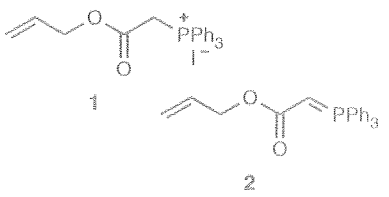
Do you have an innovative shortcut or unique laboratory hint you'd like to share with your fellow chemists? If so, please send it to: Aldrich (attn: Lab Notes, Aldrichimica Acta).

For submitting your idea, you will receive a complimentary, laminated periodic table poster (Cat. No. Z15,000-2, $9.90 value). If we publish your *Lab Note*, you will also receive **The Detective's Eye: Investigating the Old Masters** (see previous page). We reserve the right to retain all entries for consideration for future publication.

"Please Bother Us."

by

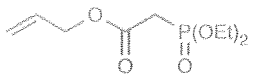
Jai Nagarkatti, President



Dr. David Dean of Smith Kline Beecham Pharmaceuticals (U.K.) suggested that we offer the phosphonium salt **1** and its ylide **2**. The allyl ester group of the α,β-unsaturated esters (resulting from the Wittig reaction of aldehydes and ketones with **2**) can be readily removed using standard palladium or rhodium chemistry.

Naturally, we added these products to our listings.

Vyplel, H. et al. *J. Med. Chem.* **1991**, *34*, 2759.



The phosphonoester analogs of Wittig reagents frequently expand the scope of Wittig reactions by offering different E/Z-selectivity and modified workup conditions (i.e., easier removal of by-products). Thus, we took Dr. Dean's suggestion one step further and have added allyldiethylphosphonoacetate as a new Aldrich product as well.

Hoffman, R.W. et al. *Liebigs Ann. Chem.* **1990**, 23.

Electrochemistry in Organic Synthesis

Albert J. Fry
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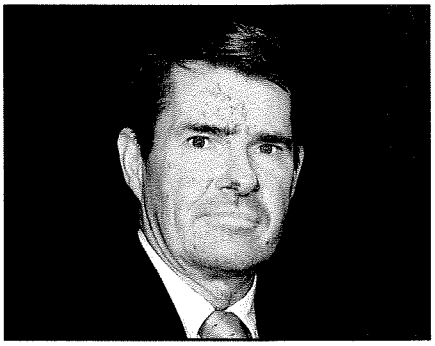
Wesleyan University
Middletown, Connecticut 06457

After many years as an exotic branch of organic chemistry, electrochemistry has become an important organic synthetic tool in recent years. This is primarily a result of advances made in the last decade or so, as well as increasing availability of electrochemical equipment. Many processes are now known which can be carried out more cleanly, quickly, cheaply, or in higher yield using electrochemistry than with other methods, and some reactions are known which can only be carried out electrochemically. There is a large organic electrochemical literature. For this review I have selected a number of examples from that literature to illustrate the kinds of reactions which can be carried out electrochemically. Unfortunately, many useful reactions could not be included because of space limitations. There are however a number of books and reviews on organic electrochemistry which can be consulted for further information.[1]

Electrochemistry deals with oxidation and reduction, depending on whether the reaction of interest takes place at the anode or the cathode of the cell, respectively. However, its scope is actually considerably broader: many reagents, including acids, bases, halogens, reactive metals and metal ions, etc., can themselves be made electrochemically for use *in situ*.[1] Electrochemical generation of reagents can be of considerable value when the reagent is expensive, hazardous or otherwise difficult to work with in large quantities, produces toxic by-products, or must be added to the medium at high dilution. One can, for example, easily produce reagents at steady-state concentrations as low as $10^{-5}M$ or less, simply by controlling the amount of current passing through the cell.[2] This review will primarily cover processes which occur by direct electrochemical reaction. There are a number of extensive reviews on processes in which a substance produced electrochemically is the actual reagent in the overall transformation.[1,3]

Electrochemical Reductive Cleavage of Single Bonds

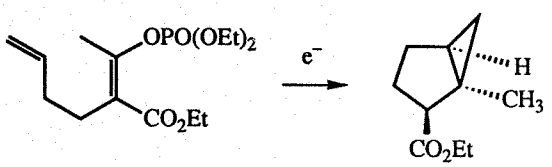
Probably the simplest electrochemical reaction is the cleavage of a carbon-heteroatom bond. Most studies have involved alkyl halides, but the reaction is more general (eq 1). Although radicals are short-lived intermediates in such reductions[4] and radical derived products are occasionally isolated (eq 2),[5] in most cases the radical is usually immediately reduced to a carbanion. Equation 1 therefore constitutes a mild, neutral, and very general method for generating carbanions. The latter can react intramolecularly to form cyclized products (eqs 3-5)[6-9] or can be trapped by added electrophiles, including CO_2, aldehydes, ketones, acid anhydrides, acid chlorides, imines, trialkylsilyl and stannyl halides, and activated alkenes (eq 6).[10] Reduction in the presence of D_2O or T_2O allows regioselective



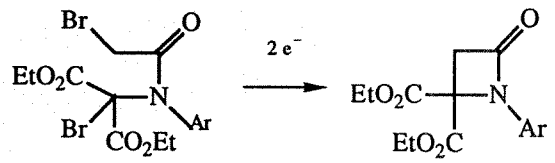
$$R\text{-}X + 2\,e^- \longrightarrow R^- + X^-$$

$$X = Cl, Br, I, OSO_2R', SO_2R', SR', NR_3, \text{ etc.}$$

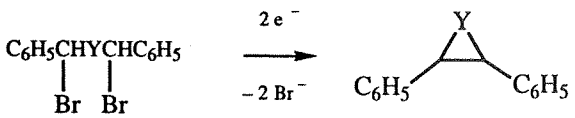
(eq 1)



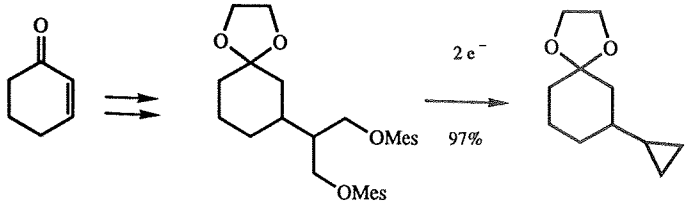
(eq 2)



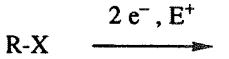
(eq 3)



(eq 4)

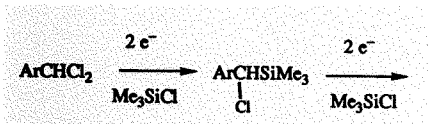


(eq 5)

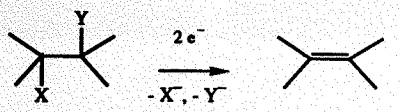


(eq 6)

introduction of deuterium or tritium.[11] Metal ion catalysis frequently improves the efficiency of electrophilic trapping.[12] Stepwise introduction of trialkylsilyl groups can be effected by reduction of a geminal dihalide in the presence of a silyl halide (eq 7).[13] Alkenes can be prepared by reductive elimination of vicinal dihalides and other β-substituted alkyl halides (eq 8). The reaction has been used for synthesis of strained alkenes (eqs 9-10)[14,15] and in schemes for protection and deprotection

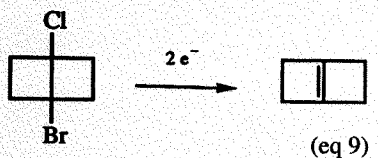


(eq 7)

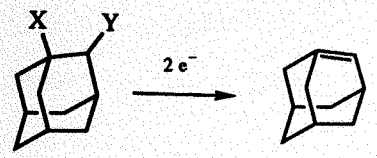


X = Hal ; Y = Hal, OR, NR_2, SR

(eq 8)



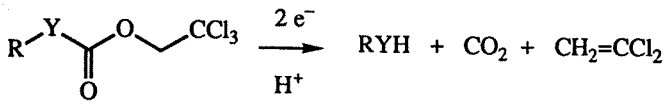
(eq 9)



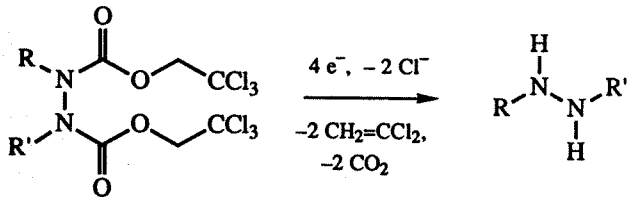
X = Y = Br or I

(eq 10)

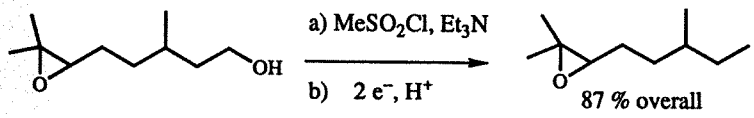
of alcohols, thiols, amines, carboxylic acids, hydrazines, and alkenes (eqs 11-12).[16-18] In a protic medium the carbanion is protonated. One can take advantage of the high selectivity associated with such cleavages to remove functional groups in the presence of sensitive functionality (eqs 13-14).[19,20] Fry and coworkers carried out an extensive study of the electrochemical reduction of α,α'-dibromoketones (**1**) in protic media.[21] The initial intermediate is a 2-oxyallyl bromide, which immediately ionizes and is protonated to afford a hydroxylallyl cation (**2**) which then reacts with a nucleophile in the medium providing an α-substituted ketone (**Scheme 1**). Reduction in the absence of nucleophiles affords an α-methylene ketone.[22] Reduction of α,α-dibromoketones, on the other hand, affords products which appear to derive from a zwitterion (**3**) or its diradical equivalent (**Scheme 2**).[23] Reduction of α,ω-dihalides in the presence of activated alkenes yields cyclized materials (eq 15).[24]



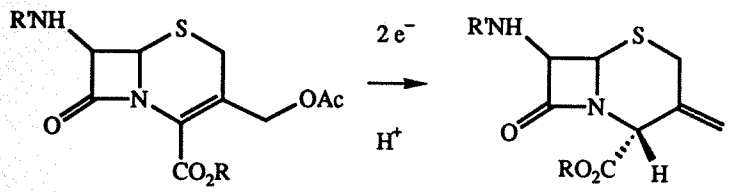
R = an alkyl or acyl group; Y = O, S, or NR' (eq 11)



(eq 12)

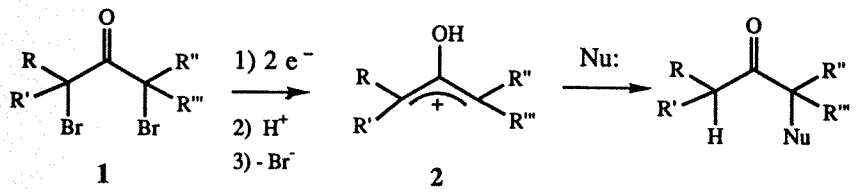


(eq 13)



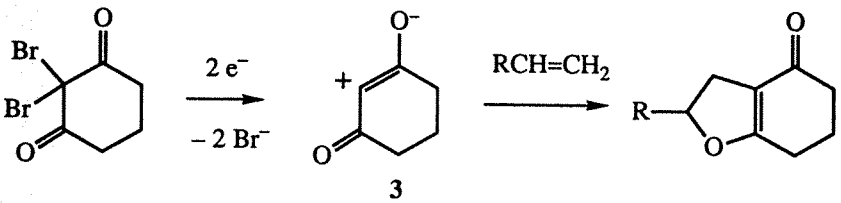
(eq 14)

Scheme 1



1 **2**

Scheme 2



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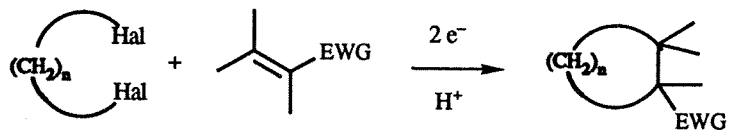
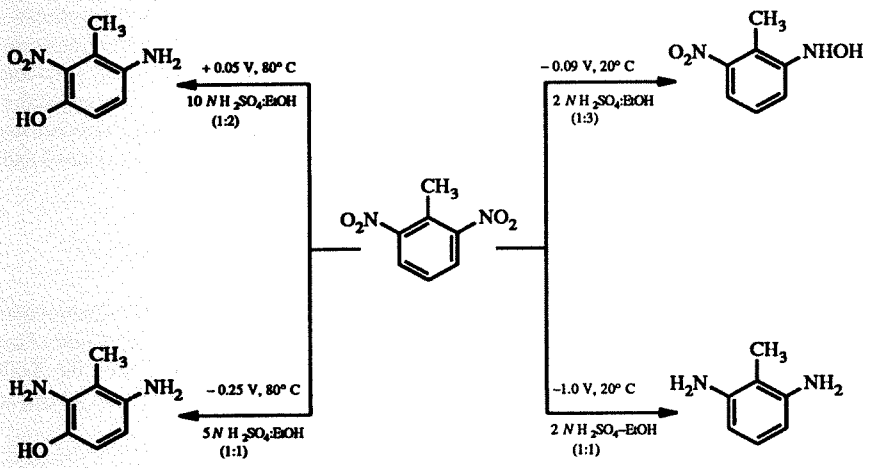
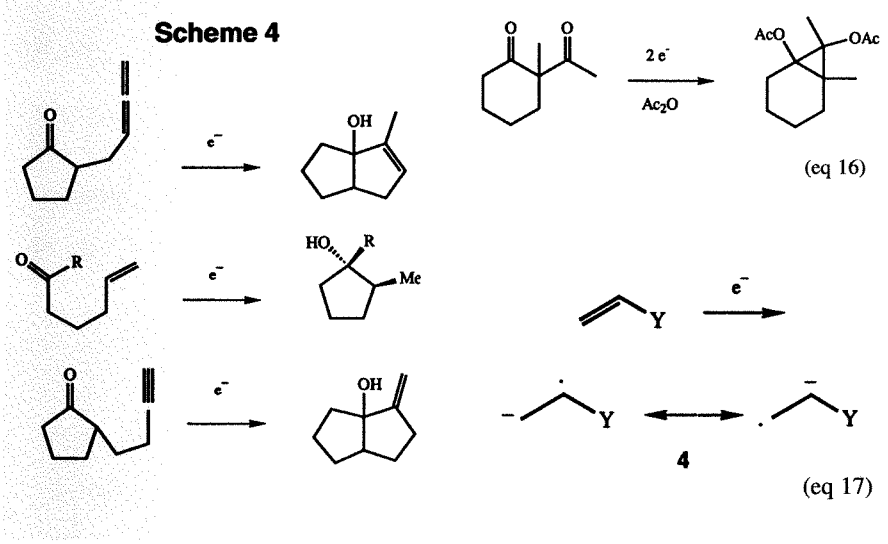


(eq 15)

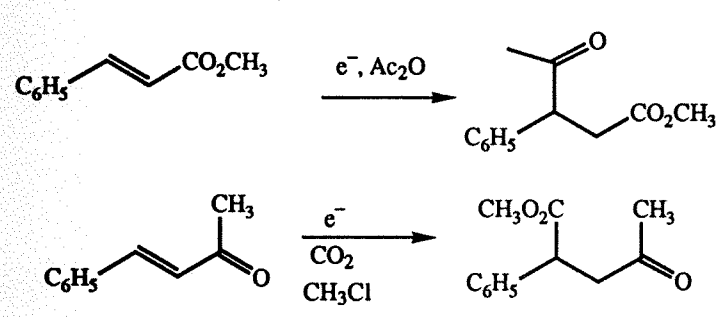
Scheme 3



Scheme 4



Scheme 5



Electrochemical Modification of Functional Groups

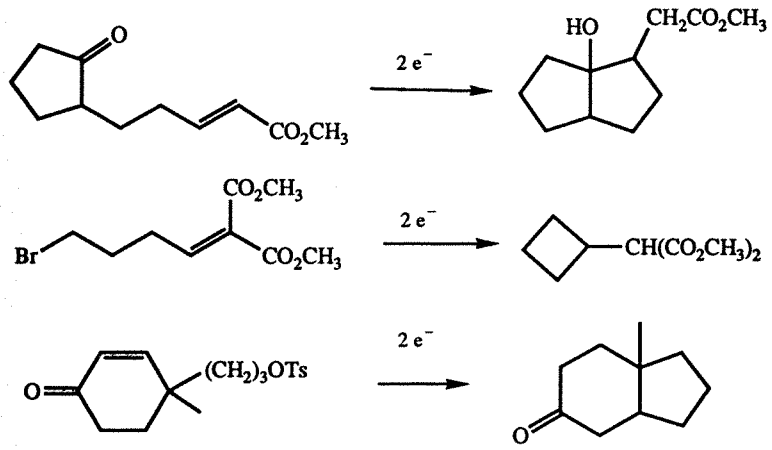
A variety of organic functional groups, including carbonyl, thiocarbonyl, imine, azo, nitroso, nitro, and diazonium, can be reduced electrochemically.[1,25] Furthermore a given functional group can frequently be converted electrochemically into several different products depending upon conditions. For example, a nitrobenzene may be converted into an aniline, phenylhydroxylamine, *p*-aminophenol, azoxybenzene, azobenzene, hydrazobenzene, or benzidine by proper control of the reduction potential, pH and temperature (**Scheme 3**).[26]

One does have to keep a sense of perspective here. Electrochemistry may not be the method of choice when a chemical reductant is already available to effect a desired conversion. For example, it would be absurd to use electrochemistry to reduce an aldehyde or ketone to the corresponding alcohol when the same conversion can be done easily using a metal hydride. Similarly, there are a number of good chemical and catalytic methods for converting nitro compounds into amines. Electrochemistry can be competitive when high selectivity is needed or when the necessary reagent is expensive or less effective. For example, electrochemical reduction of nitro compounds to hydroxylamines can be carried out easily in a simple apparatus,[1,25a] whereas catalytic reduction is prone to over-reduction, and chemical reduction to the hydroxylamine stage requires the expensive reagent SmI_2.[27a] (For those applications which do require SmI_2, it is much cheaper to prepare *in situ* electrochemically than to use the preformed material).[27b] Electrochemical reduction is also useful when one wishes to trap reactive intermediates: electrolytic reduction of carbonyl compounds in aprotic media affords ketyls, which can be trapped intramolecularly by nearby sites of unsaturation (**Scheme 4**).[28] Similarly, electrochemical reduction of 1,3-diketones in the presence of acetic anhydride affords 1,2-cyclopropanediol derivatives (eq 16).[29]

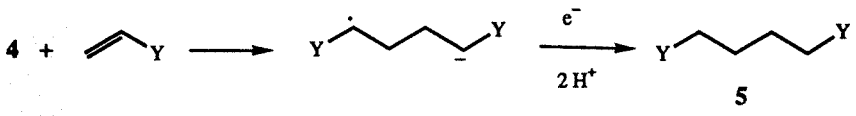
Electrochemical Reductions of Conjugated Systems

Electrochemical reduction of activated alkenes has proven to be a versatile synthetic process, particularly in non-aqueous media, where the initial intermediate is a radical anion (**4**) (eq 17), which carries negative charge at the β-carbon and can undergo reaction at that site with electrophiles (**Scheme 5**).[30] Little and Baizer, among others, have reported a number of intramolecular variants on this process (**Scheme 6**).[31-33] The propensity of species **4** to afford dimeric products by Michael-type attack upon the starting material to give so-called "hydrodimers" (**5**)

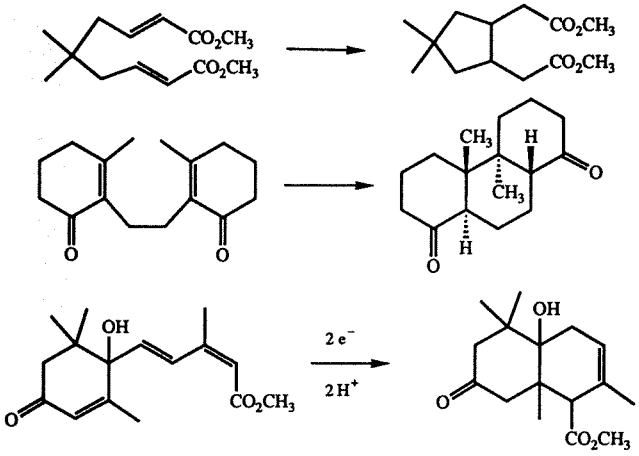
Scheme 6



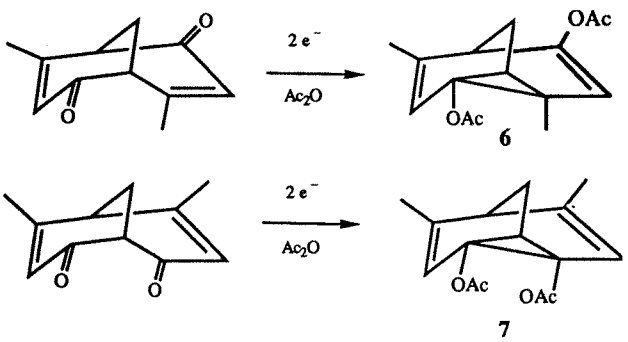
Scheme 7



Scheme 8



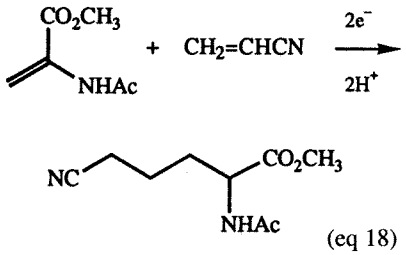
Scheme 9



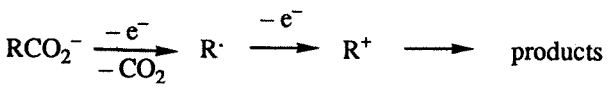
(**Scheme 7**) is of considerable interest.[1,34] The reaction can be carried out intramolecularly (**Scheme 8**) and between unlike components to afford mixed hydrodimers; one such reaction is the key step in a short synthesis of lysine (eq 18).[35] Although hydrodimerization usually occurs "tail-to-tail' so as to connect the two β-carbons, head-to-tail and head-to-head dimers have occasionally been isolated, as in the synthesis of the barbaralanes **6** and **7** (**Scheme 9**).[36]

Electrochemical Oxidation of Carboxylic Acids

One of the oldest reactions of organic chemistry is the electrochemical oxidation of carboxylates to afford dimers, i.e., the Kolbe reaction (eq 19). Most functional groups are

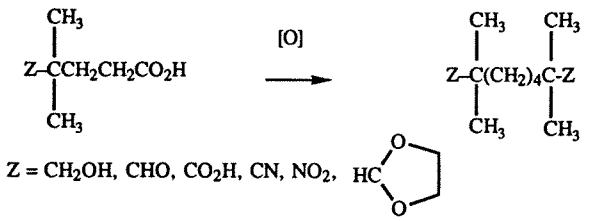


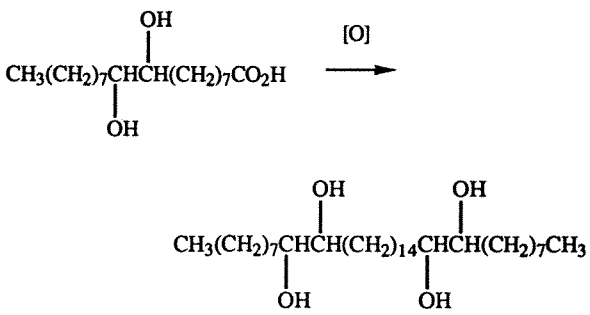
(eq 18)



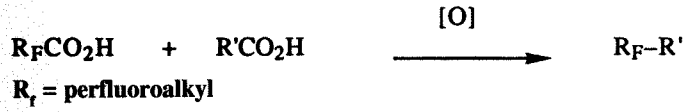
(eq 19)

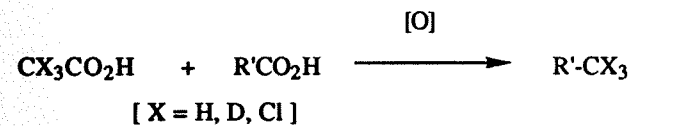
Scheme 10

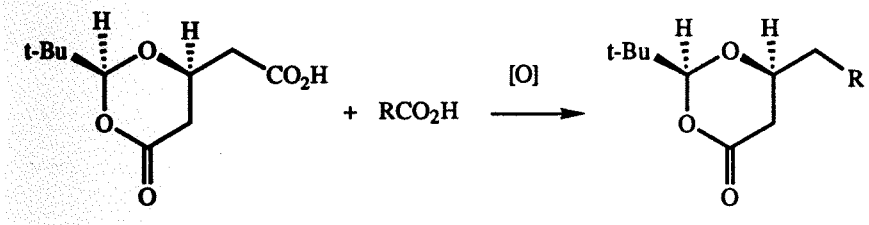




Scheme 11

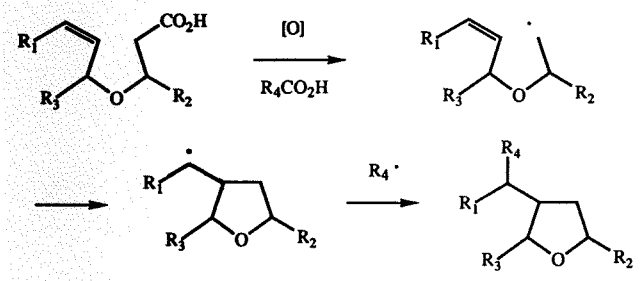




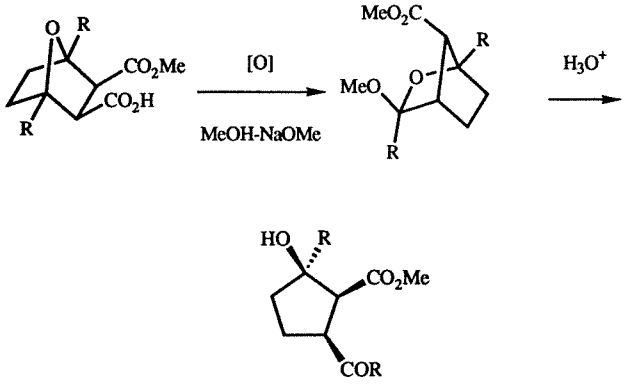


stable under Kolbe conditions[37] (**Scheme 10**) and mixed Kolbe reactions can be carried out between two carboxylic acids (**Scheme 11**).[38] A statistical mixture of all possible dimers is produced, hence such "crossed Kolbe" reactions are most useful where one of the components is cheaper than the other. Schäfer has reported crossed Kolbe reactions in which the radical intermediate from anodic oxidation of an unsaturated acid cyclizes before coupling (**Scheme 12**) and has used this sequence to synthesize complex tetrahydrofurans and pyrrolidines.[39] Under certain experimental conditions (high applied voltage, carbon anode) and especially when the intermediate radical carries one or more electron-supplying groups, further oxidation to a carbocation takes place. A variety of reactions depending upon this feature have been reported (**Scheme 13**).[40] Oxanorbornane half-acid esters undergo stereoselective conversion to highly substituted cyclopentane derivatives (**Scheme 14**).[41] Vicinal dicarboxylic acids can be anodically bis-decarboxylated to alkenes (**Scheme 15**).[42b] Bloomfield has reported especially efficacious conditions for anodic bis-decarboxylation.[42b]

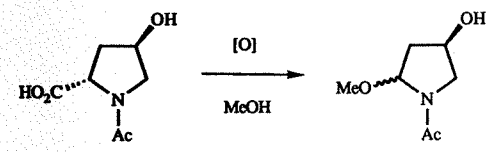
Scheme 12

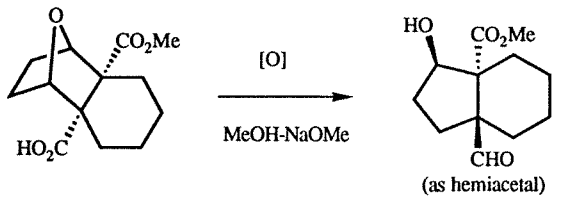


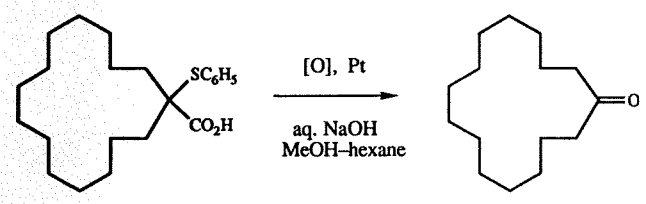
Scheme 14

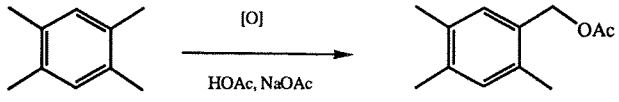


Scheme 13







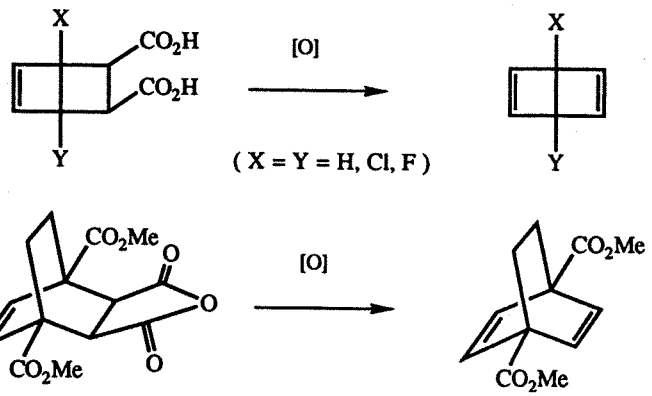


(eq 20)

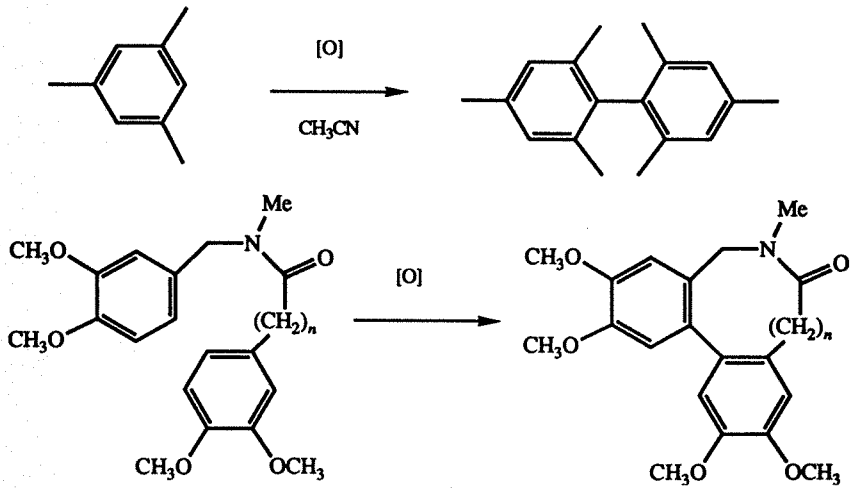
Electrochemical Oxidation of Aromatic Compounds

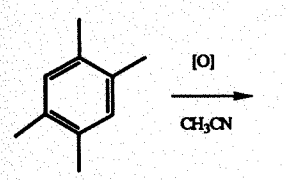
Aromatic hydrocarbons, phenol ethers, and aromatic amines undergo a diverse range of reactions under acidic conditions, including side-chain substitution (eq 20),[43] ring-to-ring coupling (**Scheme 16**),[44] and side chain-to-ring coupling (eq 21).[45] Which path a given substrate takes depends upon its structure and the experimental conditions.[1a] Oxidation of phenols affords species such as **8** which undergo nucleophilic attack at the position *para* to the phenol oxygen atom (**Scheme 17**).[46] Yamamura has applied this reaction in elegant fashion to the formation of polycyclic intermediates for natural product synthesis (**Scheme 18**).[47] Moeller has recently studied an analogous anodic reaction of enol ethers, in which a cationic intermediate cyclizes intramolecularly onto a nucleophilic alkene moiety (eq 22).[48] Anodic oxidation of hydroquinone mono and dialkyl ethers in alkaline methanol affords quinone mono- and bis- ketals, respectively (**Scheme 17** and eq 23).[46,49] Swenton has developed a large number of useful applications based upon this reaction, including preparation of a number of key intermediates in natural product synthesis.[50] Pirrung has recently shown that species **9** are converted photochemically to substituted cyclopentenones (**Scheme 19**).[51]

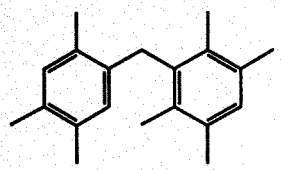
Scheme 15



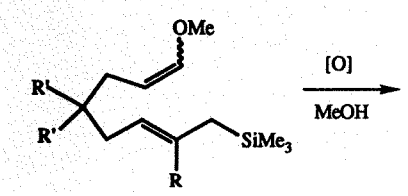
Scheme 16

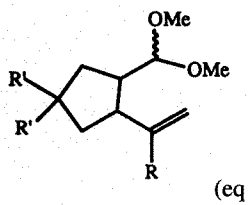






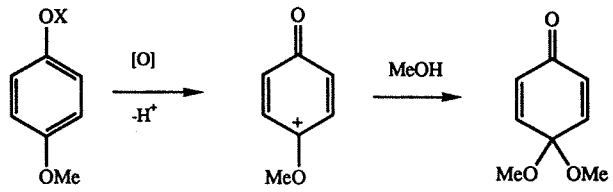
(eq 21)





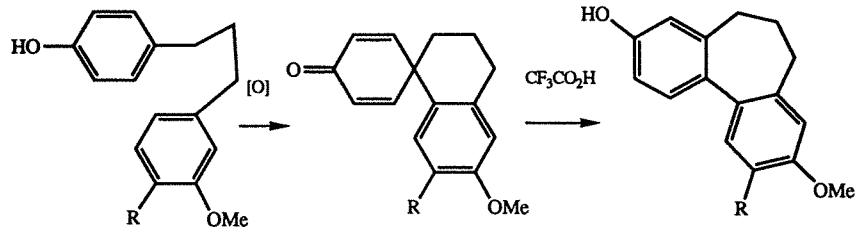
(eq 22)

Scheme 17

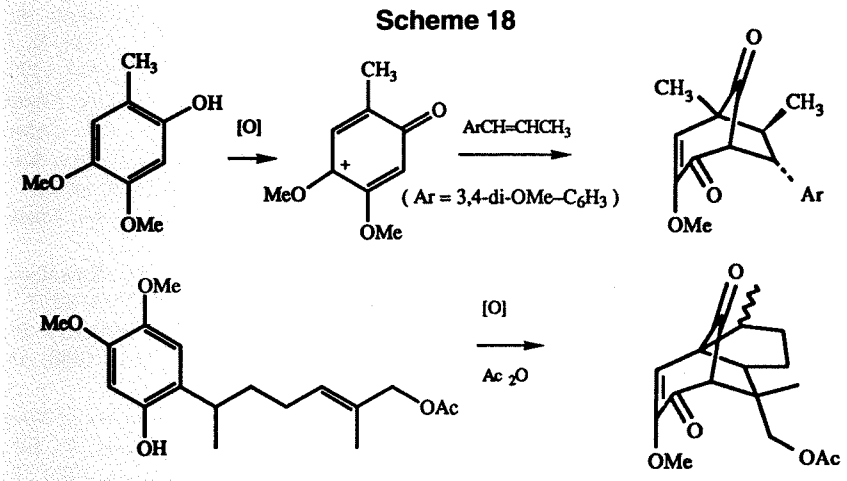


8

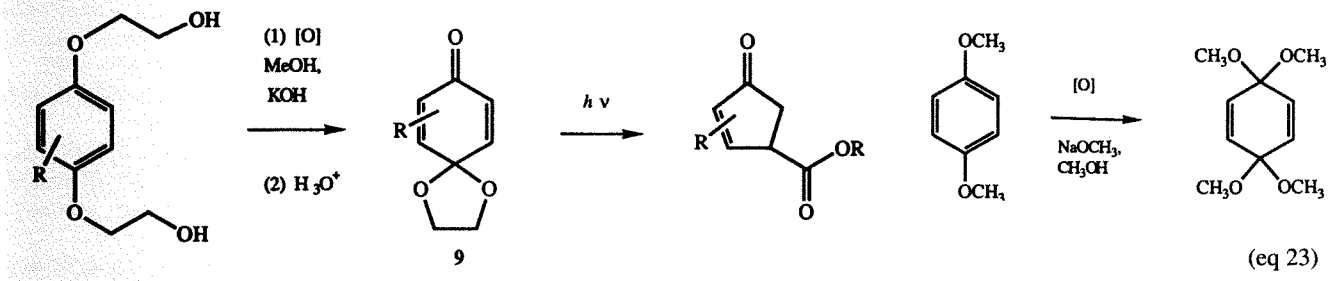
X = H, Me_3Si, *t*-$BuMe_2Si$, $MeOCH_2$



Scheme 18

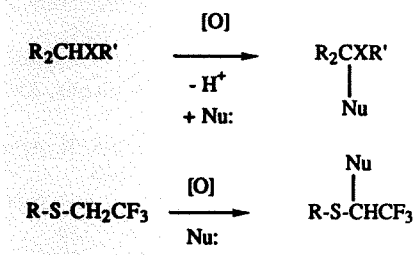


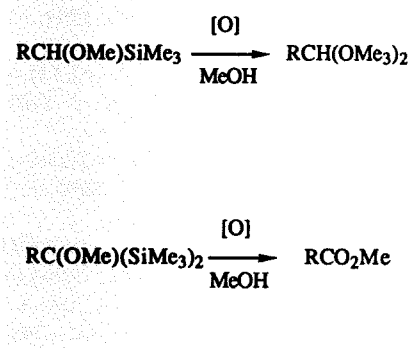
Scheme 19



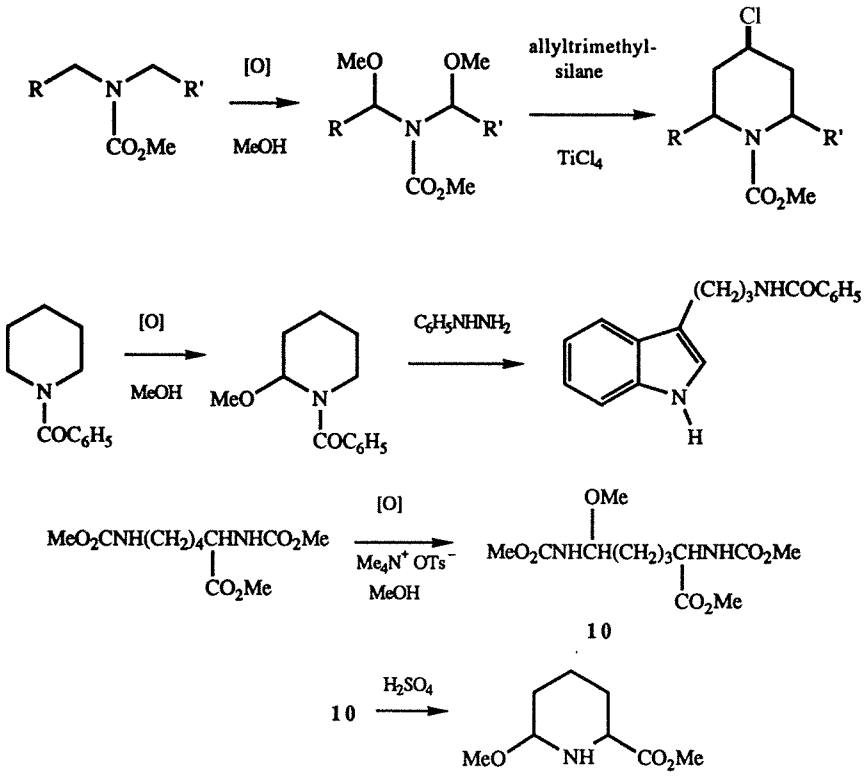
(eq 23)

Scheme 20





Scheme 21



Functionalization Alpha to Heteroatoms

A new, important, and very general anodic process has been discovered in recent years in the electrochemical oxidation of nitrogen, sulfur, and oxygen compounds. This process, the so-called α-functionalization reaction (**Scheme 20**), has been intensively studied in a number of variations upon the process, including applications to the synthesis of heterocycles, e.g., a number of piperidine, pyrrolizidine, and indolizidine alkaloids (**Scheme 21**).[52a]

Experimental Aspects

Every synthetic organic laboratory should have electrochemical equipment. The equipment is simple, inexpensive and versatile, i.e., it can be used for a wide variety of electrolytic processes. One inhibiting factor

in the past was the availability of equipment. One had to obtain each component of the experiment from a separate source, and generally even had to have the cell constructed by a glassblower. [Imagine what organic synthesis would be like if we had to have our three-necked flasks made to order in the glassblower's shop!] Fortunately, these days the situation is much improved. There are companies which offer a wide variety of electrochemical supplies,[53] and one such company[54] sells a complete kit containing all of the components needed to carry out an electrolysis (power supply, cell, electrodes, and step-by-step directions). There is not sufficient space available in this review, nor is this the proper place, for a detailed discussion of experimental details. My advice is rather to first learn what electrochemistry can do for you— if after examining the examples and references in this article you want to try an electrolysis, there are a number of good references available which discuss the theory and experimental details and which are written with the organic chemist in mind.[1] Companies in the field are generally eager to offer advice.[53,54]

Scale and Scale Up

The largest single factor governing the scale on which one can carry out a given electrochemical process is the electrical resistance of the solvent system, because heating effects become serious in high-resistance solvents at high currents. Although solvents as nonpolar as tetrahydrofuran can be used for small scale work,[13] it is more common to use a fairly polar organic solvent or an aqueous-organic mixture. Kadish has tabulated the resistance of a variety of common organic solvents.[55]

In general, using a reasonably polar organic solvent system, it is not difficult to prepare up to 20 grams or so of a desired substance electrochemically. Larger amounts can be prepared with some modification of the experimental equipment used; frequently this will involve changing from batch to flow cell operation.[1a] Successful scaleup to greater than laboratory-scale quantities requires careful attention to experimental design, but there are no intrinsic barriers to large-scale electrolysis: commercial organic electrochemical syntheses producing more than 100,000lb/year are known.

Acknowledgements

The hospitality and helpfulness of the faculty and staff of the University of California at Santa Barbara, especially Professor R. Daniel Little, during a sabbatical leave from Wesleyan University during which this article was written, are gratefully acknowledged. The National Science Foundation and the State of Connecticut provided financial support for those aspects of the work discussed herein which were carried out at Wesleyan University.

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About the Author

Albert J. Fry was born in Philadelphia, Pennsylvania. He received the B.S. degree in chemistry from the University of Michigan in 1958 and the Ph.D. degree in organic chemistry from the University of Wisconsin in 1963 for work with Professor David Lemal on the synthesis of novel carbenes and carbene precursors. After a year of postdoctoral research in organic photochemistry with Professor George Hammond at the California Institute of Technology, he joined the faculty of Wesleyan University. He has been Professor of Chemistry since 1977 and has served several terms as departmental chairman during his tenure.

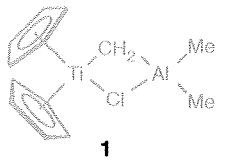
Professor Fry has carried on research in the mechanistic and synthetic aspects of organic electrochemistry for over 25 years. His interests include the mechanism, stereochemistry, and applications of the electrohemical reduction of alkyl halides, the electrochemical behavior of aromatic and non-benzenoid aromatic hydrocarbons, and the application of quantitative techniques of linear sweep and cyclic voltammetry to mechanistic analysis. Recently, he has begun a collaboration with Professors Susan Sobolov of Wesleyan University and James Fenton of the University of Connecticut, directed toward the use of enzyme-modified electrodes in large scale synthesis.

Prof. Fry is the author of *Synthetic Organic Electrochemistry*, 2nd ed. (Wiley, 1989) and the co-editor of *Topics in Organic Electrochemistry* (Plenum, 1986) with Dr. Wayne E. Britton, a former student. He has had a long-time interest in encouraging organic chemists to explore the use of electrochemistry in synthesis, and to that end started The Electrochemicals Company to supply electrochemical equipment, instruction, and advice in this exciting new area.

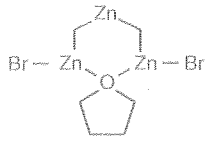
Methylenation Reagents

The conversion of a carbonyl group into an exocyclic vinyl group (methylenation) is an important synthetic transformation. Thus, methylenation reagents are valuable synthetic tools for the organic chemist and biochemist. Through judicious selection of the precise reagent and reaction conditions, high selectivities and yields can be achieved on a wide variety of substrates.

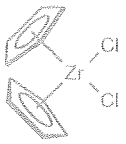
The Wittig reaction is a time-honored process for preparing terminal alkenes from simple ketones and aldehydes,[1-5] and we list a variety of reagents (phosphoranes, phosphonates, phosphonium salts, and salts admixed with a strong base) for this method. However, the Wittig reaction is limited to aldehydes and ketones with minimal steric hindrance that do not readily enolize.[1,3,6] The following newer methylenation reagents are offered as an alternative for such substrates.



1
Tebbe



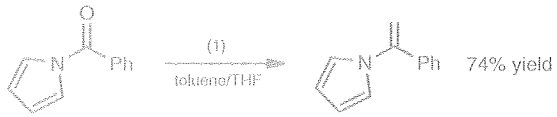
2
Nysted



3
Zirconocene Dichloride

The Tebbe Reaction

The "transition metal ylide" (**1**), known as the Tebbe reagent, readily methylenates ketones,[6a] aldehydes,[7] esters,[8] lactones,[8] and amides[9] without the limitations imposed by base-sensitive functionalities or sterically-hindered substrates. This example from the literature illustrates the utility and efficiency of this reagent.

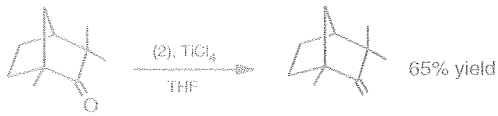


General Procedure[10]

To the N-acyl heterocycle in toluene/THF at 0°C is added dropwise a 0.5M toluene solution of the Tebbe Reagent (two-fold excess). After stirring at room temperature, the reaction is quenched at 0°C with methanol. When gas evolution has ceased, the mixture is diluted with ether, dried, filtered, and the crude product isolated by solvent removal.

The Nysted Reaction

The Nysted reagent (**2**) has been used in the conversion of keto-steroids to the corresponding methylene derivatives.[11] For sterically hindered ketones where Wittig methylenation fails and use of the Tebbe reagent gives very low yields, the Nysted reagent offers another possible route to the desired alkene.

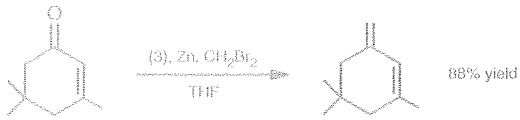


General Procedure[12]

A nitrogen-purged round-bottomed flask equipped with a stirrer, thermometer, condenser, and addition funnel is charged with a 30% excess of the Nysted reagent and cooled to -78°C. The desired ketone is added, followed by an equimolar amount of $TiCl_4$ while maintaining the temperature below -50°C. After warming to 25°C, the mixture is refluxed for 24 hours. The mixture is cooled, quenched with water, and the product isolated by ether extraction.

Zirconium-Promoted Methylenation

Recently, a zirconocene dichloride (**3**) promoted methylenation procedure has been found useful for cases when the more Lewis acidic titanium-based reagents give poor results.[13] Using **3** with dibromomethane and zinc allows the rapid methylenation of aldehydes, ketones and enones at room temperature in high yields.



General Procedure[13]

A nitrogen-flushed flask is charged with zinc, zirconocene dichloride, ketone, THF and dibromomethane. After stirring for 3 hours the mixture is quenched with water. The product is isolated by extraction.

References:

(1) Maercker, A. *Org. React.* **1965**, *14*, 270. (2) House, H.O. *Modern Synthetic Reactions*; Benjamin: Menlo Park, CA, 1972, pp 709-862. (3) *Organophosphorous Reagents in Organic Synthesis*; Cadogan, J.I.G., Ed.; Academic: New York, 1979. (4) Bestman, H.J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 65. (5) Kulkarni, Y.S. *Aldrichim. Acta* **1990**, *23*, 39. (6)a) Pine, S.H. et al. *Synthesis* **1991**, *2*, 165. b) Sowerby, R.L. et al. *J. Am. Chem. Soc.* **1972**, *94*, 4558. c) Fieser, M.; Fieser, L.F. *Reagents for Organic Synthesis*; Wiley: New York, 1975; Vol. 5, pp 458,527. d) McMurry, J.E. et al. *Tetrahedron Lett.* **1980**, *21*, 2477. e) Boeckman, R.K., Jr. et al. *ibid.* **1973**, *36*, 3497. (7) Tebbe, F.N. et al. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (8) Pine, S.H. et al. *ibid.* **1980**, *102*, 3270. (9) Pine, S.H. et al. *J. Org. Chem.* **1985**, *50*, 1212. (10) Wattanasin, S.; Kathawala, F.G. *Synth. Commun.* **1989**, *19*, 2659. (11)a) Nysted, L.N. US Patent 3 865 848, 1975; *Chem. Abstr.* **1975**, *83*, 10406q. b) Nysted, L.N. US Patent 3 960 904, 1976; *Chem. Abstr.* **1976**, *85*, 94618n. (12) Unpublished results, Aldrich Chemical Company, Inc. (13) Tour, J.M. et al. *Tetrahedron Lett.* **1989**, *30*, 3927.

The Aldrich Library of FT-NMR Spectra

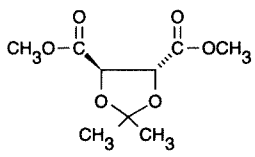
A

Aldrich 35,906-8 *CAS [37031-29-1]*

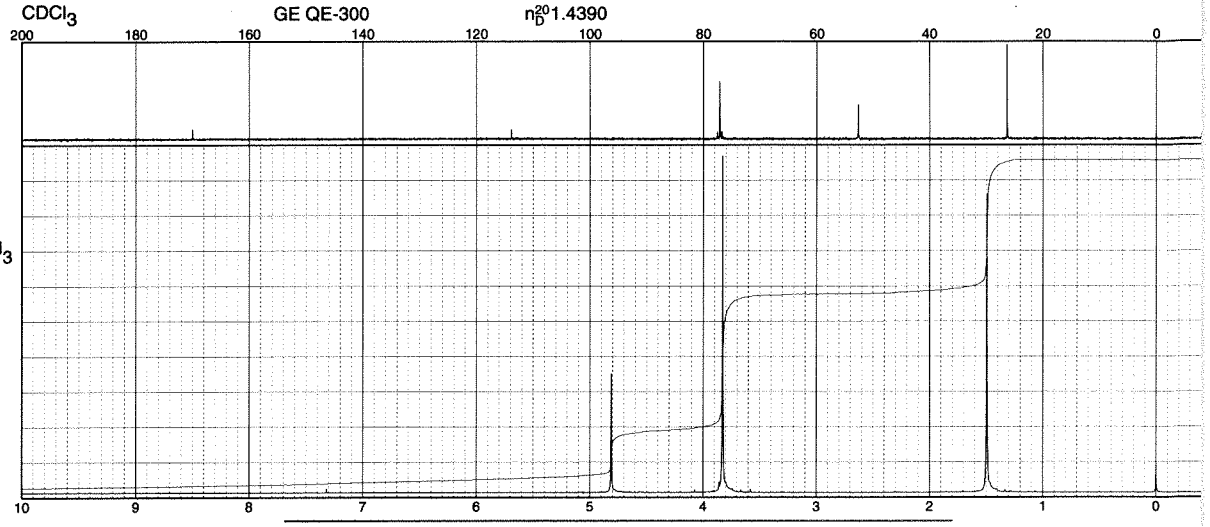
(4*R*,5*R*)-(-)-Dimethyl 2,3-*o*-isopropylidene-l-tartrate

$C_9H_{14}O_6$ Fp >230°F
FW 218.21
bp 150°C (19 mm)
d 1.188
n_D^{20}1.4390

159.99
113.87
77.13
52.68
26.37



$CDCl_3$ GE QE-300



B

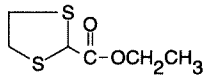
Aldrich 22,630-0 *CAS [20461-99-8]*

Ethyl 1,3-dithiolane-2-carboxylate

$C_6H_{10}O_2S_2$ Fp >230°F
FW 178.27
bp 85°C
d 1.249
n_D^{20}1.5390

60 MHz: ***1***, 566A
FT-IR: ***1***, 676B
VP-FT-IR: ***3***, 739C

171.34
61.95
50.43
38.78
14.01



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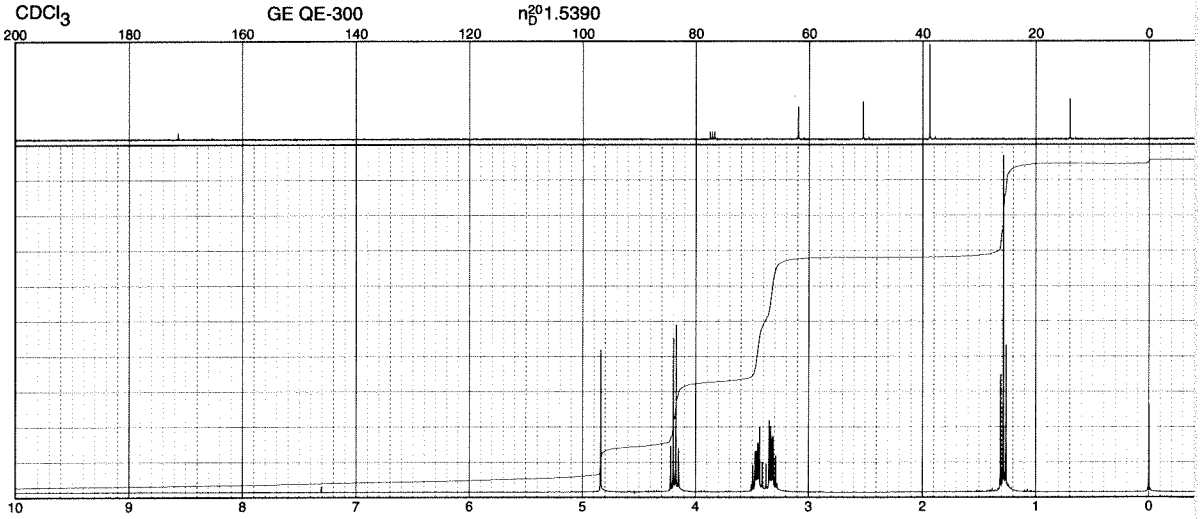


C

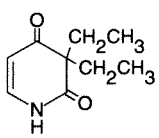
Aldrich 21,010-2 *CAS [77-04-3]*

Pyrithyldione

$C_9H_{13}NO_2$
FW 167.21
bp 188°C (14 mm)

60 MHz: ***2***, 679A
FT-IR: ***1***, 794D

199.57
178.54
142.04
107.92
65.00
32.76
9.38



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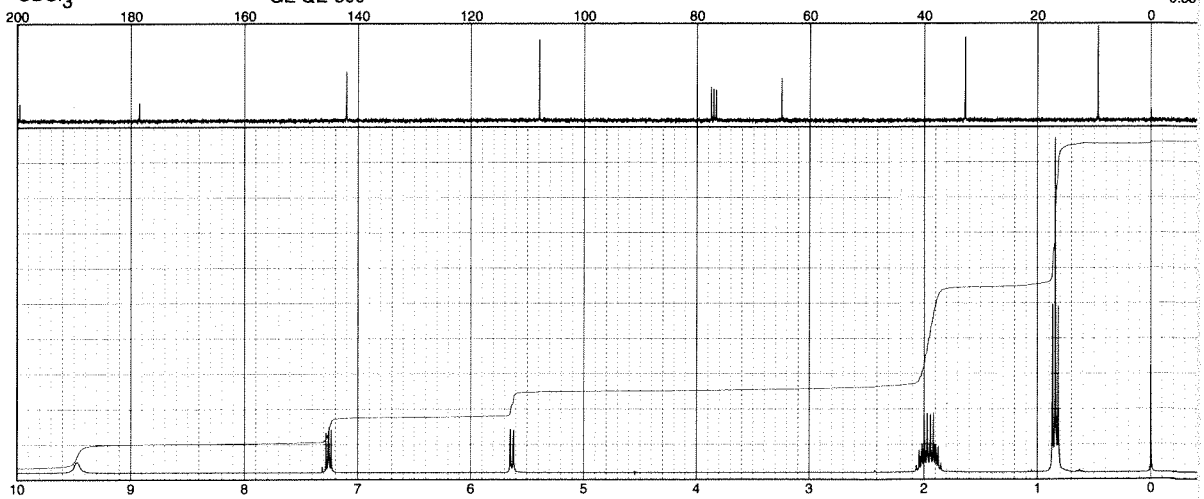


A

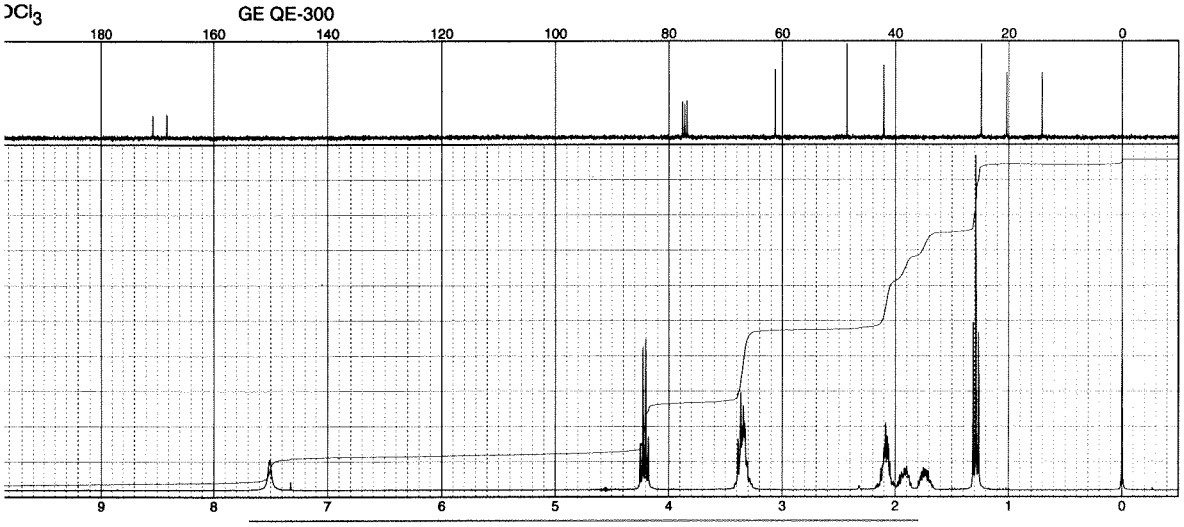
ldrich C550-5 *CAS [3731-16-6]*
Carbethoxy-2-piperidone

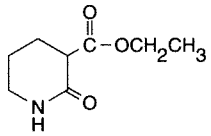
$C_8H_{13}NO_3$
FW 171.20
mp 81°C

60 MHz: *1*, 665A
FT-IR: *1*, 795B

170.79	42.06
168.28	24.86
61.27	20.36
48.60*	14.12*

$CDCl_3$ GE QE-300





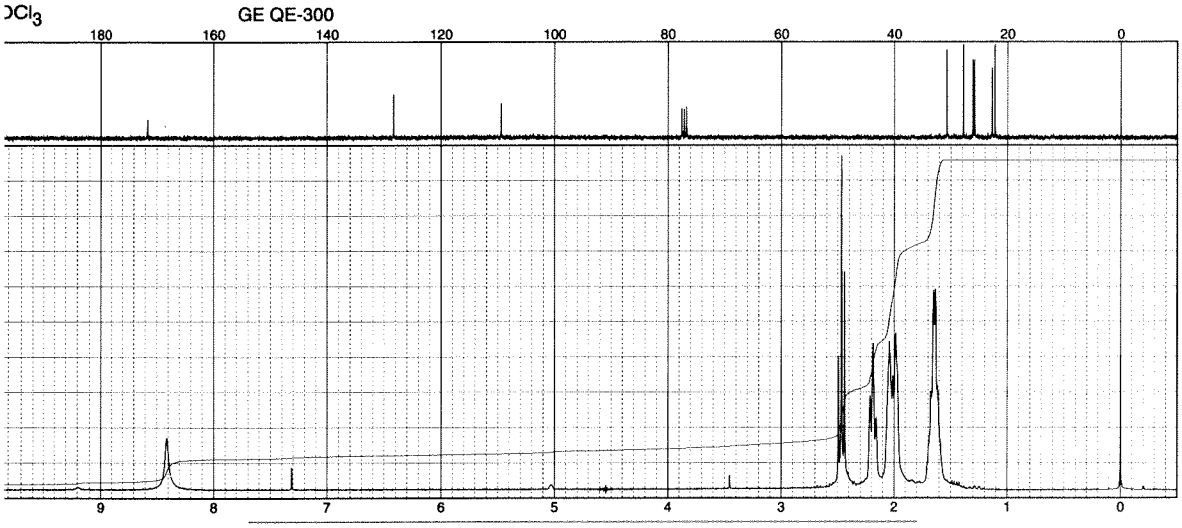
B

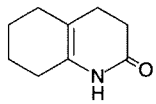
ldrich 29,964-2 *CAS [10333-11-6]*
4,5,6,7,8-Hexahydro-2(1*h*)-quinolinone

$C_9H_{13}NO$
FW 151.21
mp 145°C

171.62	26.14
128.36	25.83
109.43	22.73
30.71	22.22
27.84	

$CDCl_3$ GE QE-300





C

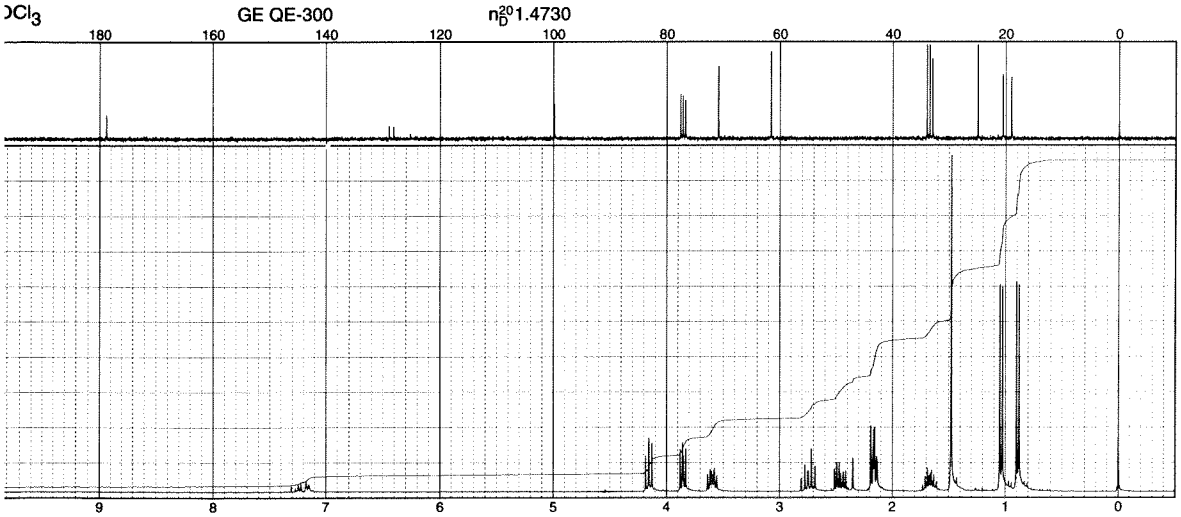
ldrich 33,423-5 *CAS [98203-44-2]*
)-3-Isopropyl-7a-methyltetrahydro
rrrolo(2,1-*b*)oxazol-5(6*h*)-one

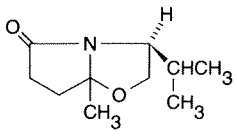
$C_{10}H_{17}NO_2$
FW 183.25
bp 70°C
d 1.027
n_D^{20}1.4730

Fp 137°F

178.80	33.45*
99.83	32.96
70.89	24.94*
61.62*	20.52*
33.93	19.01*

$CDCl_3$ GE QE-300





The Ireland-Claisen Rearrangement

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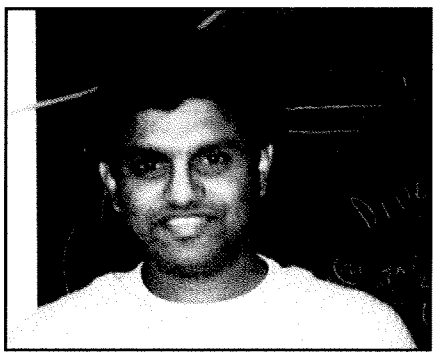
University of Toledo
Toledo, OH 43606.

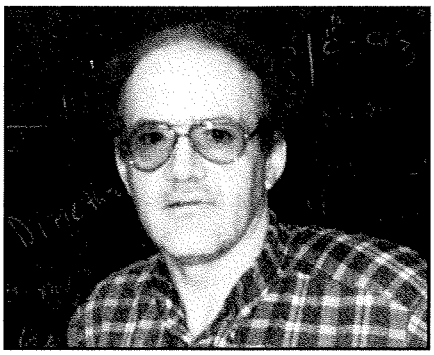
Introduction

The Ireland-Claisen rearrangement, first reported in 1972,[1] has developed over the ensuing years to become a powerful tool in organic synthesis. The importance of this rearrangement derives from the flexibility it provides the synthetic organic chemist to control the diastereoselectivity of two newly generated stereocenters as well as the predictability of product stereochemistry. This review covers the development of this reaction from its inception to its current role in synthetic methodology.

The Ireland-Claisen rearrangement refers to the [3,3]-sigmatropic rearrangement of allylic esters (**1**) as ester enolates (**2**) to give 3,4-unsaturated acids (**3**) (**Scheme 1**).[1] The rearrangement is a suprafacial, concerted, non-synchronous, pericyclic process. When the sp^2-hybridized C_1 and C_6 positions of the allyl vinyl ether are substituted, the rearrangement can proceed via two achiral transition states to give two racemic diastereomers, bearing two centers of asymmetry at C_2 and C_3 of the product.

Prior to the development of Ireland's modification, other popular variants of the aliphatic Claisen rearrangement included the vinyl ether[2], the Johnson orthoester[3] and the amideacetal rearrangements.[4] Base-catalyzed reactions of allylic esters were also reported, but employed harsh conditions and gave low yields.[5] The major advantage of the Ireland modification over these base-catalyzed rearrangements is the ease of preparation and subsequent facile rearrangement of allyl vinyl ethers as their lithium enolates.



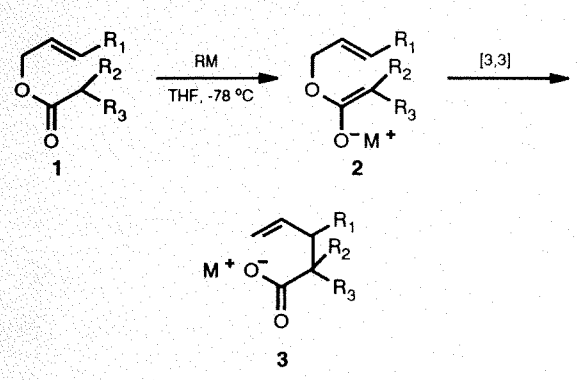


Generation of Ester Enolates

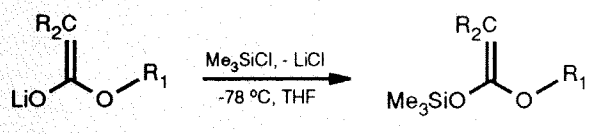
Theoretically, alpha allyloxy enolates can undergo either [3,3]-sigmatropic or competing [2,3]-Wittig type rearrangements. Surprisingly, ester enolates, especially silyl ketene acetals, do not undergo a [2,3]-Wittig rearrangement.[6]

In his initial work, Ireland employed lithium ester enolates generated by the method of Rathke,[7] but these proved unsatisfactory as they rearranged to give unwanted aldol condensation side products.[1] However, the lithium enolates, when silylated by TMSCl, afford trimethylsilyl ketene acetals (**Scheme 2**) which in turn rearrange readily to give 3,4-unsaturated acids. One problem with this approach is the formation of 2-6% C-silylated product.[1] This was overcome by using *tert*-butyldimethylchlorosilane (TBSCl) as the silylation reagent which provides predominantly the O-silylated ketene acetal.[8]

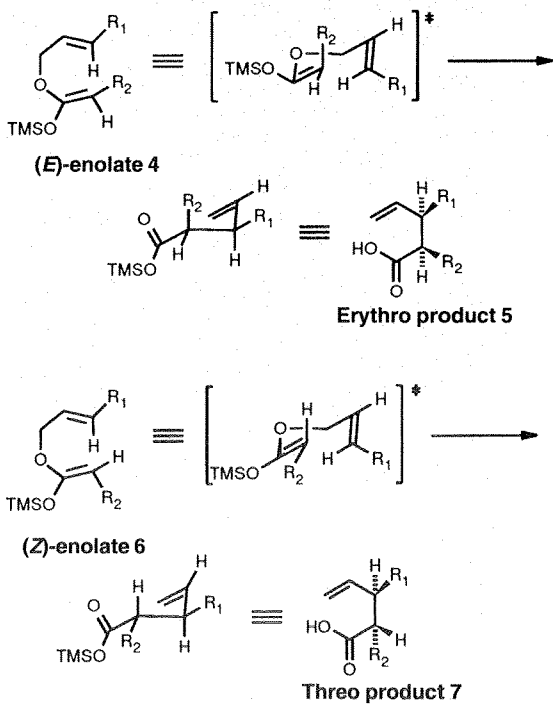
Scheme 1



Scheme 2



Scheme 3



Stereoselective Generation of Ester-Enolates

The geometry of the products of the Ireland-Claisen rearrangement can be predicted by the stereochemistry of the double bonds involved in the ketene acetal rearrangement. The (*E*)-enolate (**4**) gives predominantly an erythro product (**5**), while the (*Z*)-enolate (**6**) gives a threo compound (**7**) as the main product (**Scheme 3**).[9] The rearrangement is proposed to proceed through a four centered "chairlike" transition state as shown, thus allowing stereoselection of the products.[9,10]

The geometry of the silyl ketene acetal can be controlled during the ester enolization process by varying the solvent system. The formation of (*Z*)-enolates is favored by THF as the solvent, while the use of 23% HMPA/THF favors the formation of the (*E*)-enolate (lithium enolate). Regardless of the allylic bond configuration (*cis* or *trans*), the stereochemistry is retained on silylation and the two compounds give predominantly the erythro and threo isomers, respectively, on rearrangement (**Scheme 4**).[9]

Mechanism of Ester-Enolate Control - Thermodynamic or Kinetic?

It was initially proposed that the *E*:*Z* ratio of the enolate esters was kinetically determined, regardless whether THF or a mixture of HMPA/THF was used.[9,11] The two possible transition states **1** and **2** are shown in **Figure 1**. In the absence of HMPA, the lithium atom is strongly coordinated to the carbonyl oxygen leading to an unfavorable interaction between R and R_1. In the presence of HMPA, the lithium atom is highly solvated. In this case, favorable steric interactions between R and R_1 lead preferentially to (*Z*)-enolate formation. Note that these steric considerations had initially been used to explain ketone enolate selectivity and can also be used to explain ester enolate selectivity.

Corey's studies on enolate selectivity led to the conclusion that the use of hindered bulky bases like lithium *tert*-octyl butyl amide (LOBA) gave superior selectivity to (*E*)-enolates as compared to LDA (**Table 1**).[12] He argued that the stereochemical outcome in the presence of HMPA was not a kinetic effect, but was due to equilibration to the more thermodynamically stable (*Z*)-enolate. Corey's conclusion was based on his experiments using TMSCl as an internal quenching agent during the enolization with a lithium base (**Table 2**). The investigations of Rathke also support this conclusion (**Scheme 5**).[13]

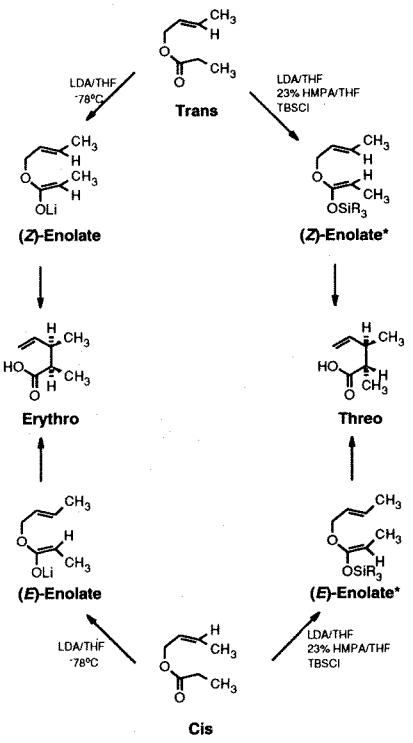
The addition of 1-4 equivalents of HMPA or TMEDA did not change the *E*:*Z* ratio, but the addition of 0.2 equivalent of 3-pentanone caused rapid isomerization to an equilibrium mixture of enolates with an *E*:*Z* ratio of 16:84. Rathke suggested the reverse aldol condensation isomerization mechanism illustrated in **Scheme 6**.[13] It was possible to control the deprotonation of 3-pentanone in THF solution so as to produce predominantly the (*E*)-isomer (**8**) by addition of the ketone to 10% excess lithium 2,2,6,6-tetramethyl piperidide (LiTMP) at 0° C (*E*:*Z* ratio 87:13), or to produce predominantly the (*Z*)-isomer (**9**) by addition of the ketone to a slight deficiency of LiTMP (*E*:*Z* ratio 16:84). He concluded that the formation of the (*E*)-enolate could be the result of kinetically controlled deprotonation, but the formation of the (*Z*)-enolate is thermodynamically favored.

To thoroughly examine the aspects of selectivity in ketene acetal formation, Ireland conducted a number of experiments, varying different parameters and using ethyl propionate as the ester.[14]

Solvent Effects

The effect of solvent on the stereoselectivity of silyl ketene acetal formation of ethyl propionate with LDA is indicated in **Table 3**. The addition of metal-chelating solvents such as HMPA, TMEDA and DMPU reversed the selectivity in favor of the (*Z*)-isomer, as opposed to the predominant formation of the (*E*)-isomer in pure THF. The best selectivity was attained by increasing the amount of DMPU to 45%. However, when the amount of TMEDA is increased, the yield decreases substantially.

Scheme 4



* Note that configurations are opposite due to priority of Si over Li.

Figure 1

Possible configurations of the T.S. of the of the Li ester-enolate with THF as the solvent

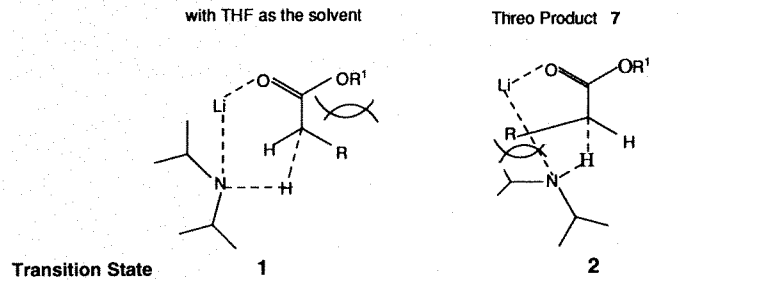


Table 1. ENOLATE SELECTIVITY WITH DIFFERENT BASES

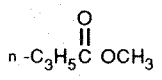
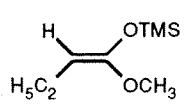
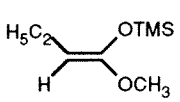
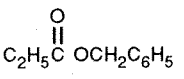
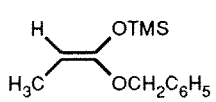
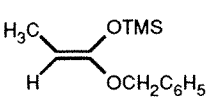
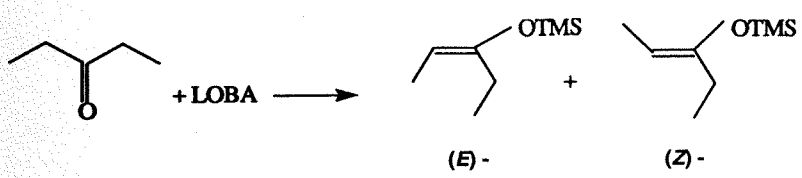
Substrate	TMS Ketene Acetal		*E*:*Z*	
	E	*Z*	LDA	LOBA
			91:9	95:5
			80:20	95:5

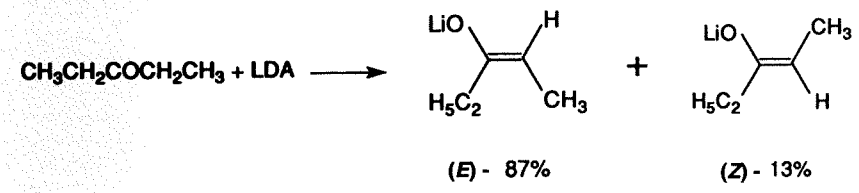
Table 2. Enolate selectivity with Corey's internal quench experiments



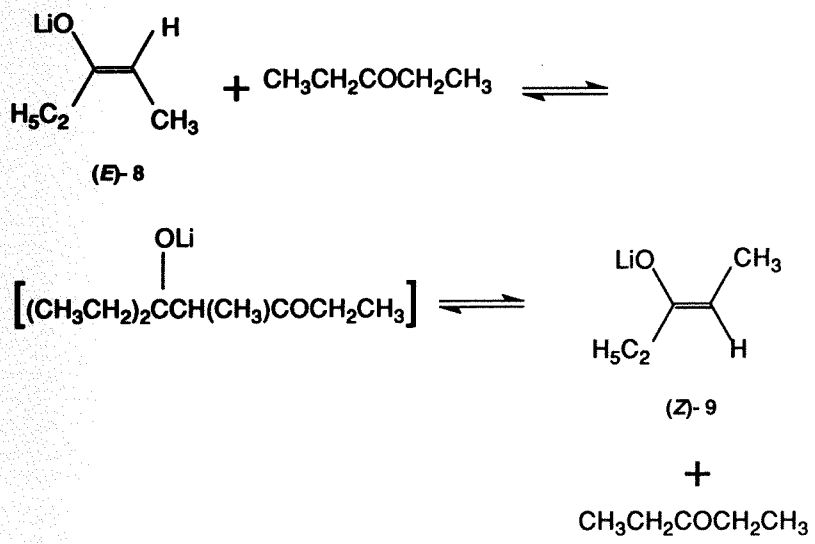
Method	Solvent	(E)-		(Z)-
internal quench	THF	98	:	2
internal quench (8 equiv. TMSCl)	HMPA/THF	37	:	63
internal quench (17 equivs. TMSCl)	HMPA/THF	46	:	54
two step procedure*	HMPA/THF	18	:	82

*slow addition of ketone to LDA followed by silylation

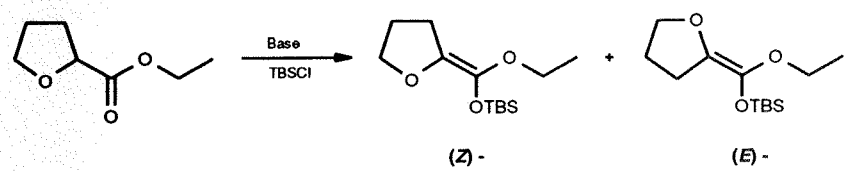
Scheme 5



Scheme 6



Scheme 7



Ester to Base Ratio

Table 4 summarizes Ireland's ester to base ratio experiments. In THF, a decrease in the ester to base ratio from 1:1 to 0.6:1 does not change the selectivity or yield. However, an increase in that ratio from 1:1 to 1:4 drastically reduces the yield from 90% to 5%. A decrease in the ester to base ratio in the mixed THF/chelating solvent system lowers the (Z)-selectivity and decreases the yield. Conversely, a slight increase in the ester to base ratio leads to an increase in (Z)-selectivity, accompanied by a drop in yield. Thus, increased (Z)-silylketene acetal selectivity can be obtained by adding a slight excess of the ester solution. It is also pertinent that addition of small amounts of a polar solvent like DMSO after enolization also increases the (Z)-selectivity.[14]

Effect of the Base

The comparison of LDA with a slightly bulkier base, i.e. lithium hexamethyl disilazide (LHMDS), showed that LHMDS is slightly more efficient for (E)-selective enolate formation than LDA in 23% HMPA/THF solvent mixture.[14]

Effect of an Alpha Oxygen Substituent on the (Z)-Enolate

The formation of the (Z)-enolate predominates due to chelation with an alpha O-atom as shown in **Scheme 7**. When the solvent is THF, the *Z:E* ratio is 90:10, whereas when 23% HMPA/THF is used the ratio drops to 63:37 with the (Z)-isomer still favored.

Ireland pointed out that the conclusions of Rathke and Corey were based on ketone enolates and not directly applicable to ester enolates. An aldol type equilibrium would be too slow and irreversible with acid derivatives such as esters and amides. To support his claim Ireland set up an analogous experiment with ethyl propionate in THF and TMSCl. After enolization of one equivalent of the ester by one equivalent of LDA, addition of 30% DMPU led to a *Z:E* silyl ketene acetal ratio of only 1:4. Furthermore, addition of 0.1 equivalents of ester to 2 equivalents of a preformed 60:40 mixture of (E)- to (Z)-lithium ester enolates led to only a small change in ratio to 69:31 (**Scheme 8**).

These observations suggest a kinetic resolution process. A preformed ratio of (Z)- and (E)- ester enolates can be altered by addition of a small amount of trapping agent that reacts at different rates with the two isomers, thus making it possible to carry out the reaction with the more reactive enolate. Ireland then set up a series of experiments using competitive trapping of the more reactive enolate with TBSCl (**Scheme 9; Table 5**).

The change in ratios is due to a competition for silylation between the two enolates (competition constant, K=k*Z*/k*E*, of 2.6 with DMPU and 1.4 with HMPA). It was concluded that "...kinetically controlled enolization in combination with a kinetic resolution process accounts for the selective

formation of (*E*)- and (*Z*)- silyl ketene acetals in THF and THF/dipolar solvent systems with bases such as LDA, LHMDS, and KHMDS."[14] Ireland's experiments thus shift the evidence in favor of a kinetic resolution process in the case of ester enolates, but do not account for the observations made by Rathke and Corey on the mechanism of enolate formation from ketones (3-pentanone).

Chelation Control of Enolate Selectivity

The lithium enolates' preference for the *Z*-conformer is well established. Investigations by Bartlett,[15] Fujisawa[16] and Burke[17] showed that in the case of a heteroatom substituent that can undergo chelation with the lithium atom, the major isomer formed is the *E*-conformer (**Scheme 10**). Although the ratio of the isomers was not measured, it could be determined from the ratio of the final products. This coordination effect has been utilized in stereoselective syntheses, wherein control of the prostereogenic sp^2 sites is achieved by an allylic oxygen substituent.[18]

Yet another method for enolate control has been developed by Corey and Kim.[19] A chiral boron reagent (**Figure 2**) has been used to promote enantioselective aldol reactions of achiral propionate esters to give either syn or anti aldol products with excellent enantioselectivity and diastereoselectivity.

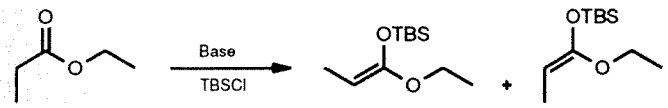
The enolate of choice can easily be controlled by use of the proper solvent:base combinations. When the chiral boron reagent [R_2BBr] and TEA in a toluene/hexane/CH_2Cl_2 solvent is used with *tert*-butyl propionate at -78°C, the transoid boron enolate is formed (O-B and methyl are *trans* to each other; Z-isomer by priority group nomenclature). These enolates react with aldehydes to give the expected anti aldol products in 90-97% e.e. However, when the base is the sterically demanding diisopropylethylamine and the solvent the more polar CH_2Cl_2, the cisoid enolate is formed to give the syn aldol product in 83-97% e.e.

The Transition State - Chair or Boat?

Prior investigations of [3,3]-sigmatropic rearrangements showed that unhindered 1,5-diene systems undergo rearrangement via a chair transition state.[20] Later evidence suggested the possibility of a chair, boat, twist helix or twist plane transition state for the closely related Claisen rearrangement.[21] Since Ireland's variant takes place at moderately low temperatures, the twist configurations are not likely. Further transition state studies of the Cope rearrangement led to the conclusion that substituents on the 1,5-hexadiene play a major role. In fact, a boat transition state is favored due to the nature of the substituents on certain ester enolates.[21]

From previous studies on the Cope[22,23] and Claisen[24,25] rearrangements, it was generally

Table 3. Effect of solvent on ester enolate selectivity



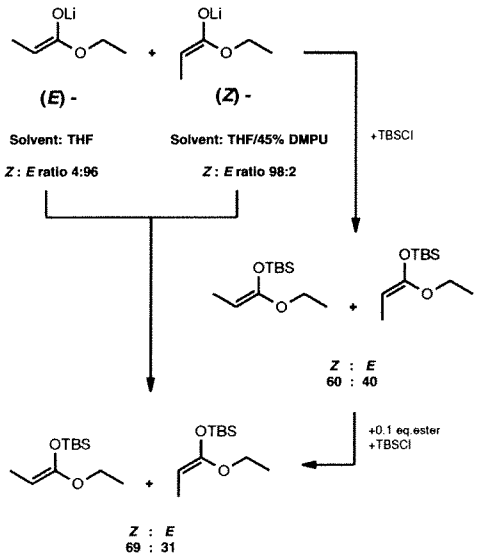
ENTRY	SOLVENT	ESTER:BASE	*Z:E*	YIELD
1	THF	1:1	6:94	90
2	THF/25%TMEDA	1:1	60:40	50
3	THF/50%TMEDA	1:1	--	0
4	THF/15%DMPU*	1:1	37:63	90
5	THF/30%DMPU	1:1	69:31	85
6	THF/45%DMPU	1:1	93:7	90
7	THF/23%HMPA	1:1	85:15	90

*DMPU=N,N'-dimethyl-N,N'-propylene urea

Table 4. Effect of ester to base ratio on the stereoselectivity in silyl ketene acetal formation of ethyl propionate with LDA

ENTRY	SOLVENT	ESTER:BASE	*Z:E*	YIELD
1	THF	1.4:1	1:1	5
2	THF	1.2:1	20:80	35
3	THF	1.1:1	6:94	90
4	THF	0.6:1	6:94	90
5	THF/30%DMPU	1.2:1	98:2	70
6	THF/30%DMPU	0.95:1	67:33	90
7	THF/30%DMPU	0.8:1	68:32	85
8	THF/30%DMPU	0.5:1	60:40	95

Scheme 8



Scheme 9

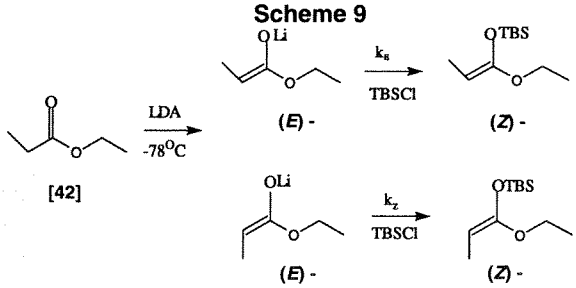
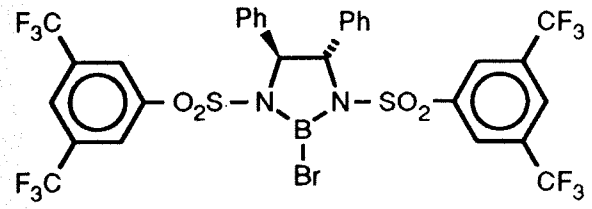


Table 5. Results of competitive trapping of the enolate with TBSCl

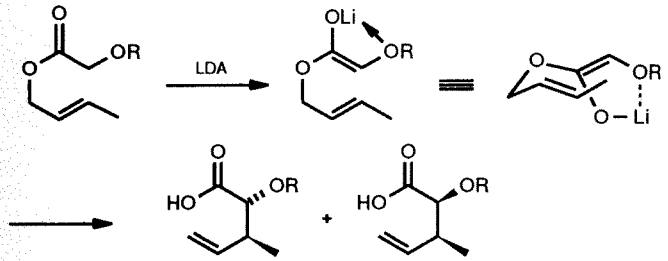
ENTRY	SOLVENT	ESTER:BASE	TBSCl	*Z:E*
1	THF/15%DMPU	0.8:1	0.9	30:70
2	THF/15%DMPU	0.8:1	0.08	14:86
3	THF/23%DMPU	0.8:1	0.9	73:27
4	THF/23%DMPU	0.8:1	0.08	66:34
5	THF	1:1	1.1	94:6
6	THF	1:1	0.9	4:96

Figure 2



Chiral Boron Reagent

Scheme 10

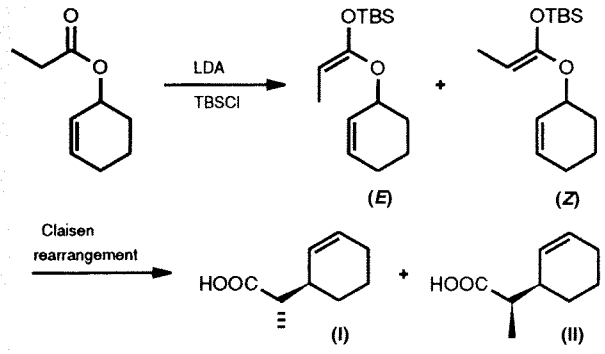


major product **minor product**

R=	MAJOR:MINOR	YIELD
-Me	10.2:1	65
-CH_2Ph	9.6:1	77
MEM*	7.2:1	70
H	2.4:1	38

*(2-methoxyethoxy)methoxy

Scheme 11



SOLVENT	*E:Z*	(I):(II)	%YIELD	FAVORED T.S.
THF	83:17	84:16	79	chair
THF/45%DMPU	4:96	72:28	91	boat
THF/23%HMPA	14:86	73:27	60	boat

found that in cyclic systems a boat transition state is preferred. Another interesting observation was made by Bartlett in his studies of the ester enolate rearrangement of cyclohexenal propanoate.[26] The (*E*)-silyl ketene acetal rearranged via a chair transition state, while the (*Z*)-silyl ketene acetal rearranged via a boat transition state. Bartlett explained his observations by considering the transition states involving the chair and boat forms (**Figure 3**).

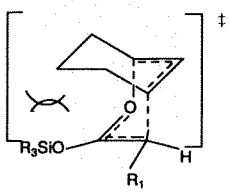
In the case of the (*Z*)-isomer there is an unfavorable interaction between the -$OSiR_3$ group and the methylene proton of the cyclohexene ring if the transition state proceeds through chair form **1**. Thus, the boat form is favored. However, the boat transition state of the (*E*)-isomer has greater steric interaction between the R group and the cyclohexene ring as in **2** (**Figure 3**), thus favoring the chair form.

Ireland carried out a systematic investigation of the effects of various cyclic and acyclic systems on the rearrangement to determine the underlying factors leading to stabilization of either the chair or boat transition state.[27]

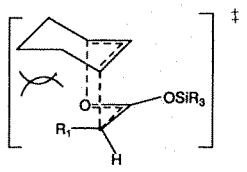
Cyclohexene and Pyranoid Derivatives

Ireland's results with cyclohexenyl propionate were identical to those of Bartlett's. Though diastereoselectivity was observed with both the (*E*)- and the (*Z*)-silyl ketene acetals, the (*E*)-isomer rearranged via a chair transition state while the (*Z*)-silyl ketene acetals rearranged via a boat transition state (**Scheme 11**). The rearrangement employing a pyranoid derivative involved a boat transition state for either (*E*)- or (*Z*)- silyl ketene acetals (**Scheme 12**). These results suggest that the ring oxygen atom can contribute between 1.0 kcal/mol (*Z*-silyl ketene acetal) and 2.2 kcal/mol (*E*-silyl ketene acetal) to the relative stabilization of a boat over a chair transition state. Since both the cyclohexene and the pyranoid rings are sterically similar, the stabilization of the boat transition state is, most likely, due to stereoelectronic rather than steric factors.

Figure 3



Transition State 1 (*Z*)-



Transition State 2 (*E*)-

A more useful picture of the rearrangement can be obtained by considering the chair and boat forms of the transition states of both (*E*)- and (*Z*)- conformers of the enolate (**Figure 4**).

Cyclopentene and Furanoid Derivatives

In the case of a cyclopentene derivative both the (*E*)- and the (*Z*)- isomers rearrange by a chair transition state (**Scheme 13**). However, the furanoid derivative rearranged by a boat transition state for both the ketene acetal configurations, thereby supporting the results of the pyranoid-cyclohexene series. The O-atom leads to relative stabilization of the boat form of the transition state over the chair form on the order of 1.4 kcal/mol (*E*-conformer) and 1.9 kcal/mol (*Z*-conformer).

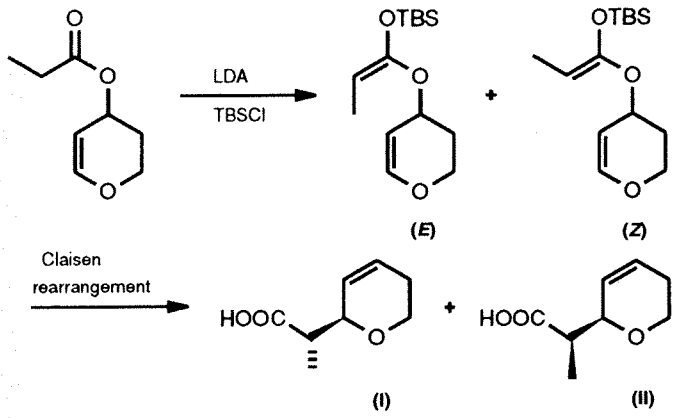
The chair and boat forms of the transition states of the (*E*)- and (*Z*)-enolates of cyclopentene-furanoid glycal derivatives are depicted in **Figure 5**.

Methoxy Allyl Propionate Derivative

The (*E*)- and (*Z*)-silyl ketene acetals of methoxy allyl propionate gave a mixture of carboxylic acids with a preference for the isomer expected via the chair transition state. Thus, in the acyclic series, the effect of the O-atom is not as important as it is in the cyclic series for stabilizing the boat transition state.

Using alpha-secondary deuterium isotope effects, Gajewski proposed that the transition state of the aliphatic Claisen rearrangement resembles an oxoallyl radical-allyl radical pair, rather than a 2-oxocyclohexane-1,4-diyl (**Scheme 14**).[28] This results in a transition state with much more advanced

Scheme 12



SOLVENT	(I):(II)	%YIELD	FAVORED T.S.
THF	29:71	77	boat
THF/45%DMPU	86:14	35	boat

Scheme 13

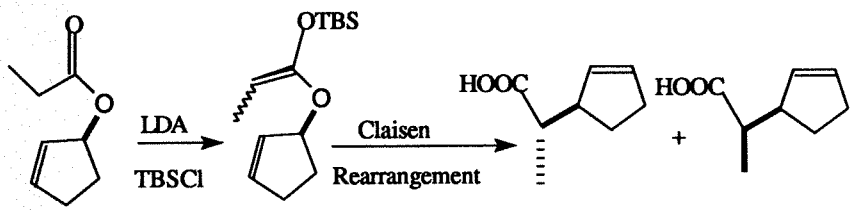


Figure 4. Transition states of cyclohexene-pyranoid glycal derivatives

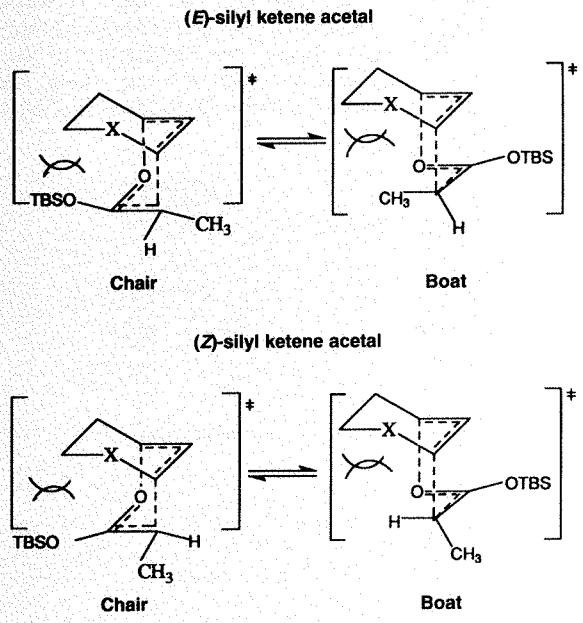
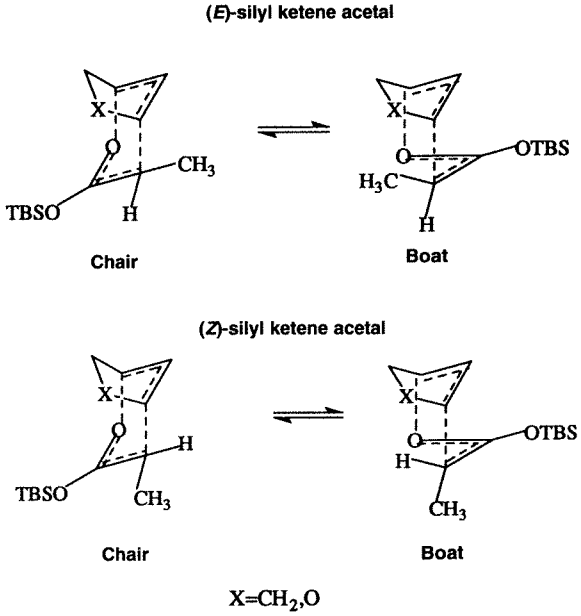
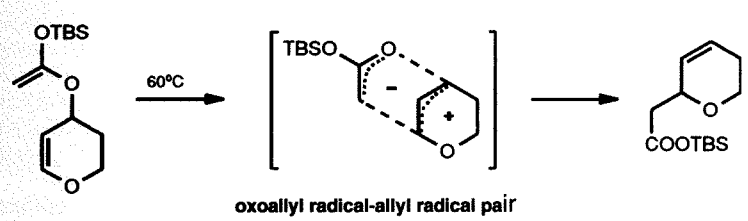


Figure 5

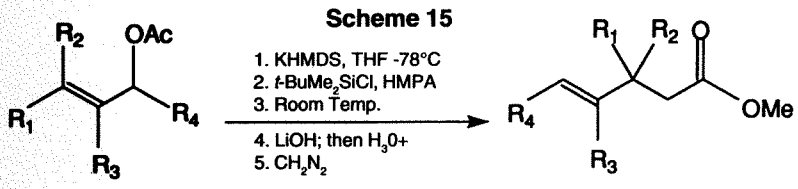


Scheme 14



oxoallyl radical-allyl radical pair

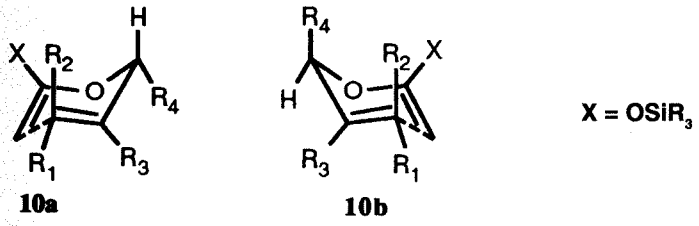
Scheme 15



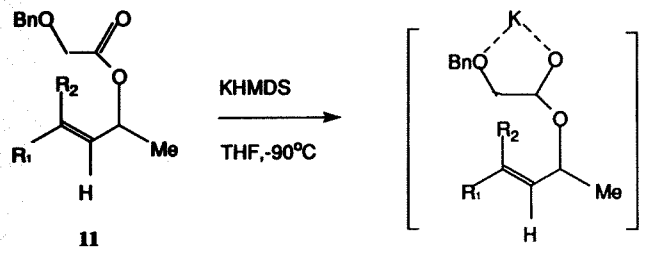
8 [a-c] **9 [a-c]**

ESTER	R1	R2	R3	R4	%YIELD
8a&9a	Me	H	H	$SnBu_3$	60
8b&9b	Me	Me	H	$SnBu_3$	62
8c&9c	$SnBu_3$	H	H	Me	54

Figure 6. Possible Transition States of the Enolate

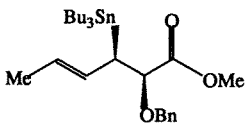


Scheme 16

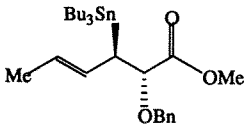


Config.	R_1	R_2
11 (*E*)-	$SnBu_3$	H
11 (*Z*)-	H	$SnBu_3$

1. TMSCl (excess) THF, -90°C heat to RT
2. H_3O^+
3. CH2N2



13 syn



14 anti

O(3)-C(4) bond breaking than in the parent unsubstituted system. Thus, one would expect a rate enhancement effect from a C(6)-donor substituent to be especially effective in glycal systems.

Ireland concluded that there is a definite stereoelectronic effect which stabilizes the boat over the chair form. The energy differences between the chair and the boat forms in the transition state are small and hence tend to be influenced by substituent interactions. In the absence of steric interactions, the pyranoid and furanoid systems will rearrange by a boat transition state. A simple acyclic substituent with a C(6)- oxygen atom will not rearrange via the chair form.

Variations of the Ireland-Claisen Rearrangement

An interesting variation of the Ireland-Claisen rearrangement developed by Ritter uses an organotin ester and the chelation effect of the counterion to produce primarily the (*Z*)-enolate from the O-protected butenyl stannane (**8**). This rearrangement gives a high diastereoselectivity ratio (**Scheme 15**).[29]

The chair transition state (**10a**), with R_4 in the pseudoequatorial position, is energetically favored over (**10b**), with R_4 in the pseudoaxial position, resulting in the exclusive formation of the (*E*)-isomers (**9a - c**). The (*E*)-tributylstannylbutenol reacted six times faster than the (*Z*)-isomer, reflecting the energy difference between the transition states with the tributyltin moiety in a pseudoequatorial (**10a**) or pseudoaxial (**10b**) position (**Figure 6**).

Ritter also investigated the chelation effect of the counterion to form predominantly the (*E*)-enolate from O-protected butenyl glycolates. The rearrangement of (*Z*)- or (*E*)-4-tributylstannyl-3-buten-2-yl (benzyloxy)acetate (**11**) (**Scheme 16**), through intermediate **12**, gave (*E*)-2-benzyloxy-3-tributylstannyl-4-hexenoic acid methyl ester in a 92% yield.

Due to the chelation control of enolate geometry, the syn ester (**13**) is the main product (syn:anti ratio 39:1) from the glycolate ester (**11**) (*E*). The glycolate ester (**11**) (*Z*) rearranges to give an anti:syn ester ratio of 40:1, thus emphasizing the utility of the rearrangement of organotin compounds to afford diastereoselective products.

Brown and co-workers recently reported a useful method for controlling enolate geometry through the use of dialkylboron reagents of the type R_2BX (X = Cl, OTF) in the presence of tertiary amines.[30] They found that the formation of the (*E*)-enol borinate is favored by the following:

(i) use of R_2BCl instead of R_2BOTF;
(ii) use of Et_3N instead of *i*-Pr_2EtN;
(iii) use of a dialkylboron group with a larger steric requirement (i.e. dicyclohexylboron instead of 9-BBN).

A recent publication by Corey extends this work to the highly enantioselective and

diastereoselective Ireland-Claisen rearrangement of achiral allylic esters.[31] The rearrangement utilizes a recyclable chiral boron reagent (**Scheme 17**), resulting in greater than 97% e.e. in some cases.

The (*E*)- or (*Z*)-enolate is selected using the specific solvent combinations along with the chiral catalyst as shown in **Tables 6 and 7**. The (*E*)-isomer rearranged to give predominantly threo products while the (*Z*)-isomer rearranged to form mainly the erythro carboxylic acids. The diastereoselectivity of the rearrangements is consistent with the assigned geometry of the boron enolate and the expectation of the preferred chair geometry of the transition state.

Applications of the Ireland-Claisen Rearrangement

The rearrangement has been used in the synthesis of polyether antibiotics,[21,32] sesquiterpenes,[33] steroids,[34] iridoids,[35] tetronates,[36] marine natural products,[37] amino acids,[38] C-glycosides,[39] large carbocycles[40] and chiral stannanes[29] and silanes.[41] Recent applications include the synthesis of long chain or large ring molecules and demonstrate the utility of this rearrangement in controlling stereocenters.

A clever strategy utilizing a boron mediated aldol condensation in tandem with the Ireland-Claisen rearrangement provided a synthetic route to ebelactone-A, an esterase inhibitor.[42] Furthermore, a general method for the synthesis of unsaturated diesters with a high degree of stereocontrol at four chiral centers as well as two trisubstituted double bonds was devised (**Scheme 18**). Interestingly, the rearrangement could be carried out without protection of the keto group at C_7.

After the rearrangement of the diester **16A**, the resulting diacid was esterified to give the desired meso all syn diester **18A** (63% yield, 86% d.s.). The unsymmetrical diester **18B** is obtained in 53% yield and 95% d.s. from **16B**. An important aspect is that the electrophilic ketone carbonyl group is not attacked and there is no epimerization at the adjacent stereocenters. This is probably due to the flanking methyl groups which protect it from the sterically hindered base LDA and also blocks intramolecular aldol condensation. This synthesis demonstrates the use of a "double" Ireland-Claisen rearrangement to create two contiguous stereocenters.

A new, high yield synthesis of coumarin derivatives employing the rearrangement was reported by Collado and is shown in **Scheme 19**.[43] The rearrangement does not occur unless the phenolic hydroxyls are protected as, for example, their benzyl ethers.

Curran and co-workers have used the Ireland-Claisen rearrangement in a stereoselective synthesis of chiral iridoid aglycones (**Scheme 20**).[44] The iridoids are a family of natural products which have an oxygenated fused cyclopentapyran ring system possessing anti-microbial to anti-leukemic properties.

The best stereoselectivity was obtained by the generation of the (*E*)-silyl ketene acetal. This proceeded with good diastereoselectivity by a chair transition state to give **23** and its diastereomer in a 5:1 ratio. The rearrangement of the (*Z*)-silyl ketene acetal also gave **23** as the major product in a 3:2 ratio, but this time via the boat transition state, a result in keeping with the findings of Bartlett and Ireland.

Schreiber and co-workers have described the asymmetric synthesis of the cyclohexyl moiety of FK-506, a macrolide antibiotic with potent immunosuppressive properties (**Scheme 21**).[45] The rearrangement from **27** to **28** proceeded in 71% overall yield via the boat transition state. Wang has also used this rearrangement in the synthesis of the C_{10}-C_{24} fragment of FK-506.[46]

Jasperse and Curran have used the rearrangement to form two contiguous quater-

Scheme 17

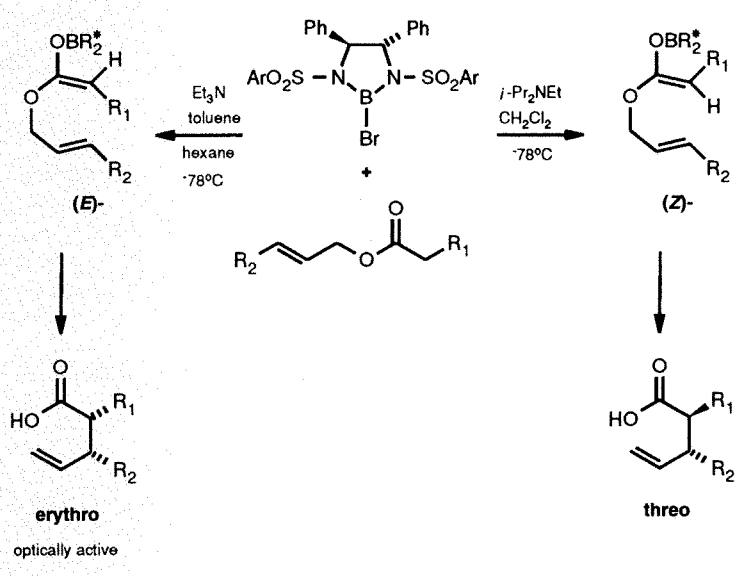


Table 6. Enantioselective rearrangement in CH_2Cl_2 via the (*E*)-boron enolate

ENTRY	R1	R2	%YIELD	THREO: ERYTHRO	e.e.%
1	Me	Me	75	99:1	<97
2	Et	Me	79	98:2	95
3	Me	Me	75	91:9	>97
4	Et	Ph	72	91:9	>97
5	Ph	Ph	100	23:77	>97
6	SPh	Me	52	39:61	>97
7	CH_2Ph	H	70	---	82
8	CH_2-1-naphthyl	H	48	---	77

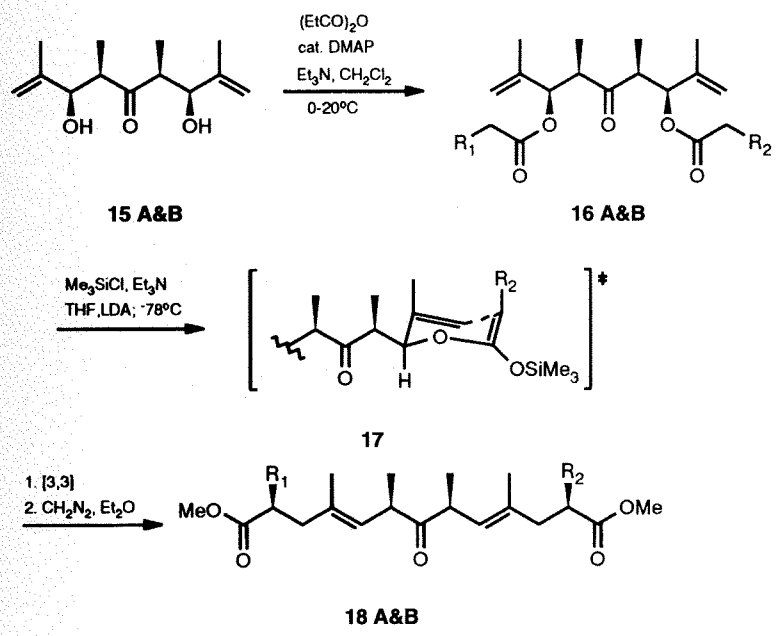
Diastereomeric ratios were determined by GC analysis of benzyl or methyl esters. e.e. values were determined by HPLC analysis of methyl esters using a Diacel OJ column.

Table 7. Enantioselective rearrangement in toluene-hexane via the (*E*)-boron enolate

ENTRY	R1	R2	%YIELD	THREO: ERYTHRO	e.e.%
1	Me	Me	65	90:10	96
2	Et	Me	79	89:11	>97
3	Me	Ph	88	96:4	>97
4	Et	Ph	69	95:5	>97
5	Ph	Ph	100	98:2	>97
6	SPh	Me	56	95:5	>97
7	SPh	Ph	45	91:9	>97
8	CH_2Ph	H	57	---	84
9	CH_2-1-naphthyl	H	63	---	79

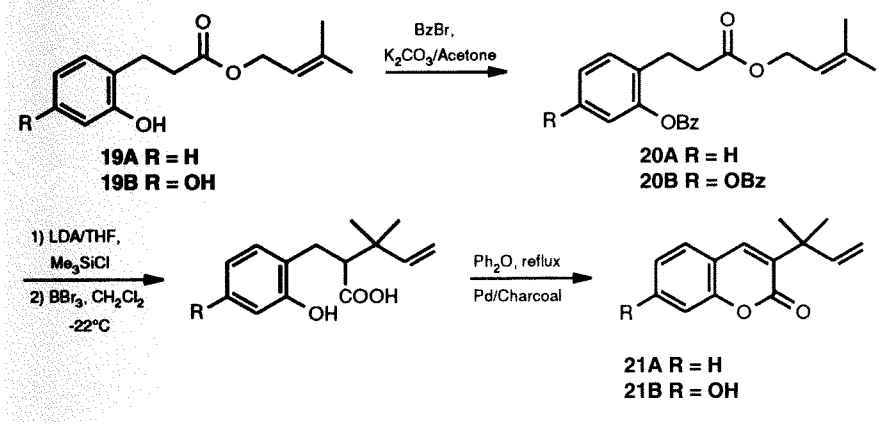
Diastereomeric ratios were determined by GC analysis of benzyl or methyl esters. e.e. values were determined by HPLC analysis of methyl esters using a Diacel OJ column.

Scheme 18

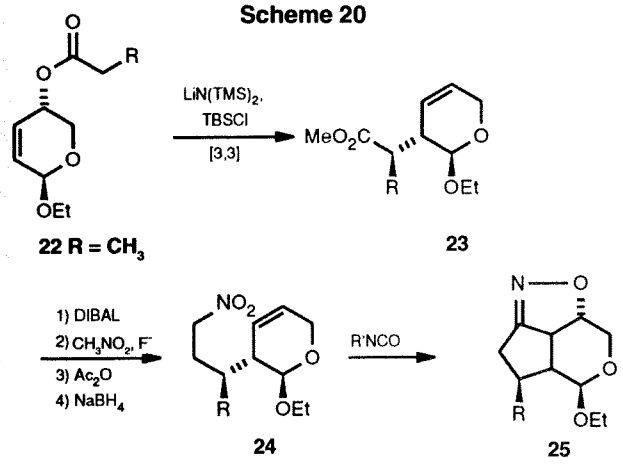


[A] R1 = R2 = Me
[B] R1 = Me; R2 = Et

Scheme 19



Scheme 20



nary centers needed for the intermediate in their synthesis of modhephene in 50% yield (**Scheme 22**).[47]

Intermediates to polyoxins which are structurally related to nucleoside peptide antibiotics were prepared by Duthaler.[48] As shown in **Scheme 23** the (*Z*)-allyl ester rearranges in a highly stereoselective manner to give predominantly the *trans*-substituted lactone, while the (*E*)-allyl ester rearranges to give mainly the *cis*-lactone.

The rearrangement was evaluated for application to the synthesis of macrocyclic lactones. Brunner and Borschberg investigated the potential synthesis of (R,S)-muscone (**37**) as shown in **Scheme 24**.[40] On rearrangement, **33** gave a mixture of **34**, **35** and **36**. The stereoselectivity of this rearrangement is rather low compared to that of acyclic systems. While of no consequence to the synthesis of the target molecule, this result highlights the fact that C-silylation may still be a problem in the case of large molecules. These findings supplement the model studies on the synthesis of medium and large carbocycles using the Ireland-Claisen rearrangement carried out by Knight, where a lack of stereospecificity was reported, and by Danishefsky.[49]

Burke has used the reaction to prepare the hydropyran subunit in his synthesis of macrodiolide and macrotriolide ionophores. He was able to effect the rearrangement of **38** to **39** in 76% yield (**Scheme 25**).[50]

In their paper titled "Stereocontrolled Synthesis of a Polyether Fragment", Bartlett describes the use of the Ireland-Claisen rearrangement to synthesize a tetrahydropyran lactone with several chiral centers.[51] The stereoselective step using the rearrangement is shown in **Scheme 26**.

The ratio of **40** to **41** is 10:1 since the use of HMPA favors the formation of the (*Z*)-enolate-ester, which in turn gives **10**.

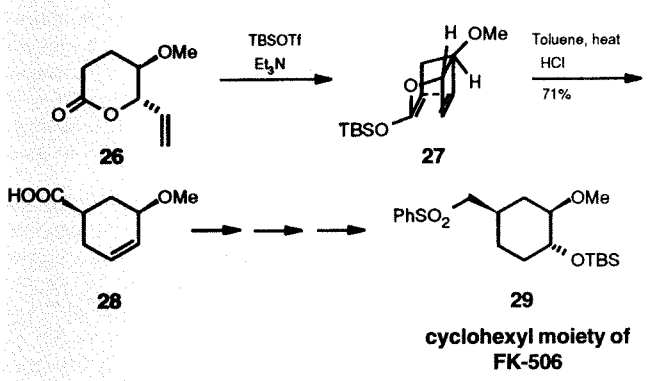
Cane and co-workers have used the rearrangement in the synthesis of chain elongation intermediates of the Monensin biosynthetic pathway.[52] They have been able to prepare **43** from **42** in 50-75% yield (Scheme 27).

Danishefsky has ingeniously used the Ireland-Claisen rearrangement to merge awkwardly positioned chiral centers in his synthesis of the C_{28}- C_{49} unit of Rapamycin, a metabolite of *Streptomyces hygroscopicus*, an antibiotic with immunosupressive properties (**Scheme 28**).[53]

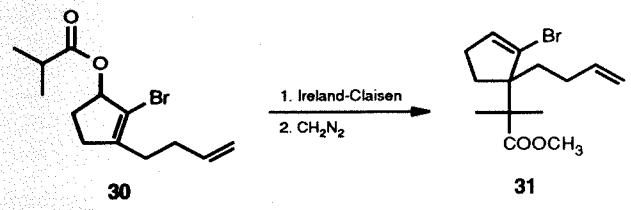
After preparing alcohol **44** and acid **45** separately, esterification in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDCI) and DMAP gave **46** which, in turn, after rearrangement of the silyl enol ether furnished **47**.

The rearrangement of lactones to carbocycles has also been carried out by Danishefsky in his synthesis of the *Fusarium* toxin equisetin.[54] Keto-lactone **48** was converted to its bisilyl derivative **49** and subsequently rearranged to yield ester **50** in 52% yield (**Scheme 29**).

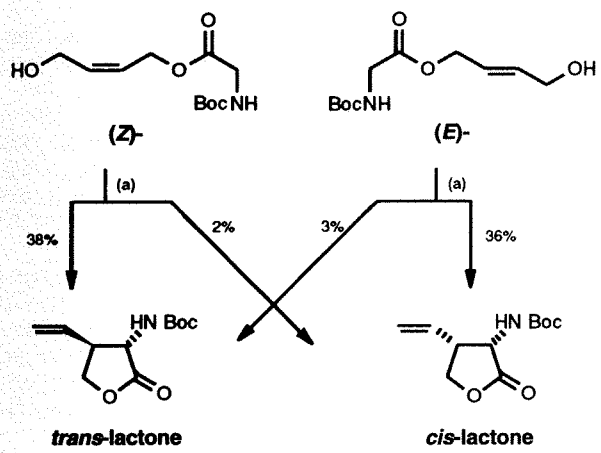
Scheme 21



Scheme 22

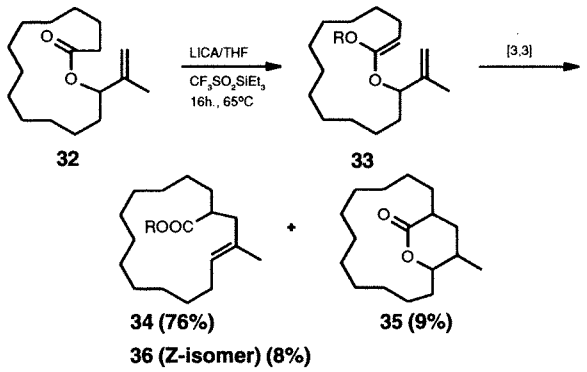


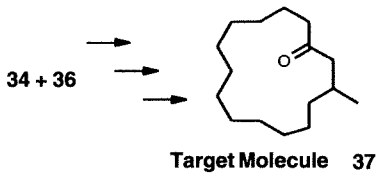
Scheme 23



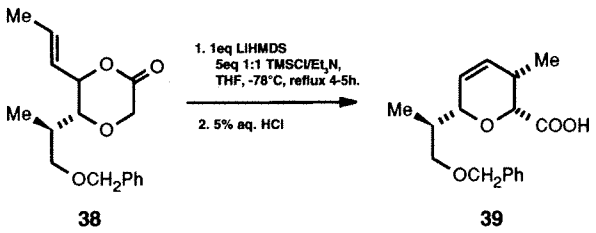
(a): 1. hexamethyldisilazane/reflux
2. LICA/THF/-76°C
3. TMSCl/-78°C to reflux

Scheme 24

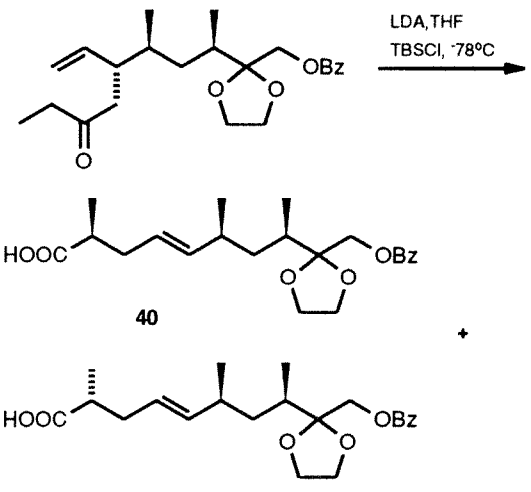




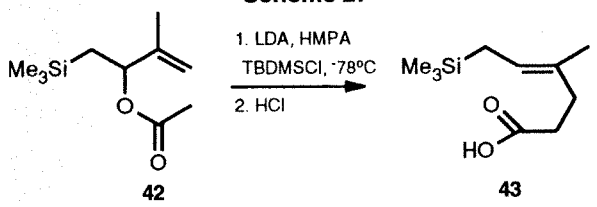
Scheme 25



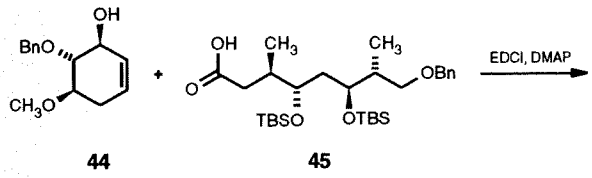
Scheme 26

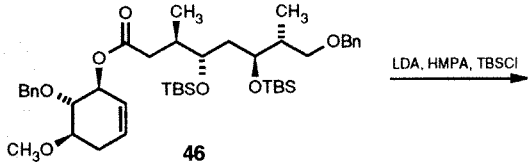


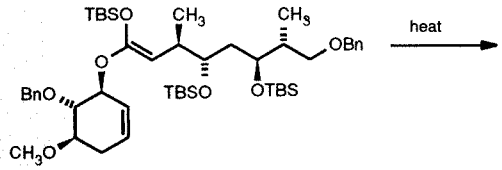
Scheme 27

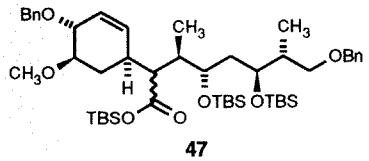


Scheme 28

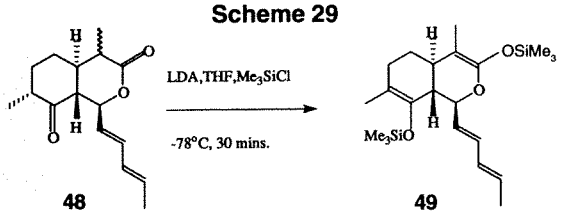


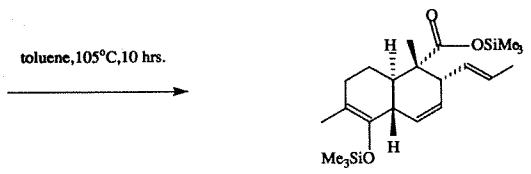


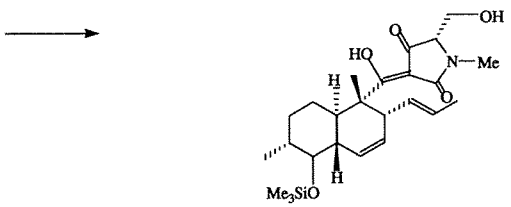




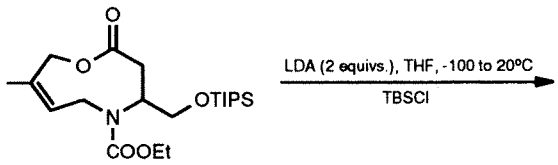
Scheme 29

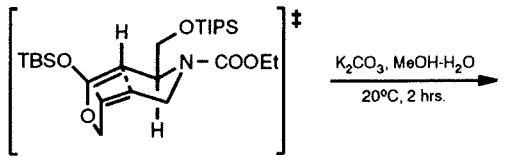




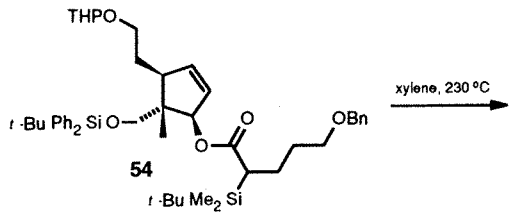


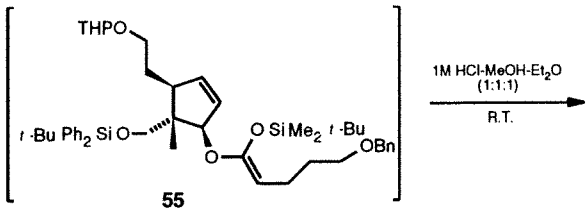
Scheme 30

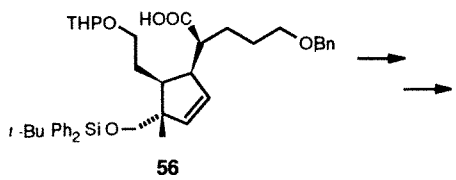


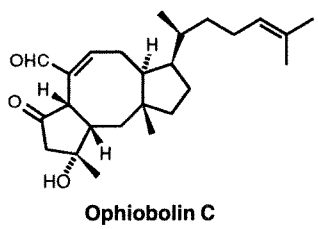


Scheme 31









The Ireland-Claisen rearrangement has also been used in syntheses involving the ring contraction of lactones (Claisen contraction). For example, Knight and co-workers have devised a strategy for the enantiospecific total synthesis of (-)-α-kainic acid using ring contraction of lactone (**51**) to pyrrolidinedicarboxylic acid (**53**) in 55% overall yield (**Scheme 30**).[55] The silyl ketene acetal **52** was proposed to rearrange through a boat transition state.

Another excellent example of Claisen ring contraction was reported by Funk for the preparation of the in,out-bicyclo[4.4.1] undecan-7-one core of the potent tumor promoter ingenol G49.[56]

In Kishi's total synthesis of ophiobolin C the silyl ketene acetal **55** prepared from **54** rearranged to stereoisomer **56** in 72% overall yield and 6:1 diastereoselectivity (**Scheme 31**).[37]

Conclusion

Over the years the discipline of synthetic organic chemistry has seen a trend towards the catalyzed stereoselective synthesis of natural products. These natural products often contain large carbocyclic rings and polyether fragments of well defined stereochemistry. The Claisen rearrangement,[57] reported more than 80 years ago, has remained an important synthetic tool.[58] The Ireland modification of this rearrangement enables the chemist to have better control over diastereoselectivity and to apply it to unsaturated esters. The Ireland-Claisen rearrangement has often been used to synthesize large carbocyclic structures with complex stereochemistry and will continue to be an important synthetic strategy in this class of compounds. The discovery that the Claisen rearrangement is routinely used by nature in the synthesis of aromatic amino acids via the shikimic acid pathway emphasizes the importance of the rearrangement in the synthetic preparation of these chiral natural products and others.[58]

Recent developments involving the use of organotin and organoboron chemistry have given excellent enantioselectivities (ca. 98% e.e.). In an age where high enantiomeric excesses and stereoselectivity are the order of the day, the rearrangements with organotin and organoboron reagents will be used more frequently in the future.

However, there are several areas that still have not been actively researched. Synthetic work involving the Claisen rearrangement (though not the Ireland-Claisen rearrangement) has already been investigated using organoaluminum as the diastereoselective agent, and has shown great promise for higher diastereoselectivity.[59] These, as well as other organometallic agents, should be utilized in the Ireland-Claisen rearrangements and may well enhance the diastereomeric selectivity currently achieved.

The effect of electron withdrawing substituents on the allylic ester is also significant. Welch and co-workers have studied the ester enolate rearrangement of allyl α-fluoroacetates and propanoates and demonstrated these rearrangements to be fairly selective.[60]

The aspect of diastereoselective synthesis of large carbocycles also leaves ample room for improvement of the rearrangement. For example, this topic has not been systematically investigated with the use of organometallic or lanthanide catalysts/diastereoselective agents which are now known to exert a significant chelation effect. The "double" Ireland-Claisen rearrangement described earlier could well be investigated for various chain lengths and cyclic compounds.

Another area which has received considerable attention is that of biochemical catalysis. A recent publication reports a highly stereospecific Claisen rearrangement catalyzed by an antibody.[61]

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Schubert Pereira was born in Bombay, India in 1967. He received his BSc and MSc from the Bombay University in 1987 and 1989 respectively. After working in the cosmetics R & D industry in India for a few years, he joined the University of Toledo's doctoral program in chemistry where he is engaged in the synthesis of siderophores for magnetic resonance imaging.

Professor Morris Srebnik received his PhD from the Hebrew University in Jerusalem in 1984, under the direction of Raphael Mechoulam. In 1985/86 he went to Purdue University on a Lady Davis Fellowship where he worked with Professor H.C. Brown on the asymmetric chemistry of organoboranes. Except for a sojourn during 1986/87 at the Aldrich Chemical Company, he remained at Purdue until 1990 when he moved to the Department of Chemistry at the University of Toledo. His research group, consisting of MSc, PhD and undergraduate students, is exploring the chemistry of organozincs, organoboranes, transmetallations and asymmetric catalysis.