

# Aldrichimica Acta

Volume 23, Number 1, 1990



## *The Invention of Chemical Reactions*

*TPAP: Tetra-*n*-propylammonium Perruthenate,  
A Mild and Convenient Oxidant for Alcohols*

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Volume 23, Number 1, 1990

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## About Our Cover:

It won't surprise the regular readers of our *Aldrichimica Acta* that there is another painting of a *Tobias* on our cover. Our chemist-collector is so fond of this story — it is such a delightfully involved story of faith — and this is the sixth *Tobias* on our covers.

Here the angel is shown instructing Tobias how to hold the fish, and the faithful dog, the first friendly dog mentioned in a biblical story, is trotting along.

We don't know who painted this — French artists in Rome, like Gaspar Dughet and Francois Perrier have been suggested — but our ignorance does not diminish by one iota the beauty of this long view. To the artist, this beauty came first; he may have added the figures only because biblical paintings were considered a higher art form than mere landscapes. Little could he know in the seventeenth century that one day a chemist would buy this for both reasons: for the *Tobias* story and for the landscape which is almost as magical as the fish.

#### *Telling Images — Images Révélatrices*

Large, 150-page catalog of thirty-six Old Master paintings now in a travelling exhibition touring Canada. All were given by the Baders to Queen's University.

The catalog illustrates all thirty-six paintings, thirteen of them in color (none of these were in the Age of Rembrandt exhibition described below). The extensive, scholarly text, written by Professor David McTavish, is in English and French.

#### *The Detective's Eye: Investigating the Old Masters*

Twenty-one paintings that have been reproduced on our *Acta* covers and five that have been on our catalog covers were among some seventy works in an exhibit at the Milwaukee Art Museum (January 19 - March 19, 1989) for which Isabel and Alfred Bader were guest curators.

If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this fully illustrated catalog, and you will learn something about our chemist-collector's interest in art and connoisseurship as well.

#### *Pictures from the Age of Rembrandt*

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

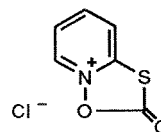
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# Lab Notes

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) and if we publish it, you will receive, at no cost, a handsome Aldrich coffee mug as well as a copy of **Pictures from the Age of Rembrandt**. We reserve the right to retain all entries for consideration for future publication.

## "Please Bother Us."

by  
*David Crich*



Dr. David Crich, University College, London, kindly suggested that we offer this thiazolizinium salt. It was used recently in his convenient, highly selective synthesis of 2-deoxy- $\beta$ -D-glycosidic linkages from the corresponding ulosonic acid O-glycosides<sup>1</sup> via Barton's thiohydroxamate-based decarboxylation methodology.<sup>2</sup>

Naturally, we made this compound.

(1) Crich, D.; Ritchie, T.J. *Chem. Commun.* **1988**, 1461. (2) Barton, D.H.R.; Crich, D.; Motherwell, W.B. *Tetrahedron* **1985**, *41*, 3901.

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

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# The Invention of Chemical Reactions

Derek H. R. Barton  
Department of Chemistry  
Texas A&M University  
College Station, TX 77843

The invention of chemical reactions is not a popular academic activity. There are probably no graduate courses on this subject. Perhaps the reason for the lack of interest is the widespread belief that all new chemical reactions are discovered by accident. Indeed, many of our important reactions were discovered in this way. For example, three reactions which have significantly changed chemical synthesis are the Birch reduction (originally discovered by Wooster), the Wittig reaction and H.C. Brown's hydroboration. In each case, the first experiment was done with a completely different idea as to what the reaction product would be. In each case, a fortunate accident occurred.

For several decades now I have argued that it is possible to invent chemical reactions of synthetic significance. The first step, of course, is to recognize which reaction you wish to invent. A chemical reaction is a change in bonding. If one already knows a way to carry out this bonding change, then a new way can only be of importance if it improves the yield or the selectivity of the process. For example, two classical methods for reducing a ketone to the corresponding methylene compound are the Wolf-Kishner reduction and the Clemmensen reduction. The first involves strongly alkaline conditions; the second, strongly acidic conditions. Neither reaction could be used in, say, carbohydrate or peptide chemistry. We have devised an indirect path around this difficulty in the following way.

Some fifteen years ago, thanks to my consulting relationship with the Schering-Plough Corporation, I realized that the removal of a hindered secondary hydroxyl group from an aminoglycoside antibiotic molecule was not an easy reaction. I decided to solve this problem in a new way, for the deoxygenated antibiotics could show an improvement in their activity.

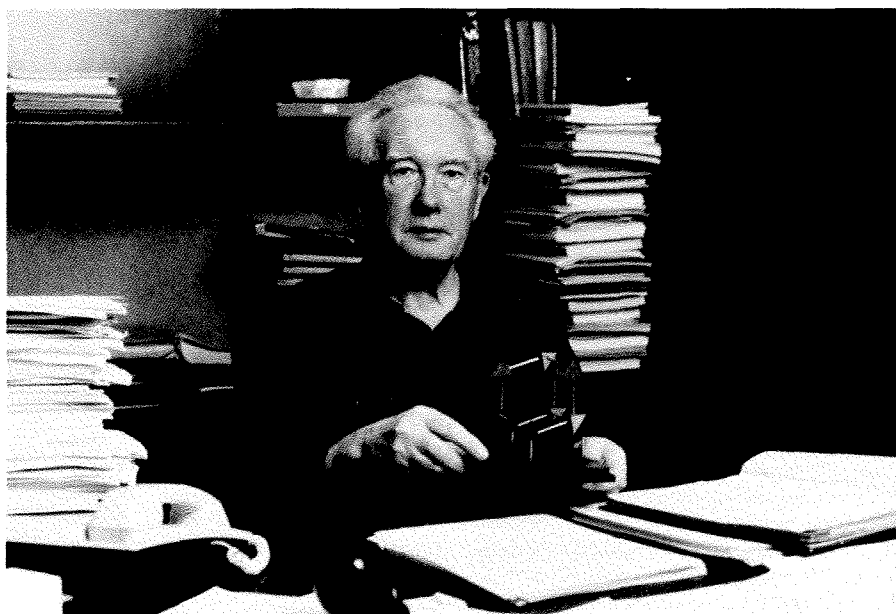
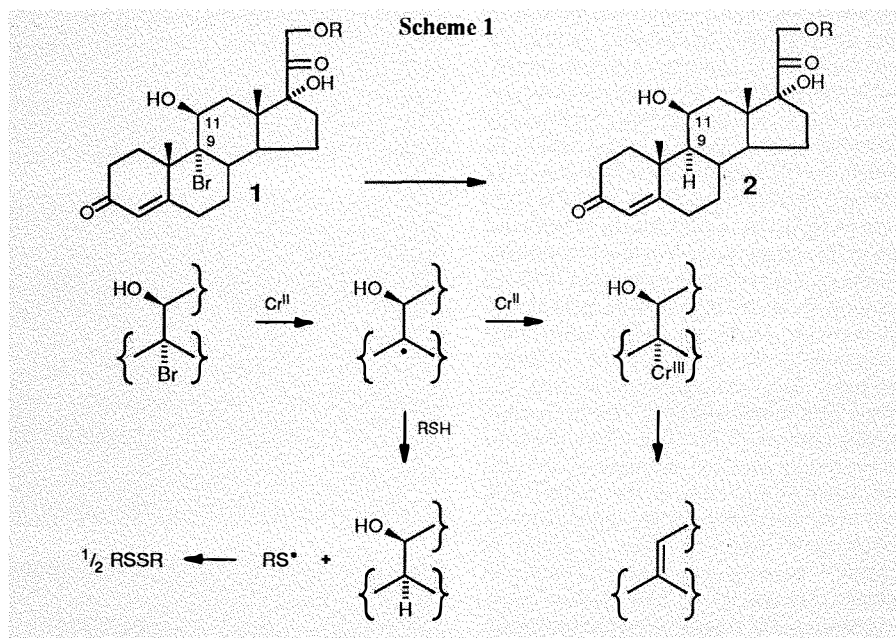
Not much attention had been given to the use of carbon radicals in carbohydrate chemistry because the general belief was that such reactions could never be selective. However, one selective radical reaction was known—the reduction of halides with tributyltin hydride, a process discovered accidentally by Van der Kerk<sup>1</sup> in 1957. However, the tin hydride reactions are not suitable for large-scale work. A practical procedure is to use chromous acetate, which can be generated *in situ*, and a radical-trapping reagent such as a thiol.

Scheme 1 deals with a specific problem in steroid synthesis. Hydrocortisone acetate (2,

R=Ac) is an important commercial product. Since the bromo derivative (1, R=Ac) is easily prepared, it seemed a simple operation to reduce out the bromine. However, this was not so, as all practical reductants, including chro-

mous ion, caused elimination of water as indicated in Scheme 1.

We invented<sup>2,3</sup> a process which gives nearly quantitative yields. We simply supposed that the dogma of the day, that organochromium



Professor Derek H.R. Barton, recipient of the A.C.S. Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich.



compounds were involved in the first step, was wrong. Thus, the simple hypothesis that a radical was formed by  $\text{Cr}^{(II)}$ , which could be trapped by hydrogen-atom transfer from a thiol, gave a simple solution to a hitherto intractable problem. The modern synthesis<sup>4</sup> of hydrocortisone acetate uses this reaction on a very large scale.

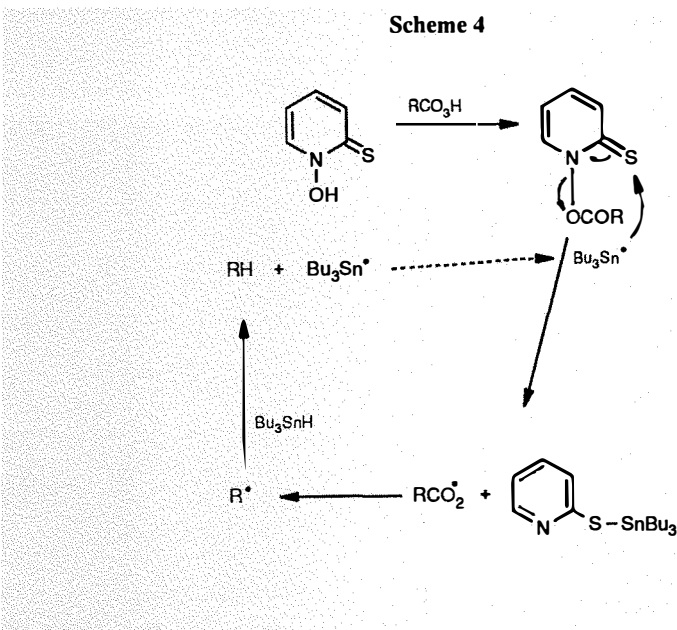
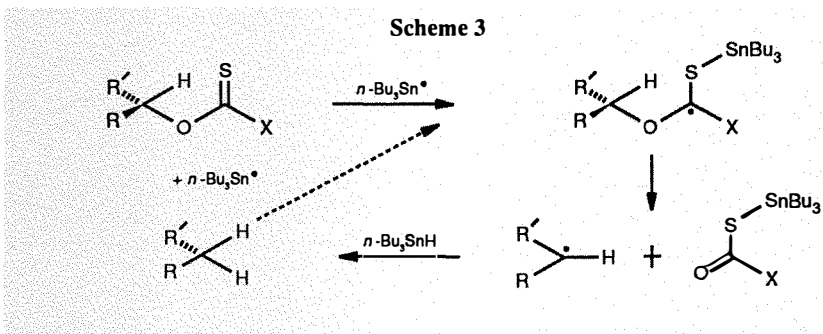
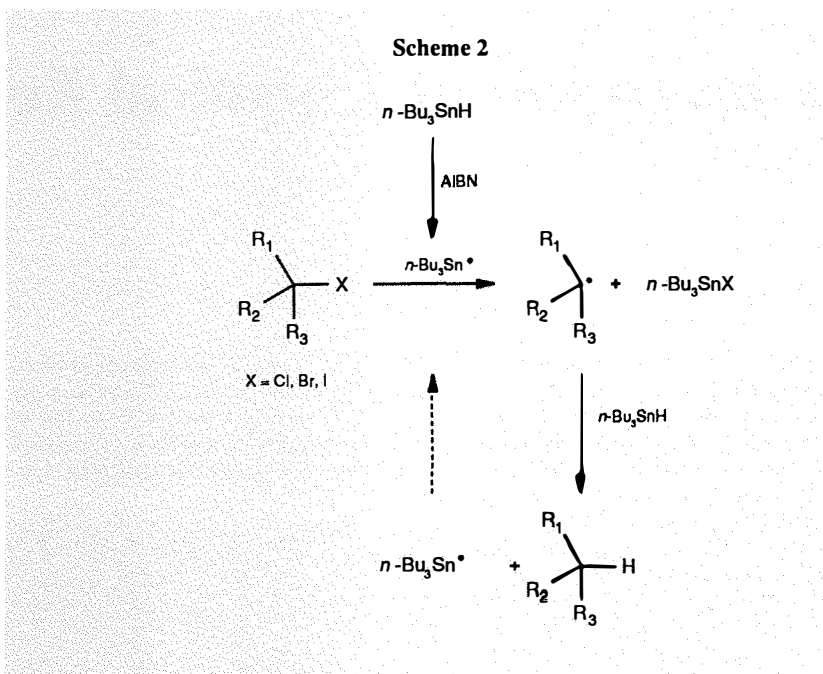
The tin hydride reduction process of Van der Kerk works well (Scheme 2) because of the weakness of the tin-hydrogen bond. We say that the carbon radical is disciplined by this bond, just as the  $\text{C}_5$ -carbon radical in the hydrocortisone synthesis (Scheme 1) is disciplined by the weak S-H bond.

However, a carbon-bromine bond is weaker than the corresponding carbon-oxygen bond. When seeking to invent a reaction, careful attention must be paid to thermodynamic considerations. Thus, there must be one or more driving forces (which may include entropy increase) to make the reaction thermodynamically possible. For a radical deoxygenation process, it was clear that a high-energy derivative of the hydroxyl group would be needed, so I invented the reaction shown in Scheme 3. Here, driving forces are the affinity of the tin radical for sulfur, the overall conversion of the thiocarbonyl function to carbonyl, and the entropy increase associated with the dissociation of the intermediate radical into two particles. Again, the carbon radicals are disciplined by the weakness of the tin-hydrogen bond. This deoxygenation process, the Barton-McCombie reaction,<sup>5</sup> rapidly became popular because of the high yields obtained for secondary alcohols and because the reagent, tributyltin hydride, is compatible with most of the functional groups encountered in carbohydrate chemistry. The X group in Scheme 3 was originally<sup>5</sup> phenyl, imidazolyl and thiomethyl (xanthate). Later, Robins<sup>6</sup> made X = phenoxy. The reagent phenyl chlorothionoformate ( $\text{PhO-CS-Cl}$ ) is more reactive than the preceding reagents and also more efficient.<sup>7</sup> The related reagent methyl chlorothionoformate ( $\text{MeO-CS-Cl}$ ) has also been used effectively.<sup>8</sup>

Our recent contribution to this subject<sup>9</sup> is to introduce the reagents pentafluorophenyl chlorothionoformate ( $\text{C}_6\text{F}_5\text{O-CS-Cl}$ ) and 2,4,6-trichlorophenyl chlorothionoformate ( $2,4,6\text{-Cl}_3\text{C}_6\text{H}_2\text{O-CS-Cl}$ ). These give derivatives which react rapidly and quantitatively with tributyltin hydride to afford the desired deoxy derivatives. The electron-withdrawing aryl groups increase the rate of attack on the thiocarbonyl function.

If we look back, we can see that we do now have a solution to the problem of converting a ketone to a methylene function in carbohydrate molecules. Ketones, even hindered ones, can be reduced with borohydride-type reducing agents to secondary alcohols. Even if stereochemically mixed alcohols are formed, conversion to a suitable thiocarbonyl derivative followed by tin hydride reduction will afford the desired methylene compound in good yield.

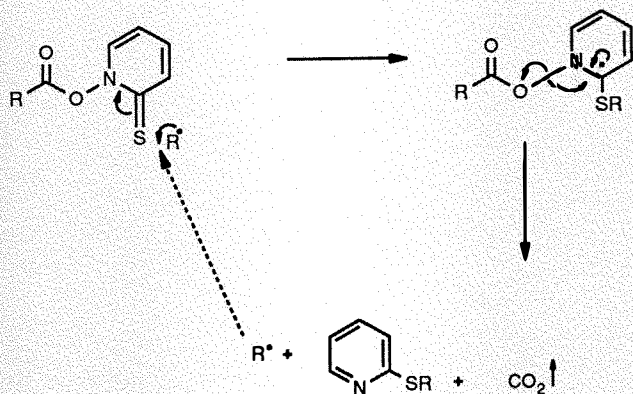
A more broadly based type of radical chem-



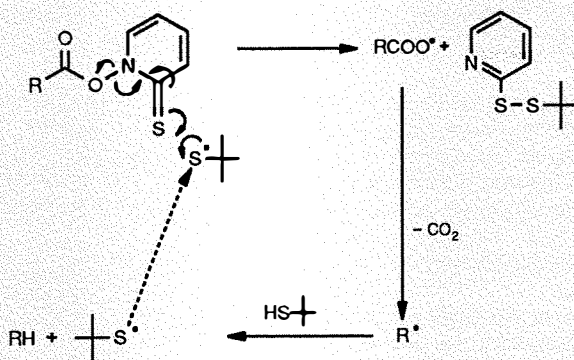
istry derived from the acyl derivatives of thiohydroxamic acids, has been invented recently.<sup>10,11</sup> In particular, the acyl derivatives of *N*-hydroxy-2-thiopyridone (Scheme 4) lend themselves to the facile production of radicals either on heating to 80° or, better, by irradiation

with a tungsten lamp at room temperature, or at any other temperature. The ultimate disciplinary group in this system is the thiocarbonyl group. If the tributyltin hydride is omitted, then a smooth decarboxylative rearrangement is seen (Scheme 5). If suitable

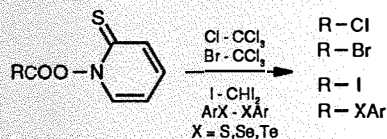
Scheme 5



Scheme 6



Scheme 7



radical traps are added, then many different classes of compounds can be prepared (Schemes 6, 7, Table 1). In a flow system, high concentrations of carbon radical can be generated and detected by ESR spectroscopy.<sup>12</sup> The acyl derivatives of *N*-hydroxy-2-thiopyridone also lend themselves to the precise measurement of radical rearrangements in an elegant way with much scope for variation of radicals.<sup>13,14</sup>

It is characteristic of the acyl derivatives of *N*-hydroxy-2-thiopyridone to give clean radical chemistry with very high yields of single products.<sup>15</sup> Besides carbon radicals, the use of acyl carbamate derivatives permits an improved synthesis of nitrogen radicals and of aminium radical cations under milder conditions than could be used before.<sup>16</sup> A modification of the system has given a convenient synthesis of alkoxy radicals.<sup>17</sup>

All this radical chemistry is based on logical thought. There may be other radical-generating systems that are even more convenient to use. Systems that responded to infrared radiation would be interesting.

Let us now turn the ketone-to-methylene problem on its head and ask ourselves how methylene can be converted to ketone. In the absence of other functional groups, this is a much more difficult problem. As is often the case, leading ideas come from thinking about Natural Products Chemistry.

Nature makes much use of oxidation, both in the biosynthesis of important compounds and in the detoxification and excretion of xenobiotics. Thus, in the biosynthesis of hydrocortisone (2, R=H), Nature starts with squalene which is epoxidized stereospecifically. The epoxide is then cyclized ionically to lanosterol, 3. Oxidative removal of three methyl groups, hydrogenation of the side-chain double

bond and (formal) migration of the other double bond from the 8(9) to the 5(6) position gives cholesterol, 4. Further oxidation removes six carbons from the side chain to afford, after oxidation at 3 and double bond shift, progesterone, 5. Finally, hydroxylation at 17, 21 and 11 affords hydrocortisone (2, R=H). There are at least seven oxidizing enzymes involved in the conversion of 3 to 2. All of them are iron-containing porphyrins related to the oxidative P<sub>450</sub>-type enzymes in the liver that efficiently hydroxylate almost any foreign molecule that passes in the blood stream.<sup>18</sup> For the removal of the three methyl groups from lanosterol, that at C<sub>14</sub> is removed as formic acid and the two at C<sub>4</sub> as carbon dioxide. Thus, initially, hydroxylated molecules are oxidized to the corresponding carbonyl group. Thus, Nature effects easily the functional-group challenge of converting unactivated methylene into carbonyl.

There are two well known mechanisms for the selective oxidation of saturated hydrocarbons. The first is the Fenton reaction of H<sub>2</sub>O<sub>2</sub> with Fe<sup>(II)</sup> which leads to the production of hydroxyl radicals.<sup>19</sup> The second is the iron-based porphyrin system of the P<sub>450</sub> enzymes referred to above. In porphyrin models based on this system, it is clear that alkoxy-radical-like chemistry is seen.<sup>20</sup> Saturated hydrocarbons are attacked with a selectivity normal in radical reactions (*tert* > *sec* > *prim*), sulfides are oxidized to sulfoxides and olefins are epoxidized.<sup>21,22</sup>

The Gif system<sup>23</sup> for the selective oxidation of saturated hydrocarbons involves a new and different mechanism. We have now five different Gif-type systems, all of which oxidize saturated hydrocarbons selectively to ketones and have an unusual selectivity order of *sec* > *tert* > *prim*. Names, based on geography, have been given to five variants of the original Gif system—Gif<sup>III</sup> is iron powder suspended in pyridine-acetic acid with oxygen or simply open to the air.<sup>24</sup> Gif<sup>IV</sup> is the same with a catalytic amount of an iron species and suspended zinc dust to provide the electron input.<sup>25</sup> Gif-Orsay is the same as Gif<sup>IV</sup>, but with zinc dust replaced by the cathode of an electrochemical cell.<sup>26</sup> This is a much more efficient system with respect to electron input. Finally,<sup>27</sup> we have added GoAgg<sup>I</sup> (pyridine-acetic acid-stoichiometric Fe<sup>(II)</sup>-KO<sub>2</sub> under argon) and GoAgg<sup>II</sup> (pyridine-acetic acid-catalytic Fe<sup>(III)</sup>-H<sub>2</sub>O<sub>2</sub> under argon or air). The name comes from G for Gif, O for Orsay and Agg for Texas A&M.<sup>27</sup>

These systems show a remarkable selectivity for hydrocarbon oxidation even in the presence of large amounts of isopropyl alcohol, ethanol<sup>26</sup> or even acetaldehyde.<sup>28</sup> Another curious fact is that cyclic hydrocarbons are oxidized at about the same rate as the corresponding olefins.<sup>29</sup>

The oxidation of cyclohexene affords cyclohexenone, not cyclohexene epoxide.<sup>30</sup> Various natural products behave in the same way.<sup>31a</sup>

The formation of  $\alpha,\beta$ -unsaturated ketones is characteristic for 1,2-di- and trisubstituted olefins. In contrast, we have recently shown

that 1-substituted and especially 1,1-disubstituted olefins are cleaved efficiently into a carbonyl compound and formaldehyde. The cleavage went very well with 1,1-diphenylethylene and with 1-methyl-1-phenylethylene. We showed that the corresponding epoxides and glycols were not intermediates in this cleavage reaction.<sup>31b</sup>

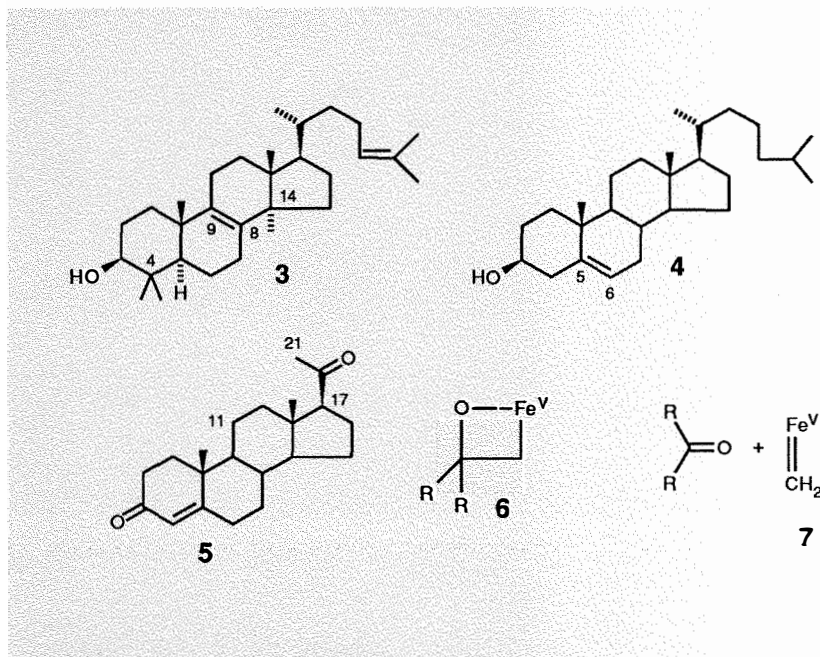
Recent work has shown<sup>27</sup> that all the Gif-type systems depend for their selectivity on a common iron oxenoid species. We have postulated this to be an Fe<sup>(V)</sup> species on the basis of logical arguments. It is thus comparable to the radicaloid species Fe<sup>(IV)</sup>=O (+•) or Fe<sup>(III)</sup>-O• (+•) involved in P<sub>450</sub> model studies based on porphyrin ligands.<sup>32,33</sup> In terms of our theory, we would postulate the addition of the Fe<sup>(V)</sup> oxenoid species to the double bond 6 followed by cleavage to the ketone and a methylene carbene 7. We would expect the latter to be oxidized to formaldehyde. A number of experiments showed that formaldehyde was indeed formed, while blank experiments demonstrated that formaldehyde was not formed without substrate.

This is not the place to retrace the history of the Gif systems, but the original idea was to imitate the P<sub>450</sub> enzyme system taking the fundamental equation C-H + 2e<sup>-</sup> + 2H<sup>+</sup> + O<sub>2</sub> → C-OH + H<sub>2</sub>O. Thus, calculations of electronic yield (or of coulombic yield for the electrochemical variation) are based on this equation. Although the mechanism is seen to be very different from the P<sub>450</sub> systems, we have retained this convention.

In the original studies, saturated hydrocarbons like cyclohexane or cyclooctane were oxidized to 20-30% ketone. Addition of further reagents (e.g., zinc dust and acetic acid) appeared to increase this yield only slightly. Preliminary kinetic studies showed that cyclohexane was converted to cyclohexanone (and some cyclohexanol) without any intermediate. Cyclohexanol is not the precursor of cyclohexanone nor is the latter reduced to cyclohexanol.

More recent work has shown that the apparent constancy in yield is due to overoxidation. Using an excess of hydrocarbon and running the oxidation to 20% conversion, a nearly quantitative yield of ketone (with some alcohol) is obtained based on hydrocarbon converted. Since hydrocarbons and ketones are easily separated, this would be a superior way of making, say, cyclohexanone were it not for the expense of the pyridine. This is true of both the Gif<sup>IV</sup> and of the GoAgg<sup>II</sup> systems.

A key observation in considerations about mechanism was the fact that in the oxidation of adamantane (8), the selectivity (C<sup>2</sup>/C<sup>3</sup>) changed dramatically with oxygen pressure. By definition C<sup>2</sup> is the total of oxidation products at the secondary position (ketone 9, and alcohol 10) while C<sup>3</sup> is the amount of *tert*-alcohol 11. The selectivity for a normal attack by alkoxy radicals on adamantane is 0.15.<sup>34</sup> Oxidation by a porphyrin P<sub>450</sub> model gave an even lower number.<sup>32a</sup> Thus, it is the tertiary position which is selectively attacked. Oxidation of adamantane by Gif<sup>IV</sup> gives a C<sup>2</sup>/C<sup>3</sup> of



10-20, indicating a strong selectivity for the secondary position. As the oxygen pressure is reduced, C<sup>2</sup>/C<sup>3</sup> increases and can be greater than 100 without reducing significantly the % oxidation at the secondary position (always mainly ketone). This key experiment has been repeated many times by four different investigators.

If we were making secondary and tertiary radicals from adamantane, the partition of products would be determined by a ratio of two second-order rate constants. As the concentration of oxygen is lowered C<sup>2</sup>/C<sup>3</sup> should remain constant, although the total of oxidized products would, of course, diminish to zero. The conclusion is inescapable that the mechanism of oxidation at the tertiary position in adamantane is different from that at the secondary position.

At this point, a mass-balance study showed that a significant proportion of the adamantane could not be accounted for. Examination of the basic fraction showed the presence of three adamantane derivatives (12, 13 and 14) in all of which the adamantyl residue was substituted in the tertiary position. The basic fraction was studied in detail (by GC/MS) in collaboration with Professor Jankowski<sup>35a</sup> and there was no detectable amount of secondary coupling to adamantane. Further study showed that there was a competition between pyridine and oxygen to substitute the tertiary position. It is surely a tertiary radical which is involved in this competition.

In recent studies,<sup>35b</sup> we have compared the reactivity of secondary and tertiary adamantane radicals generated from the *N*-hydroxy-2-thiopyridone derivatives of the appropriate carboxylic acids (see above). Both radicals compete for oxygen, pyridine and thione. In comparable Gif<sup>IV</sup> oxidations, there is little coupling of pyridine to any secondary position, so our conclusions are confirmed.<sup>35,36</sup>

There are two mechanistic interpretations

**Table 1**

Radical trap	Product
—	R-S-Py
<i>n</i> -Bu <sub>3</sub> SnH	R-H
<i>t</i> -BuSH	R-H
Br-CCl <sub>3</sub>	R-Br
Cl-CCl <sub>3</sub>	R-Cl
I-CHCl <sub>2</sub>	R-I
O <sub>2</sub> + (PhS) <sub>3</sub> Sb	ROH
(Ar-X) <sub>2</sub> X=S, Se, Te	Ar-X-R
Z= CO <sub>2</sub> Me, CN, NO <sub>2</sub> , SO <sub>2</sub> Ph, etc.	
SO <sub>2</sub>	RSO <sub>2</sub> -S-Py
P(SPh) <sub>3</sub>	R-P(SPh) <sub>2</sub>
Z=alkyl, alkoxy	R= CF <sub>3</sub> (CF <sub>2</sub> ) <sub>n</sub> , n= 2

of these facts. First, there could be two different reagents, one of which attacked the tertiary positions and the other the secondary positions. The alternative would be one reagent which attacks both secondary and tertiary positions to give a derivative. The latter evolves into radicals at the tertiary positions, but not at the secondary positions. The second possibility is far more in keeping with the C-H bond strengths and we have adopted it.

It seemed to me that all the facts so far observed could be explained by a reagent which inserted into the C-H bond to give an iron-carbon bond.<sup>37a</sup> The evolution of a *tert*-adamantyl  $\sigma$ -iron bond into radicals at room temperature has a close analogy.<sup>37b</sup> The more stable secondary iron-carbon bond might evolve into an iron carbene double bond which would certainly be cleaved by oxygen to give ketone. This would explain why the more reducing conditions of the Gif system (in an apparent paradox) give ketone rather than secondary alcohol. These considerations then

gave us a working hypothesis which is summarized in Scheme 8.

The true  $C^2/C^3$  in the adamantane oxidation requires that total amount of tertiary products (11, 12, 13 and 14) be added into the calculation. This gives a number (about 1.2) which is independent of oxygen pressure down to low pressures of oxygen. This number is very different from 0.15 or less, typical of oxenoid radical reactions.

At the time of our iron-carbon  $\sigma$ -bond hypothesis, this seemed to us to be remote from biological oxidation processes. However, an interpretation<sup>37c</sup> of the chemistry of penicillin cyclase (essential for penicillin biosynthesis) and also of soybean lipoxygenase assumes the attack of an Fe=O grouping to give an iron-carbon  $\sigma$ -bond as a first step. The enzymatic evidence is less sure than our studies on adamantane. It may be that we have been unwittingly studying Nature's second mechanism for hydrocarbon oxidation.

We explain the selectivity in the Gif oxida-

tion as a compromise between C-H bond strengths (*prim* > *sec* > *tert*) and steric hindrance to insertion (*tert* > *sec* > *prim*).

In the original scheme, we did not specify the valence of the iron oxenoid species. In recent work,<sup>27</sup> we showed that  $GoAgg^I(Fe^{III} + KO_2)$  and  $GoAgg^{II}(Fe^{III} + H_2O_2)$  afforded the same iron species oxidizing saturated hydrocarbons in a typical Gif fashion. Following the logic of the  $P_{450}$  equation, this suggests that it is an  $Fe^{(V)}$  oxenoid species which is responsible for the formation of the iron-carbon bond which then evolves into ketone. We suspect that two  $Fe^{(V)}$  species in a cluster may be involved in ketone formation.

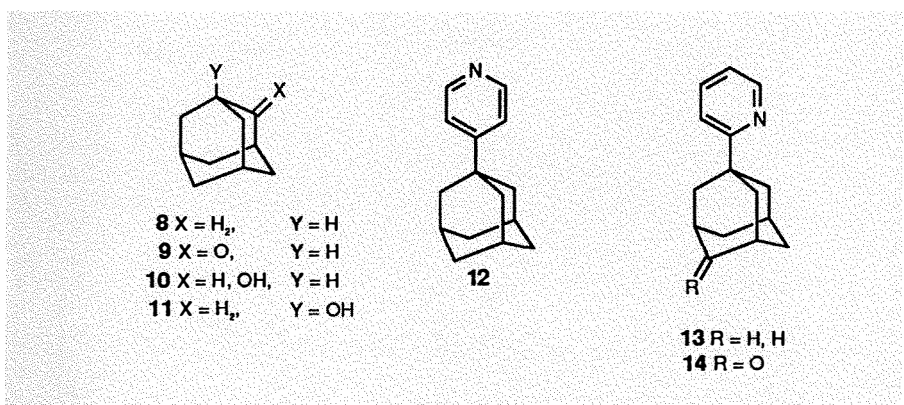
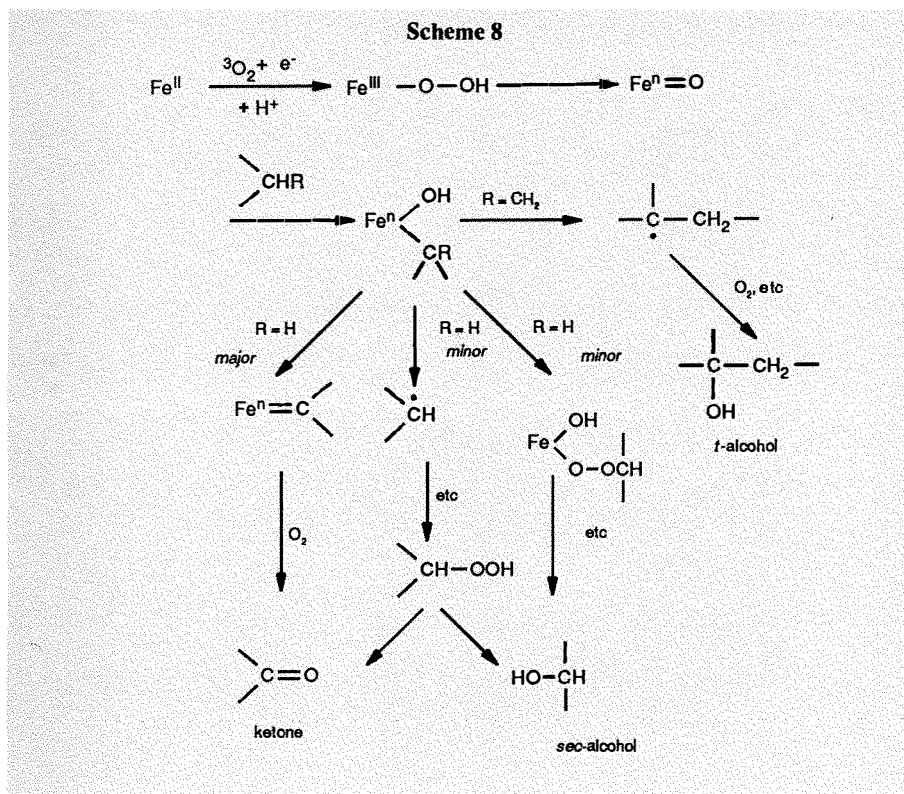
Be this as it may, our colleague, Professor D.T. Sawyer, and his collaborators have recently modified the ligands in  $GoAgg^{III}$  by starting with a complex of picolinic acid. This gave a beautiful ketonization of a series of saturated hydrocarbons with typical Gif selectivity.<sup>38</sup> Two additional experiments were the oxidation of 1,4-dihydrobenzene (15) to phenol and of 1,3-cyclohexadiene (16) to benzene. Clearly, 15 and 16 are not converted to the same radical 17, or the same products would be formed. The difference in behavior can be explained by the two different  $Fe^{(V)}$  species 18 and 19. The former undergoes normal ketonization to furnish phenol whereas the latter undergoes a Fe-H  $\beta$ -elimination process driven by the aromaticity of the benzene formed.

Recently, an important summary of current research on functionalization of alkanes has been published.<sup>36</sup>

In the course of our efforts to capture the iron-carbon  $\sigma$ -bond in Gif<sup>III</sup> and Gif<sup>IV</sup> systems, we added diphenyl diselenide. At once we observed the formation of phenylseleno derivatives of the saturated hydrocarbons used (adamantane and cyclohexane). Using an excess of hydrocarbon in Gif<sup>III</sup>, there is no formation of oxidation products. Only phenylseleno derivatives are formed with a perfect mass balance in hydrocarbon. Up to 90% of the selenium appears as the phenylseleno derivatives and the rest is converted into 2-phenylselenopyridine.<sup>39</sup> There is reaction only if oxygen is present and consumed.

Diphenyl diselenide is an excellent trap for radicals and so its formation of phenylseleno derivatives instead of oxidation products could be construed in this sense. However, the regioselectivity and chemoselectivity of the Gif-type systems are so far from what would be normal for radical chemistry that we reject this possibility. The sequel provides a further justification for this conclusion.

When  $Fe^{(IV)}$  bispicolinate was present in the same concentration as hydrogen peroxide in  $GoAgg^{III}$  with an excess of cyclohexane, hydroxyl radicals were produced by Fenton chemistry. The hydroxyl radicals gave cyclohexyl radicals which reacted with the pyridine to give cyclohexylpyridine (major product), dicyclohexyl and oxidation products (minor). On addition of diphenyl diselenide, the cyclohexyl radicals were efficiently captured to give cyclohexyl phenyl selenide. When all the



Fe<sup>(II)</sup> had been oxidized to Fe<sup>(III)</sup> and all the diphenyl diselenide converted to cyclohexyl phenyl selenide, further addition of hydrogen peroxide produced cyclohexanone in the usual way.<sup>40</sup>

This is an important experiment because it shows that when the right conditions are chosen for Fenton chemistry, coupling of cyclohexyl radicals with pyridine is observed. However, in the habitual ketonization reaction (Fe<sup>(III)</sup> + H<sub>2</sub>O<sub>2</sub>) cyclohexyl radicals are not formed.

A newly invented reaction may be useful at the time of invention but be surpassed by a higher yielding reaction later. Such was the case with nitrite photolysis.

After Reichstein and his colleagues<sup>41</sup> had determined the structure of aldosterone (20) by a remarkable feat of classical degradation, tremendous effort was expended on its total and partial synthesis. The masked aldehyde function at C-18 made partial synthesis from another steroid improbable, so there was need to invent a new reaction for substitution of unactivated neopentyl methyl groups. I conceived<sup>42</sup> of a radical reaction (Barton reaction) of the type shown in Scheme 9. This was quickly reduced to practice. The readily available corticosterone acetate (21) was smoothly transformed to its nitrite 22. On photolysis, this afforded the crystalline oxime 23. The latter with nitrous acid<sup>43</sup> readily gave pure aldosterone acetate 24. Although the overall yield was not high (~20%), this new reaction did permit the synthesis of 60 grams of aldosterone acetate when the rest of the world supply was in milligram quantities. Thus, the biology of aldosterone could be fully evaluated.

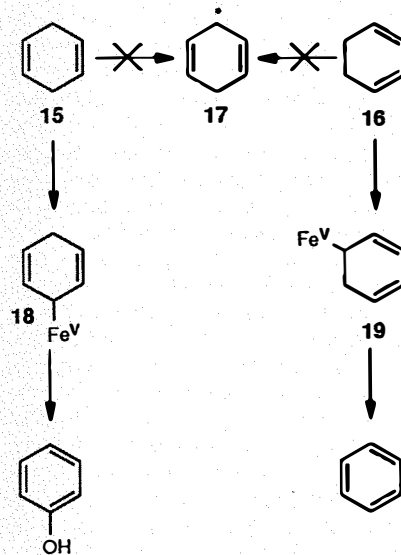
Our choice of nitrites as starting materials was based on the hypothesis that they would afford alkoxy radicals on photolysis, that the axial alkoxy radical would abstract hydrogen from a neighboring axial methyl and that the derived carbon radical would capture NO, the other photolysis product. The nitroso-methyl group was then postulated to isomerize to oxime, a perfect precursor of an aldehyde.

We did consider<sup>42</sup> that hypohalites could also show similar radical chemistry and, in fact, demonstrated this with hypochlorites.<sup>44</sup> This reaction was also found independently by Walling and Padwa.<sup>45</sup> However, there was a better reaction awaiting discovery—the reaction of lead tetraacetate and iodine with primary, secondary or tertiary alcohols to furnish tetrahydrofurans. This discovery by the Ciba group<sup>46</sup> gives better yields than the nitrite photolysis reaction because the alkoxy radical is formed reversibly with the iodine reagent. Such reversibility is not seen in nitrite photolysis. However, the lead tetraacetate-iodine reagent is much more vigorous, so nitrite photolysis can still play a role in molecules which have easily oxidized functional groups.

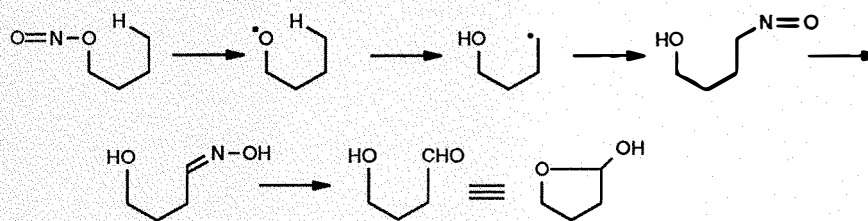
The lead tetraacetate-iodine reagent of the Ciba group, as well as other iodination procedures, served us well in the first solution of the problem of how to convert a saturated acid into the corresponding  $\gamma$ -lactone.<sup>47</sup> We con-

ceived (Scheme 10) that diiodoamides, formed from amides, would on photolysis produce iodoamide radicals. These would abstract hydrogen to give carbon radicals quenchable with iodine. Ionic chemistry would then afford iodoimino-lactones easily hydrolyzable to the desired  $\gamma$ -lactones. This reaction gave reasonable yields and has been used from time to time in synthesis.

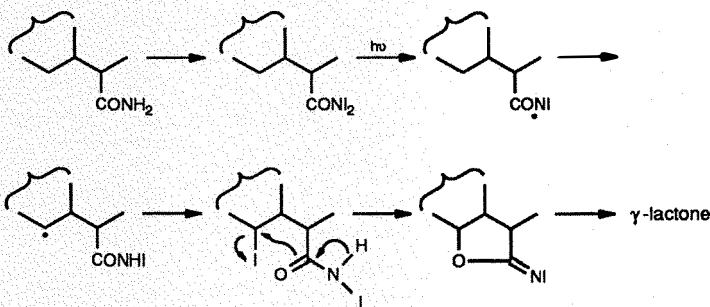
The synthesis of dodecahedrane was a major synthetic objective for many years. The first synthesis by Paquette and collaborators was a brilliant achievement.<sup>48</sup> A more recent remarkable advance has been Prinzbach's "pagodane" route.<sup>49</sup> Recently, the pagodane route has been greatly improved by a spectacular application of the amide-iodine cyclization procedure (Scheme 11). Thus, the diamide 25 was irradiated in the presence of 12 equivalents of iodine in dichloromethane to give the desired diketone 26 in 90% yield on a 2-millimole scale with good reproducibility.



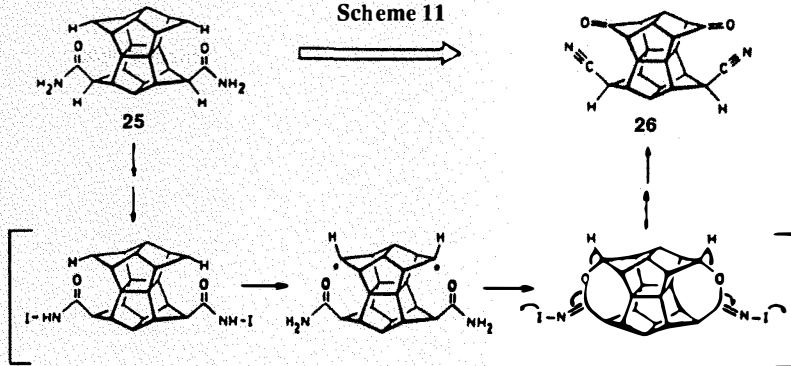
Scheme 9



Scheme 10



Scheme 11





Many bonds are made and broken. Some of the intermediates are indicated in Scheme 11. In this case, steric compression in the starting material increases the yield above what is seen with more usual molecules. Dodecahedrane chemistry promises to be as important a field of chemistry as adamantane chemistry became after von Schleyer's inspired synthesis made this hydrocarbon readily available.<sup>50</sup>

#### Acknowledgements

I hope that this article will stimulate other, and younger, chemists to concentrate their efforts on the field of the invention of chemical reactions. If the actual thought process that conceives a reaction is a personal matter, the demonstration of the truth and the application require collaborators. I would like to thank all my present and former colleagues for helping me to realize my thoughts and for sometimes showing me how wrong I was. A small number have learned how to invent reactions all by themselves, without my influence.

Mention must be made of a number of senior authors with whom I have collaborated. This has always been a special pleasure, since both parties learned from the experience.

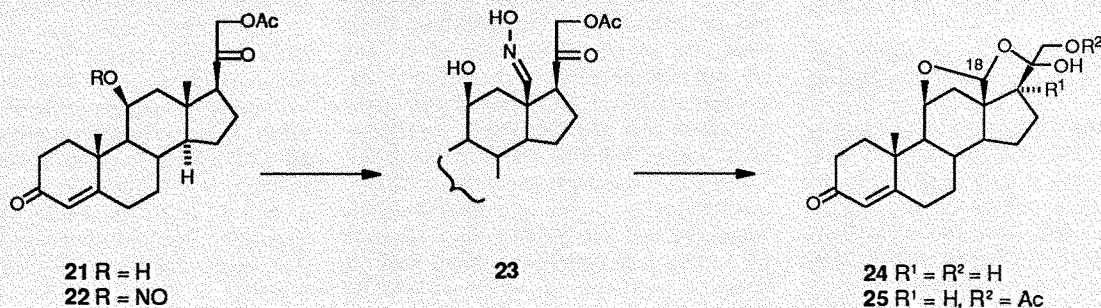
I must thank also all those organizations that have made my work possible by providing the means. Especially, I wish to thank my friends, past and present, in industry who have often stimulated me by their problems and who have helped me with doubly valuable flexible money.

I would also like to thank Texas A&M University, and especially the Chemistry Department, who have made welcome a European Retirement Refugee and have helped him to build up again a promising research group. Last, but not least, I thank the NIH, the NSF, the Welch Foundation and my friends in industry for their ongoing support.

#### References:

- 1) Van der Kerk, G.J.M.; Noltes, J.G.; Luitjen, J.G.A. *J. Appl. Chem.* **1957**, *7*, 356.
- 2) Barton, D.H.R.; Basu, N.K. *Tetrahedron Lett.* **1964**, 3151.
- 3) Barton, D.H.R.; Basu, N.K.; Hesse, R.H.; Morehouse, F.S.; Pechet, M.M. *J. Am. Chem.*

- Soc.* **1966**, *88*, 3016.
- 4) Shephard, K.P.; Van Rheenen, V. *J. Org. Chem.* **1979**, *44*, 1582.
- 5) Barton, D.H.R.; McCombie, S.W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
- 6) Robins, M.J.; Wilson, J.S. *J. Am. Chem. Soc.* **1981**, *103*, 933. Robins, M.J.; Wilson, J.S.; Hansske, F. *ibid.* **1983**, *105*, 4059.
- 7) RajanBabu, T.V. *ibid.* **1987**, *109*, 609. *Idem J. Org. Chem.* **1988**, *53*, 4522.
- 8) Prisbe, L.J.; Martin, J.C. *Synth. Commun.* **1985**, *15*, 401.
- 9) Barton, D.H.R.; Jaszberenyi, J.C. *Tetrahedron Lett.* **1989**, *30*, 2619.
- 10) Barton, D.H.R.; Crich, D.; Motherwell, W.B. *Chem. Commun.* **1983**, 939.
- 11) Crich, D. *Aldrichim. Acta* **1987**, *20*(2), 35. Barton, D.H.R.; Zard, S.Z. *Pure Appl. Chem.* **1986**, *58*, 675. *Idem Philos. Trans. R. Soc. London* **1985**, *B311*, 505. *Idem Janssen Chimica Acta* **1987**, *4*, 3.
- 12) Ingold, K.U.; Luszyk, J.; Maillard, B.; Walton, J.C. *Tetrahedron Lett.* **1988**, *29*, 917.
- 13) Newcomb, M.; Williams, W.G. *ibid.* **1985**, *26*, 1179. Newcomb, M.; Park, S.V. *J. Am. Chem. Soc.* **1986**, *108*, 4132. Newcomb, M.; Glenn, A.G.; Williams, W.G. *J. Org. Chem.* **1989**, *54*, 2675.
- 14) Newcomb, M.; Sanchez, R.M.; Kaplan, J.J. *Am. Chem. Soc.* **1987**, *109*, 1195. Curran, D.P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826.
- 15) Some examples from other laboratories: Della, E.W.; Tsanaktsidis, J. *Aust. J. Chem.* **1986**, *39*, 2061. *Idem ibid.* **1989**, *42*, 61. Quinkert, G.; Billhardt, U.-M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, V.; Heim, N.; Wacher, M.; Schwalbe, T.; Kurth, Y.; Bats, J.W.; Durner, G.; Zimmermann, G.; Kessler, H. *Helv. Chim. Acta* **1987**, *70*, 771. Stofer, E.; Lion, C. *Bull. Soc. Chim. Belg.* **1987**, *96*, 623. Flanagan, D.M.; Jouillie, M.M. *Heterocycles* **1987**, *26*, 2247. Strazewski, P.; Tamm, C. *Synthesis* **1987**, 298. Eaton, P.E.; Maggini, M.J. *Am. Chem. Soc.* **1988**, *110*, 7231. Dauben, W.G.; Kowalczyk, B.A.; Bridon, D.P. *Tetrahedron Lett.* **1989**, *30*, 2461. Alfonso, C.M.; Barros, M.T.; Godhino, L.; Maycock, C.D. *ibid.* **1989**, *30*, 2707.
- 16) Newcomb, M.; Park, S.V.; Kaplan, J.; Marquardt, D.J. *ibid.* **1985**, *26*, 5651. Newcomb, M.; Deeb, T.B. *J. Am. Chem. Soc.* **1987**, *109*, 3163.
- 17) Beckwith, A.L.J.; Hay, B.P. *ibid.* **1988**, *110*, 4415.
- 18) A full discussion of P<sub>450</sub>-type enzymes and their chemistry is given in *Cytochrome P<sub>450</sub> Structure, Mechanism and Biochemistry*; Ortiz de Montellano, P.R., Ed.; Plenum Press: New York, 1986.
- 19) Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125.
- 20) (a) Guengerich, F.P.; Macdonald, T.L. *ibid.* **1984**, *17*, 9. (b) White, R.E.; Coon, M.J. *Ann. Rev. Biochem.* **1980**, *19*, 315. (c) Ullrich, V. *Top. Curr. Chem.* **1979**, *83*, 67. (d) Groves, J.T. *Adv. Inorg. Biochem.* **1979**, 119.
- 21) (a) Groves, J.T.; Krichnan, S.; Avari, G.E.; Nemo, T.E. *Adv. Chem. Ser.* **1980**, *191*, 277. (b) Tabushi, I.; Koga, N. *ibid.* **1980**, *191*, 291. (c) Nee, M.W.; Bruice, T.C. *J. Am. Chem. Soc.* **1982**, *104*, 6123. (d) Lindsay Smith, J.R.; Sleath, P.R. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1009. (e) Lee, W.A.; Bruice, T.C. *J. Am. Chem. Soc.* **1985**, *107*, 513.
- 22) (a) Hayaishi, O.; Katagiri, O.; Rothberg, S. *ibid.* **1955**, *77*, 5450; (b) Mason, H.S.; Foulks, W.L.; Paterson, E. *ibid.* **1955**, *77*, 2914. For recent reviews on the selective oxidation of hydrocarbons, see: Crabtree, R.H. *Chem. Rev.* **1985**, *85*, 245; Green, M.L.H.; O'Hare, D. *Pure Appl. Chem.* **1985**, *57*, 1987. Halpern, J. *Inorg. Chim. Acta* **1985**, *100*, 41. Rothwell, I. *Polyhedron* **1985**, *4*, 177.
- 23) Barton, D.H.R.; Gastiger, M.J.; Motherwell, W.B. *Chem. Commun.* **1983**, 41.
- 24) Barton, D.H.R.; Hay-Motherwell, R.S.; Motherwell, W.B. *Tetrahedron Lett.* **1983**, 1979.
- 25) Barton, D.H.R.; Gastiger, M.J.; Motherwell, W.B. *Chem. Commun.* **1983**, 41.
- 26) Balavoine, G.; Barton, D.H.R.; Boivin, J.; Gref, A.; LeCoupene, P.; Ozbalik, N.; Pestana, J.A.X.; Riviere, H. *Tetrahedron*, **1988**, *44*, 1091 and references there cited.
- 27) Barton, D.H.R.; Halley, F.; Ozbalik, N.; Young, E.; Balavoine, G.; Gref, A.; Boivin, J. *Nouv. J. Chim.* **1989**, *13*, 177.
- 28) Geletii, Y.V.; Lavrushko, V.V.; Shilov, A.E. *Dokl. Akad. Nauk. SSSR* **1986**, *288*, 139.
- 29) Barton, D.H.R.; Ozbalik, N.; Senglet, N., in preparation.
- 30) Barton, D.H.R.; Boivin, J.; Gastiger, M.J.; Morzycki, J.; Hay-Motherwell, R.S.; Motherwell, W.B.; Ozbalik, N.; Schwartztruber, K.M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 947. Barton, D.H.R.; Boivin, J.; Motherwell, W.B.; Ozbalik, N.; Schwartztruber, K.M.;



- Jankowski, K. *Nouv. J. Chim.* **1986**, *10*, 387.  
 Barton, D.H.R.; Boivin, J.; Hill, C.H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1797.
- 31) (a) Barton, D.H.R.; Beloeil, J.-C.; Billion, A.; Boivin, J.; Lallemand, J.-Y.; Lelandais, P.; Mergui, S. *Helv. Chim. Acta* **1987**, *70*, 2187. (b) Barton, D.H.R.; Lee, K.W.; Mehl, W.; Ozbalik, N.; Zhang, L. *J. Am. Chem. Soc.*, submitted for publication.
- 32) (a) Groves, J.T.; Nemo, T.E. *J. Am. Chem. Soc.* **1983**, *105*, 6243. Groves, J.T.; Watanabe, Y. *ibid.* **1986**, *108*, 7836. (b) Collman, J.P.; Hampton, P.D.; Brauman, J.I. *ibid.* **1986**, *108*, 7861. (c) Traylor, T.G.; Nakano, T.; Miksztal, A.R.; Dunlap, B.E. *ibid.* **1987**, *109*, 3625.
- 33) Groves, J.T.; Watanabe, Y. *ibid.* **1988**, *110*, 8443. Battioni, P.; Renaud, J.P.; Bartoli, J.F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *ibid.* **1988**, *110*, 8462.
- 34) Fossey, J.; Lefort, D.; Massaudi, M.; Nedelec, J.-Y.; Sorba, J. *Can. J. Chem.* **1985**, *63*, 678.
- 35) (a) Barton, D.H.R.; Boivin, J.; Schwartzen-truber, K.M.; Ozbalik, N.; Gaudin, D.; Jan-kowski, J. *Spectroscopy Lett.* **1987**, *20*, 963. (b) Barton, D.H.R.; Halley, F.; Ozbalik, N.; Schmitt, M.; Young, E.; Balavoine, G. *J. Am. Chem. Soc.* **1989**, *111*, 7144.
- 36) *Activation and Functionalization of Alkanes*; Hill, C.L., Ed.; John Wiley and Sons: New York, 1989. Chapter VIII by C.L. Hill gives a good account of his own work with a historical perspective of alkane activation.
- 37) (a) Barton, D.H.R.; Boivin, J.; Ozbalik, N. Schwartzen-truber, K.M. *Tetrahedron Lett.* **1985**, *26*, 447. (b) Bower, B.K.; Tennent, H.G. *J. Am. Chem. Soc.* **1972**, *94*, 2512. (c) J.E. Baldwin; In *Recent Advances in the Chemistry of  $\beta$ -Lactam Antibiotics*; Brown, A.G.; Roberts, S.M.; RSC Special Publ.: London, 1985; p 62.
- 38) Sheu, C.; Richert, S.A.; Sawyer, D.T. *J. Am. Chem. Soc.*, submitted for publication. Sheu, C.; Richert, S.A.; Cofre, P.; Sawyer, D.T.; Kanofsky, J.R. *J. Am. Chem. Soc.*, submitted for publication. Cofre, P.; Richert, S.A.; Sawyer, D.T. *Inorg. Chem.*, submitted for publication.
- 39) Barton, D.H.R.; Boivin, J.; Le Coupanec, P. *Chem. Commun.* **1987**, 1379. Balavoine, G.; Barton, D.H.R.; Boivin, J.; Le Coupanec, P.; Lelandais, P. *New J. Chem.* **1989**, *13*, 691.
- 40) Sheu, C.; Sobkowiak, A.; Zhang, L.; Ozbalik, N.; Barton, D.H.R.; Sawyer, D.T. *J. Am. Chem. Soc.* **1989**, *111*, 8030.
- 41) Simpson, S.A.; Tait, T.F.; Wettstein, A.; Neher, R.; Euv, J. von; Schindler, O.; Reichstein, T. *Helv. Chim. Acta* **1954**, *37*, 1163, 1200.
- 42) Barton, D.H.R.; Beaton, J.M. Geller, L.E.; Pechet, M.M. *J. Am. Chem. Soc.* **1960**, *82*, 2640.
- 43) Barton, D.H.R.; Beaton, J.M. *ibid.* **1960**, *82*, 2641. *Idem ibid.* **1961**, *83*, 4083. For improved syntheses of aldosterone acetate and derivatives by the Barton reaction, see Barton, D.H.R.; Basu, N.K.; Day, M.J.; Hesse, R.H.; Pechet, M.M.; Starratt, A.N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2243.
- 44) Akhtar, M.; Barton, D.H.R. *J. Am. Chem. Soc.* **1961**, *83*, 2213.
- 45) Walling, C.; Padwa, A. *ibid.* **1961**, *83*, 2207.
- 46) Meystre, C.; Heusler, K.; Kalvoda, J.; Wieland, P.; Anner, G.; Wettstein, A. *Experientia* **1961**, *17*, 475. *Idem Helv. Chim. Acta* **1962**, *45*, 1317.
- 47) Barton, D.H.R.; Beckwith, A.L.J. *Proc. Chem. Soc.* **1963**, 335. Barton, D.H.R.; Beckwith, A.L.J.; Goosen, A. *J. Chem. Soc.* **1965**, 181. Baldwin, J.E.; Barton, D.H.R.; Dainis, I.; Pereira, J.L.C. *J. Chem. Soc.* **1968**, 2283.
- 48) Paquette, L.A.; *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 4495. Paquette, L.A.; Ternansky, R.J.; Balogh, D.W.; Kentgen, G. *J. Am. Chem. Soc.* **1983**, *105*, 5446.
- 49) Fessner, W.-D.; Murty, B.A.R.C.; Worth, J.; Hunkler, D.; Fritz, H.; Prinzbach, H.; Roth, W.D.; Schleyer, P. von R.; McEwen, A.B.; Maier, W.F. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 452. Spurr, P.R.; Murty, B.A.R.C.; Fessner, W.-D.; Fritz, H.; Prinzbach, H. *ibid.* **1987**, *26*, 455.
- 50) Schleyer, P. von R.; Donaldson, M.M. *J. Am. Chem. Soc.* **1960**, *82*, 4645

### About the Author

Sir Derek Barton completed his Ph.D. degree at Imperial College, London, in Organic Chemistry in 1942 under the direction of Sir Ewart (Tim) Jones. After two years in military intelligence and a year in industry, he returned to Imperial College and taught Inorganic and then Physical Chemistry from 1945-1949. An early interest in steroids and triterpenoids led him to the Method of Molecular Rotation Differences. A precise analysis of published data gave rise to a number of revised structures, many of them confirmed by later experimental work. A second interest in the gas-phase pyrolysis of chlorinated hydrocarbons led to a series of papers on mechanism, which produced an offer to become a Professor of Physical Chemistry. However, Harvard University intervened with an invitation to teach Natural Products Chemistry while (the late) Professor R.B. Woodward was on sabbatical leave. The year at Harvard produced the famous paper on the relationship between conformation and chemical reactivity which, in 1969, was recognized by the award of the Nobel Prize (shared with Odd Hassel).

The decade from 1950-1960 was spent on complex structural problems in triterpenoid and steroid chemistry. The apotheosis of this work was surely the structure of the key compound of the limonoids, limonin. As a by-product, a new reaction for an industrial process was accidentally discovered. An international team (including Duilio Arigoni, E.J. Corey and Oskar Jeger and many collaborators later famous in their own right) of organic chemists found their match in the X-ray work by J. Monteath Robertson. From then on, structural chemistry was no longer to be the motor of organic chemical progress. Now advances were to come from synthetic chemistry.

During the period 1950-1955, Professor

Barton started to work on phenolate radical coupling, leading to a two-step synthesis of usnic acid, based on biosynthetic theory. Later, in Glasgow (1955-1957), this theory was expanded to include morphine alkaloids, especially morphine, *Amaryllidaceae* alkaloids and many other natural products. The theory predicted the existence of dienone and enone alkaloids before any were known and even a new reaction, the dienol $\rightarrow$ benzene elimination before it was seen chemically. Later, he spent twenty years showing the correctness of the theory by incorporation experiments into plants. The biosynthesis of steroids was another activity of this period which culminated with the yeast sterol mutants which defined with precision the biosynthesis of ergosterol.

But to return to 1960—that year saw the announcement of a simple three-step synthesis of aldosterone acetate using a new photochemical reaction invented by Sir Derek Barton. In fact, from 1957 to the present day, he has produced a series of interesting new photochemical reactions, some of them of synthetic value.

Since 1975, Professor Barton has concentrated on the invention of new reactions, most of which have been radical reactions. He has shown how to design high-yielding radical reactions that can be used for the manipulation of sensitive molecules such as sugars, peptides and even polyenes. The more important reactions are given in the text above.

Another activity in the last decade has been the development of ligand coupling reactions, based mainly on Bi<sup>(V)</sup>. Such reactions permit the synthesis of very hindered arylated compounds in good yield and under mild conditions.

Not to be forgotten also is the long series of papers on electrophilic fluorination carried out at Rimac in collaboration with R.H. Hesse and M.M. Pechet. The principal reagents used were CF<sub>3</sub>OF and molecular fluorine. When radical reactions are inhibited, then a beautiful electrophilic reactivity is seen. The culmination point of this was the stereoselective functionalization of only one or two of the tertiary centers in steroids, even in cholesterol acetate dichloride.

Finally, Professor Barton joined in the search for the chemists' Holy Grail, the selective functionalization of saturated hydrocarbons. In the evolution of the Gif-type system, he thinks that he has found it (see text above).

After returning to Imperial College in 1957 as Professor of Organic Chemistry, Professor Barton remained for 21 years in office. In a curious act of courage (or foolhardiness), he retired from the British system at age 60 and joined the French system as Director of the Institute of Natural Product Chemistry (C.N.R.S.) in Gif-sur-Yvette in France. In spite of his administrative responsibility, the time spent at Gif was the second scientific highlight of his career. The first was, of course, the period 1950-1960.

Now, after retiring again, he is a new Professor, since 1986, at Texas A&M University. What will he do next?

# TPAP: Tetra-*n*-propylammonium Perruthenate, A Mild and Convenient Oxidant for Alcohols

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## Introduction

There is a constant need in organic synthesis to develop new oxidizing reagents that are reliable, easy to use and that demonstrate advantages over reagents in existing procedures. Even today, the simple oxidation of alcohols to carbonyl compounds is not without problems. These can involve obnoxious side products, low reaction temperatures and disposal of toxic residues; in addition, most methods are non-catalytic. For these many reasons, the reagent we have called TPAP (tetra-*n*-propylammonium perruthenate) was developed by us in 1987<sup>1</sup> to effect the mild and selective catalytic oxidation of alcohols to carbonyl compounds at ambient temperature. In this report, we describe some of the early background to the work and catalog many new examples of the oxidation that we have investigated. Additionally, we highlight some of the practical aspects of the reaction including further modifications of the experimental procedure developed since our initial publication, which greatly improve the reactions.

## Background

Ruthenium and osmium are unique in the entire Periodic Table in two respects.

First, in a handful of their complexes containing the strongly  $\sigma$ - and  $\pi$ -donating oxo ( $O^2$ ) ligand, they can sustain the extremely high +VIII oxidation state: no other element exhibits octavalency. Secondly, they are also alone in displaying eleven oxidation states (from +VIII, corresponding to an empty  $d^0$  electron configuration, to -II, corresponding to a full  $d^{10}$  configuration). Both of these factors, which dominate the high oxidation-state chemistry of these elements, arise from the fact that they are second- and third-row members of the transition-metal block, so placed within that series that they retain some of the characteristics of early transition elements. In principle, for reactions in which



their complexes are utilized for oxidation (or reduction) purposes, any one of these eleven oxidation states can be selected almost at will by the appropriate choice of ligand in the coordination sphere.

In ruthenium, a second-row transition element, the outer 4d electrons are more tightly held to the nucleus than is the case for the 5d electrons in its congener, osmium. The consequence is that, for a given oxidation state, a ruthenium complex will be more oxidizing (because it is more difficult to detach electrons from it) than the corresponding osmium complex: this generalization will certainly be operative for oxidation states from +VIII ( $d^0$ ) to +IV ( $d^4$ ) inclusive. Thus,  $Ru^{(VIII)}O_4$  is a much more powerful oxidant than is  $Os^{(VIII)}O_4$  (for  $RuO_4/[RuO_4]$  the  $E_0$  is +0.99v, whereas for  $OsO_4/[OsO_4]$  it is +0.22v;<sup>2</sup> similarly,  $[RuO_4]$  is more oxidizing than  $[OsO_4]$ ). The relatively mild oxidizing properties of  $OsO_4$  constitute a major virtue for organic chemistry: whereas  $RuO_4$  will in most cases cleave double bonds,  $OsO_4$  will, under the appropriate conditions, *cis*-hydroxylate them in one of the most selective and catalytically efficient processes known to chemists.<sup>3ab</sup> Nevertheless, the *range* of potentially available ruthenium-containing oxidants for organic chemistry is greater than that for osmium and, of

course, ruthenium is much cheaper.

Although Karl Karlovich Klaus (1796-1864), the father of ruthenium chemistry, discovered the element in 1844,<sup>4a</sup> it took him another sixteen years to isolate the highly unstable, volatile tetroxide  $RuO_4$ .<sup>4b</sup> He and others noted that it was a powerful oxidant but it was not until 1953 that a systematic survey was undertaken of its properties as an organic oxidant, though  $OsO_4$  had been in use as a *cis*-hydroxylating reagent for alkenes since the turn of the century. Djerassi found  $RuO_4$  to be a powerful, rather destructive and non-selective oxidant;<sup>5</sup> its properties in this respect have been comprehensively reviewed by Lee.<sup>6</sup> It does, however, have uses in organic chemistry, mainly in the oxidation of secondary hydroxyl groups in carbohydrates to carbonyl functions.<sup>6,7</sup>

If  $RuO_4$  is too powerful an oxidant, an obvious strategy in the development of new oxidants involving the metal is to design oxo complexes with lower oxidation states, as well as to attempt, by using selected co-ligands, to fine-tune the electronic environment of the coordination sphere. This approach has been very fruitful. Our own entry into this field, ten years ago,<sup>8</sup> was to devise a catalytic system built around the ruthenate ion (then thought to be tetrahedral  $[RuO_4]^{2-}$ , but now known, from



Karl Karlovich Klaus

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recent X-ray studies,<sup>9</sup> to be trigonal bipyramidal,  $trans-[Ru^{(VI)}O_3(OH)_2]^{2-}$  with aqueous persulfate as co-oxidant. This reagent worked well in aqueous base (the presence of which is necessary to avoid disproportionation of  $[RuO_3(OH)_2]^{2-}$  to  $RuO_4$  and  $RuO_2$ ), converting primary alcohols to carboxylic acids and secondary alcohols to ketones. Yields were high, the catalytic turnovers were in the region of 300 and the reagent worked under ambient conditions. However, although isolated double bonds are not attacked, alcohols containing allylic linkages are oxidized slowly and incompletely with some cleavage by-products being formed;<sup>10</sup> moreover, many organic substrates are insoluble in or immiscible with water and may be subject to attack by base. Clearly, an organic-soluble oxidant is necessary.

We have succeeded in preparing a number of organic-soluble ruthenium(VI) oxo catalysts. Our main success, however, has been with ruthenium(VII). The heptavalent state is a very unusual one for ruthenium; one of the very few known examples is the so-called "perruthenate" ion, made by Joly and Debray in 1888<sup>11</sup> by careful oxidation of  $trans-[RuO_3(OH)_2]^{2-}$  with hypochlorite. An X-ray crystal structure of  $K[RuO_4]$ <sup>12</sup> shows this to have a slightly distorted tetrahedral structure (Ru-O 1.79Å, substantially longer than the 1.717Å for the corresponding distance in  $RuO_4$ <sup>13</sup> as would be expected in view of the lower oxidation state in perruthenate). Raman spectroscopic studies show the tetrahedral structure to be maintained in aqueous solution.<sup>2,14,15</sup> In aqueous base we found, in early work,<sup>10</sup> that it functioned stoichiometrically rather like ruthenate as an organic oxidant but with the additional disadvantage that it cleaved isolated double bonds in unsaturated alcohols; our attempts to make the perruthenate analog of "purple benzene" (permanganate with 18-crown-6 in benzene) were only moderately successful.<sup>10</sup> However, reaction of  $K[RuO_4]$

with an aqueous solution of tetra-*n*-butylammonium hydroxide<sup>15</sup> gave  $(n-Bu_4N)[RuO_4]$ , a deep green material which dissolved readily in dichloromethane and functioned as an overall three-electron oxidant, converting primary alcohols to aldehydes and secondary alcohols to ketones without competing double-bond cleavage for unsaturated and allylic alcohols. We subsequently devised a better preparation for this material, which we called TBAP, by reaction of  $RuO_4$  with  $(n-Bu_4N)OH$  in aqueous base;<sup>1,2</sup> an even easier reagent to prepare, though, is the tetra-*n*-propylammonium salt,  $(n-Pr_4N)[RuO_4]$ , TPAP, similarly made from  $RuO_4$  and  $(n-Pr_4N)OH$  in aqueous base.<sup>1,2</sup> Both TBAP and TPAP are air-stable, non-volatile and dissolve in a wide range of organic solvents, although we normally use them in dichloromethane or acetonitrile. In the presence of *N*-methylmorpholine *N*-oxide (NMO), these reagents are catalytic at room temperature and very effective oxidants for a variety of hydroxyl-containing substrates.

### Discussion

Since the discovery of the TPAP reagent, we have had the opportunity of examining its application as an oxidant to a very wide variety of alcohols (Table I). From these results, we can draw several conclusions. First, the reagent is tolerant of a very large range of functional groups which include silyl ethers, indoles, pyrroles, acetals, sulfones, esters, epoxides, double bonds, acetylenes, cyclopropanes, lactones, vinyl halides, halides and SEM groups. Also, as this reagent is effective at room temperature with reaction times usually between 10 minutes to one hour and is easily worked up, it is extremely convenient to use in synthesis. The reagent appears to work well for very small substrate quantities (*ca.* one milligram) when other methods, such as activated dimethyl sulfoxide oxidants, are particularly difficult to handle. Scale-up of reactions is also possible and reactions up to one kilogram have been

achieved.

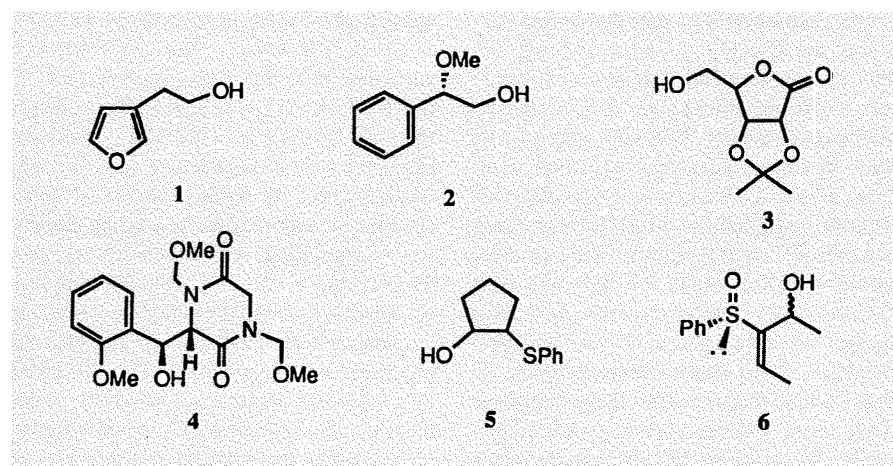
Notable from the examples quoted in the table is that oxidations on multifunctional species are possible and that the oxidation of substrates with labile  $\alpha$ -centers proceeds without racemization. Again, these features are highly desirable for complex organic synthesis. Although we have not exhaustively compared the oxidations in the table using other oxidants, many of the entries show improved yields over, for example, oxidations by standard activated DMSO which is considered by many to be the present bench-mark oxidant.

Like all oxidants, TPAP is not universally acceptable as the best oxidant for all alcohols, and we have found a few substrates, 1 to 6, which are not, or only poorly, oxidized by the reagent.

However, it is comforting from these failures, that only 6 underwent ready oxidation using the Swern reagent.

### Procedures

The TPAP reagent is a dark green solid which is stable at room temperature and may be stored for long periods of time without serious decomposition, especially if kept refrigerated. The reagent should not be heated, however, as small quantities decompose with a flame at 150-160°C. In general, reactions are carried out at ambient temperature, they are catalytic (5 mole %) with turnovers typically around 250, and are run in solvents such as dichloromethane, acetonitrile or combinations of these. It must be emphasized that TPAP oxidations can be quite vigorous. In most of the reactions we have studied, we have used *N*-methylmorpholine *N*-oxide as the co-oxidant. *If a different co-oxidant is used, TPAP should be added carefully and slowly in small portions.* In our early studies, we recommended the addition of 4Å molecular sieves to the reaction. Recently, we have found that use of the finely ground version of these sieves greatly improves the rate and efficiency of the



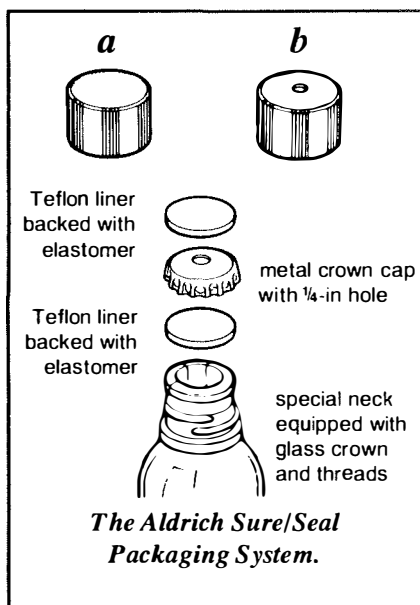
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The Aldrich Sure/Seal packaging system shown below provides a convenient method for storing and dispensing small quantities of moisture-sensitive solvents. The solvent comes in contact with only glass and Teflon®.

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For repeated dispensing of solvent, the solid cap can be replaced with a cap (b) having a  $\frac{3}{16}$ -in hole and equipped with a white natural-rubber liner. With the septum cap in place, the needle can be inserted into the bottle through holes in the poly(propylene) and crown caps piercing both the septum- and crown-cap liners.

If the solvent is stored for an extended period of time, the solid cap should be used to seal the bottle.

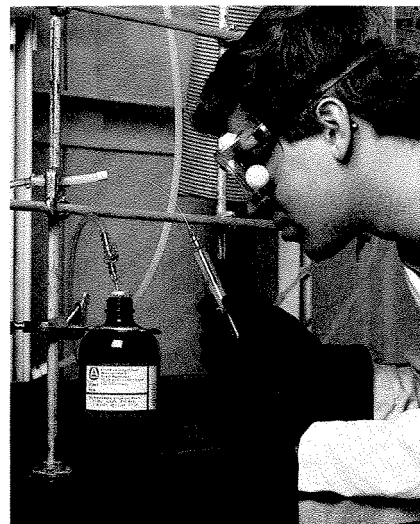


Our Technical Information Bulletin No. AL-134, *Handling Air-Sensitive Reagents*, syringes, needles, sleeve stoppers and related special equipment required for these transactions. Information Bulletin AL-135.

Technical Information Bulletin No. AL-149, *Aldrich Kilo-Lab Cylinder Packaging*, conveniently and safely transferring reagents from these special cylinders. Also, Aldrich Bulletin No. AL-150, *Equipment for Transfer of Liquids from Aldrich Kilo-Lab C*, from our Technical Services Department.

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### TRANSFER TECHNIQUES

Anhydrous solvents are best handled using a syringe. Aldrich offers a variety of septa, syringes and syringe-related hardware.

For withdrawing large quantities of solvent, the Sure/Seal bottle is first pressurized with dry nitrogen. The syringe needle is then inserted into the bottle and the required quantity of liquid withdrawn. For very small quantities, the barrel of the syringe is completely filled with dry nitrogen prior to its insertion, as pictured above. After the needle is inserted into the bottle, the plunger is depressed to expel nitrogen, thus pressurizing the bottle. The plunger can then be gradually pulled out to withdraw the required quantity of solvent. It is important that a positive pressure (not exceeding 5 psi) be maintained inside the bottle. If a vacuum is created by withdrawing liquid into the syringe, ambient moisture and air will leak into the bottle through the pierced septum. By following these recommended procedures the quality of our anhydrous solvents can be maintained for long periods of time.

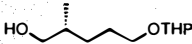
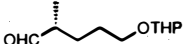
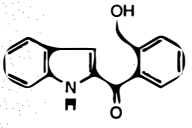
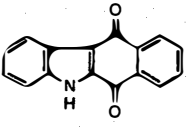
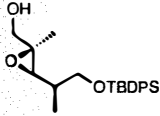
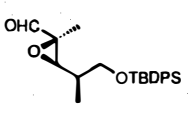


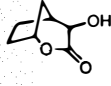
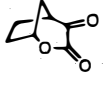
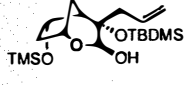
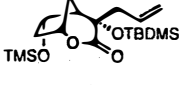
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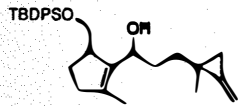
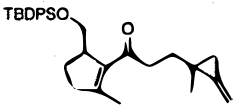
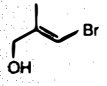
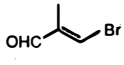
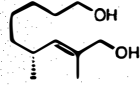
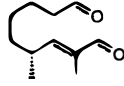
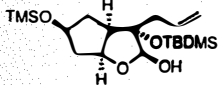
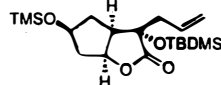
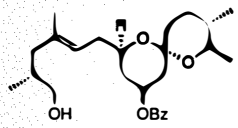
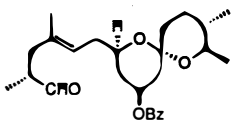
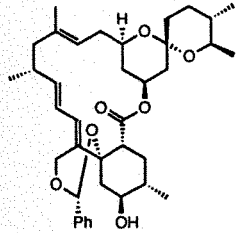
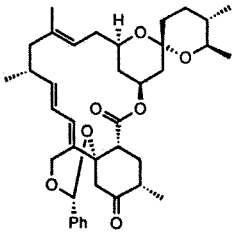
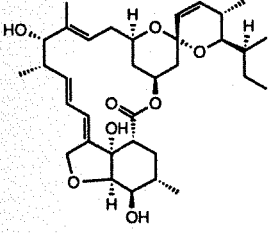
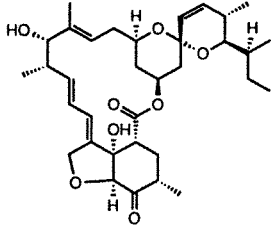
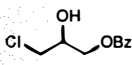
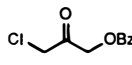
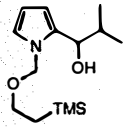
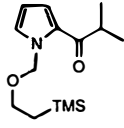
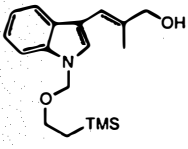
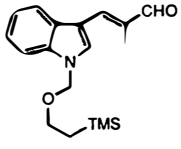
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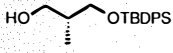
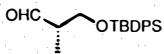
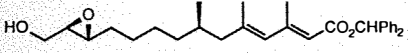
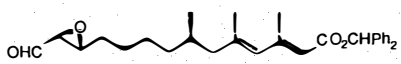
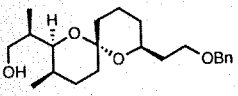
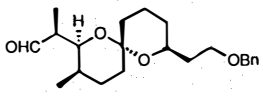

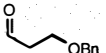
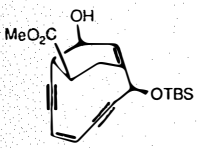
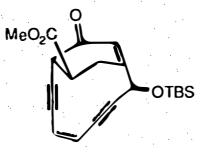
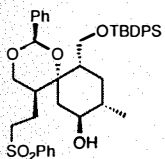
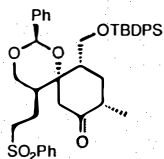
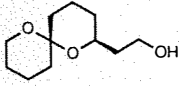
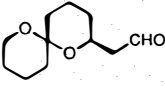
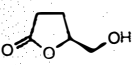
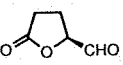
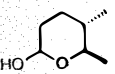
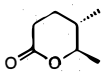
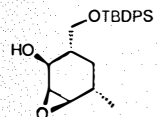
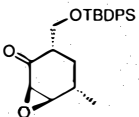
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**TABLE I**  
**TPAP Oxidation of a Variety of Alcohols**

	Alcohol	Product	% Yield	Time (hr)	Comment
1	<i>n</i> -Butanol	<i>n</i> -Butanal	95	1	a
2	Undec-10-en-1-ol	Undec-10-en-1-al	70	3	b
3	Citronellol	Citronellal	75	5	b
4	<i>E</i> -Cinnamyl alcohol	<i>E</i> -Cinnamaldehyde	91	3	b
5	Chrysanthemyl alcohol	Chrysanthemaldehyde	90	5	b
6	Benzyl alcohol	Benzaldehyde	80	2	b
7	2-Chlorobenzyl alcohol	2-Chlorobenzaldehyde	81	4	b
8	4-Methoxybenzyl alcohol	4-Methoxybenzaldehyde	68	12	a
9	3,4-Dimethoxybenzyl alcohol	3,4-Dimethoxybenzaldehyde	98	1.5	b
10	Piperonyl alcohol	Piperonaldehyde	70	1	a
11	Cyclobutanol	Cyclobutanone	95	1.1	b
12	(±)-Menthol	(±)-Menthone	85	1	b
13	<i>endo</i> -Norborneol	Bicyclo[2.2.1]heptan-2-one	73	0.3	b
14	5 $\alpha$ -Androstan-17 $\beta$ -ol-3-one	5 $\alpha$ -Androstan-3,17-dione	99	1.5	a
15	Lanost-8-en-3 $\beta$ -ol	Lanost-8-en-3-one	81	1.5	a
16			71	0.7	b
17			85	5	b
18			70	1	a Swern 35%
19			73	0.5	b
20			80	1.5	b
21			95	0.2	c

	Alcohol	Product	% Yield	Time (hr)	Comment
22			70	18	a, f Swern 38% MnO <sub>2</sub> 0%
23			94	2.5	c Swern 52%
24			82	1	d Swern 87%
25			97	0.2	c
26			95	0.5	d Swern 99%
27			83	0.2	c, h
28			42	1	c, h
29			70	-	d, e
30			73	3	c Swern 0% PCC 0%
31			81	2	c

	Alcohol	Product	% Yield	Time (hr)	Comment
32			95	0.2	c
33			74	0.2	c
34			93	3	c
35			97	0.1	c
36			96	0.1	d
37			85	0.1	d Swern 80%
38			95	0.1	c Swern 93%
39			76	0.1	c, h Swern 91%
40			80	1.5	c
41			54	2	c Swern 10%

Alcohol	Product	% Yield	Time (hr)	Comment
42 		85	0.3	c Swern 76%
43 		33	2	a Swern 12%
44 		91	0.5	c Swern 85%
45 		85	0.5	c
46 		50	-	a, g
47 		71	1.5	c
48 		78	2	c
49 		52	1	c
50 		81	0.5	d
51 		83	0.2	c

a - Procedure A; b - Procedure A but using TBAP reagent; c - Procedure B; d - Procedure C; e - See reference 16; f - See reference 17; g - See reference 18; h - See reference 19.

Bz - benzyl; THP - tetrahydropyranyl; TBDPS - *t*-butyldiphenylsilyl; TBDMS - *t*-butyldimethylsilyl; TBS - *tri-n*-butylsilyl; TMS - trimethylsilyl



oxidation reactions. In a few oxidations, especially on a large scale, we have noticed that in dichloromethane the reaction fails to go to completion for some unknown reason. Nevertheless this problem can often be overcome by simply adding some acetonitrile to effect the full conversion.<sup>16</sup> Alternatively, acetonitrile may be used as the solvent to give improved catalytic turnovers. The use of 10% acetonitrile/dichloromethane is also suitable as a solvent mixture, combining ease of reaction work-up with better turnover.

Most oxidation reactions reach completion rapidly, typically between five minutes and one hour, and therefore the TPAP reagent is extremely convenient to use. **However, care must be taken since, on a large scale, it is necessary to moderate the reaction by cooling and by slow, portionwise addition of TPAP.**

Work-up of the TPAP oxidation reactions is very straightforward. For reactions in dichloromethane, the mixture is simply passed through a short silica-gel column, which is washed with ethyl acetate, and the filtrate evaporated to afford the carbonyl compound. For reactions containing acetonitrile, it is advisable to remove the solvent by rotary evaporation prior to application on the silica-gel pad and elution with dichloromethane or ethyl acetate. This procedure should be adopted since acetonitrile in the mixture tends to co-elute any residual TPAP, hence contaminating the product.

Typical procedures for effecting these oxidation reactions are:

**Method A:** (as reported in the first *Chemical Communications* describing the TPAP reagent)<sup>1</sup>

**Method B:** (dichloromethane solvent, powdered 4Å sieves)

Solid TPAP (5 mol %) is added in one portion to a stirred mixture of the alcohol (1eq), *N*-methylmorpholine-*N*-oxide (1.5 eq) and powdered 4Å molecular sieves (500 mg/mmol) in dichloromethane (2ml/mmol) at room temperature under argon.

On completion, the reaction mixture is filtered through a pad of silica, eluting with dichloromethane or ethyl acetate, depending on product polarity. The filtrate is evaporated and the residue purified in the appropriate way to afford the carbonyl compound.

**Method C:** (acetonitrile, powdered 4Å sieves)

The procedure is the same as Method B using acetonitrile as solvent, except that it is advisable to remove the acetonitrile by evaporation and take up the reaction mixture in dichloromethane prior to the filtration through silica gel.

## Summary

The TPAP reagent appears to be a mild and very convenient catalytic reagent for the oxidation of a very wide range of alcohols to carbonyl compounds. The new experimental procedures are a considerable improvement over those previously reported and we hope they will find general acceptance in organic synthesis.

## References:

- 1) Griffith, W.P.; Ley, S.V.; Whitcombe, G.P.; White, A.D. *Chem. Commun.* **1987**, 1625.
- 2) Dengel, A.C.; El-Hendawy, A.M.; Griffith, W.P. *Trans. Met. Chem.* **1989**, *40*, 230.
- 3) a) Schröder, M. *Chem. Revs.* **1980**, *80*, 187. b) Jacobsen, E.N.; Marko, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
- 4) a) Klaus, K. *Ucheniija Zapiski Kazanskaya Univ.* **1844**, *III*, 15. b) Klaus, K.; *Bull. Acad. St. Petersburg* **1860**, *1*, 97.
- 5) Djerassi, C.; Engle, R. *J. Am. Chem. Soc.* **1953**, *75*, 3835.
- 6) Lee, D.G.; van der Engh, M. In *Oxidation in Organic Chemistry*; Trahanowsky, W.S., Ed.; Academic: London, **1973**; Vol. B, p 177.
- 7) Courtney, J.L. In *Organic Synthesis by Oxidation with Metal Compounds*; Meijs, W.J.; de Jonge, C.R.H., Eds.; Plenum: New York, **1986**; p 445.
- 8) Schröder, M.; Griffith, W.P. *Chem. Commun.* **1979**, 58.
- 9) Elout, M.O.; Haijje, W.G.; Maaskant, M.J.A. *Inorg. Chem.* **1988**, *27*, 610.
- 10) Green G.; Griffith, W.P.; Hollinshead, D.M.; Ley, S.V.; Schröder, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 681.
- 11) Debray, H.; Joly, A. *Compt. Rend.* **1888**, *106*, 1494.
- 12) Silverman, M.D.; Levy, H.A. *J. Am. Chem. Soc.* **1956**, *76*, 3317.
- 13) Schafer, L.; Seip, H.M. *Acta Chem. Scand.* **1967**, *21*, 737.
- 14) Griffith, W.P. *J. Chem. Soc. (A)* **1968**, 1663.
- 15) Dengel, A.C.; Hudson, R.A.; Griffith, W.P. *Trans. Met. Chem.* **1985**, *10*, 98.
- 16) We thank Professors S.M. Roberts and M. Liebster, University of Exeter, for first noting this modification.
- 17) Unpublished observations of Dr. W.B. Motherwell and M. Shipman.
- 18) Schreiber, S.L.; Kiessling, L.L. *Tetrahedron Lett.* **1989**, *30*, 433.
- 19) Anthony, N.J.; Armstrong, A.; Ley, S.V.; Madin, A. *ibid.* **1989**, *30*, 3209.

## About the Authors

Dr. William Griffith and Professor Steven Ley have collaborated for several years on the development of transition-metal complexes and their application to organic synthesis.

Dr. Griffith received his Ph.D. degree from Imperial College in 1960, working with Geoffrey Wilkinson and Jack Lewis, followed by postdoctoral research with Henry Taube in Chicago and Stanford. He returned to Imperial College as a lecturer and is now a reader in Inorganic Chemistry. His hobbies include being a member of a band of eight who ring the eighteenth-century bells at his local Elizabethan parish church.

Professor Ley obtained his Ph.D. degree at Loughborough University with Harry Heaney in 1972. After postdoctoral research at Ohio State University with Leo Paquette and at Imperial College with Derek Barton, he was appointed to the staff at Imperial College in 1975. He was promoted to full professor in 1983. His research involves the discovery of new synthetic methods and their application to the synthesis of biologically active molecules.



# Award-Winning Chemistry

1989 - Professor Derek H.R. Barton

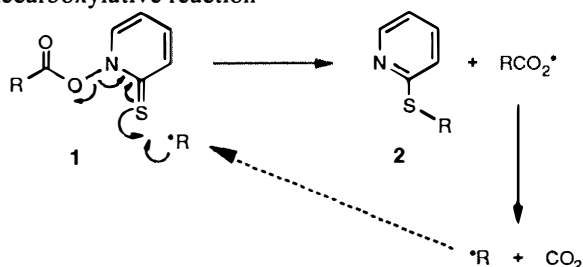
Sir Derek H.R. Barton, Nobel Laureate and Distinguished Professor of Chemistry at Texas A&M, is the recipient of the 1989 ACS Award for Creative Work in Synthetic Organic Chemistry, sponsored by Aldrich.

Professor Barton's work has made a lasting impact in several areas of organic chemistry including conformational analysis, the biosynthesis of alkaloids and steroids, photochemistry and radical reactions. With the conviction that it is possible to invent chemical reactions of synthetic importance, he has developed many useful new methodologies using a logical stepwise approach.<sup>1</sup> The important reactions that he has developed over the past 40 years have continued to find use in a variety of areas. His most recent endeavors focus on radical reactions with a broad spectrum of applications.

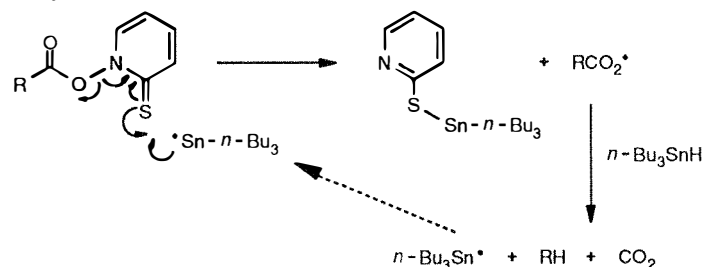
We extend our congratulations to Professor Barton and highlight below some of the valuable contributions from his laboratories.

## Decarboxylative Radical Reaction

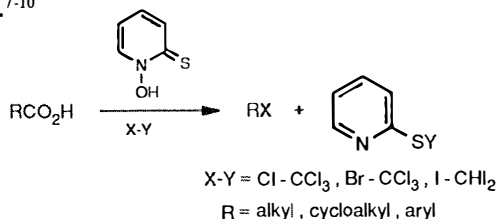
Acyl derivatives of *N*-hydroxy-2-thiopyridone (**1**) decompose smoothly at moderate temperature to give a decarboxylative rearrangement product **2** via an intermediate carbon radical.<sup>2</sup> The decarboxylative reaction



has opened many new vistas in synthetic methodology. If tributyltin hydride is present in the reaction medium, a smooth decarboxylation is achieved.<sup>3</sup>

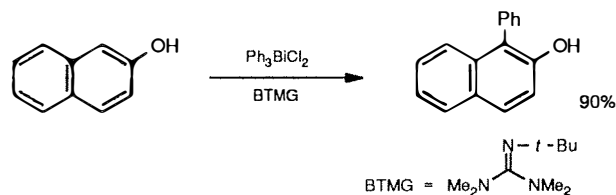


A practical alternative to the Hunsdiecker reaction has also been invented via the decarboxylative radical reaction by adding  $\text{CCl}_4$ ,  $\text{BrCCl}_3$  or  $\text{CHI}_3$  respectively for chloro, bromo or iodo derivatives. The reaction not only gives moderate to high chemical yields but also finds general applicability in aliphatic, alicyclic and aromatic compounds.<sup>4-6</sup> Barton and co-workers have further exploited the potential of this reaction through decarboxylative sulfonylation, chalcogenation and decarboxylative radical addition to quinones.<sup>7-10</sup>

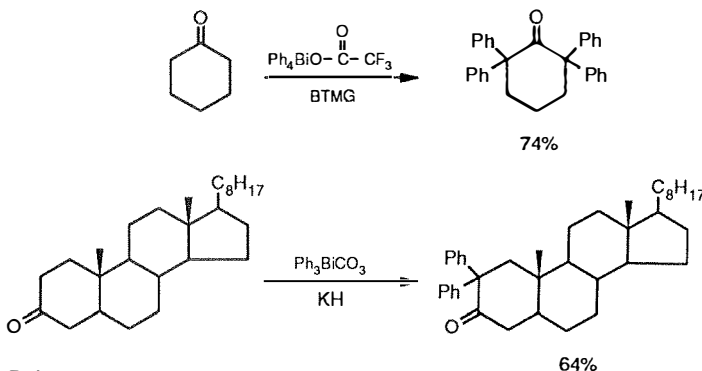


## Pentavalent Organobismuth Reagents

Triphenylbismuth dichloride phenylates 2-naphthol under basic conditions at the 1-position in high chemical yield.<sup>11</sup>



Further, a range of bismuth reagents such as the carbonate, bis(trifluoroacetate), and bis(tosylates) of triphenylbismuth, as well as tetraphenylbismuth analogs have been employed for the phenylation of phenols, enols, enolates and other anions.<sup>12</sup> The reactions are regioselective and afford high chemical yields.<sup>13</sup> A review of phenylation has recently appeared.<sup>14</sup>



## References:

- (1) Barton, D.H.R.; *Aldrichim. Acta* 1990, 23(1), 3.
- (2) Barton, D.H.R.; Crich, D.; Potier, P. *Tetrahedron Lett.* 1985, 26, 5943.
- (3) Barton, D.H.R.; Crich, D.; Motherwell, W.B. *Chem. Commun.* 1983, 939; *Idem Tetrahedron* 1985, 41, 3901.
- (4) *Idem Tetrahedron Lett.* 1983, 24, 4979.
- (5) Barton, D.H.R.; Lacher, B.; Zard, S.Z. *ibid.* 1985, 26, 5939.
- (6) *Idem Tetrahedron* 1987, 43, 4321.
- (7) Barton, D.H.R.; Lacher, B.; Misterkiewicz, B.; Zard, S.Z. *ibid.* 1988, 44, 1153.
- (8) Barton, D.H.R.; Bridon, D.; Zard, S.Z. *Tetrahedron Lett.* 1984, 25, 5777.
- (9) *Idem Tetrahedron* 1987, 43, 5307.
- (10) Crich, D. *Aldrichim. Acta* 1987, 20, 35.
- (11) Barton, D.H.R. *et al. J. Chem. Soc., Perkin Trans. 1* 1985, 2657.
- (12) Barton, D.H.R. *et al. ibid.* 1985, 2667.
- (13) Barton, D.H.R.; Charpiot, B.; Motherwell, W.B. *Tetrahedron Lett.* 1982, 23, 3365.
- (14) Abramovitch, R.A.; Barton, D.H.R.; Finet, J.-P. *Tetrahedron* 1988, 44, 3039.

For a list of Aldrich products utilized in this chemistry, see page 11 of this issue of *Aldrichimica Acta*.



# Aldrichimica Acta

Volume 23, Number 2, 1990



*The Chiral Auxiliary [(C<sub>5</sub>H<sub>5</sub>)Fe(CO)(PPh<sub>3</sub>)] for Asymmetric Synthesis*

*Carboxyolefination*

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Volume 23, Number 2, 1990

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## About Our Cover:

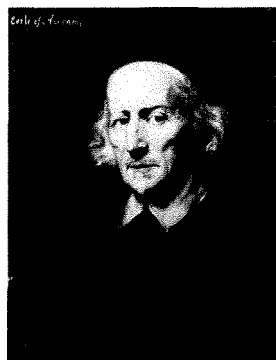


Fig. 1

Readers of the descriptions of our covers will remember how our chemist collector appreciates the works of Jan Lievens, a contemporary of Rembrandt in Leiden. Lievens' *St. Paul* graced our last catalog cover, his *Presentation in the Temple*, the cover of *Aldrichimica Acta*, Vol. 22, No. 1, 1989; both are early works. Here is a very late work, a portrait (oil on canvas, 73 x 60cm) of Jacob Junius.

The young Lievens was a truly gifted artist whose early works were comparable with those of Rembrandt. Rembrandt left Leiden for Amsterdam in 1632 and there went from strength to strength;

his latest works were his best. Lievens went to England where he came under the mesmerizing influence of van Dyck, whom he tried to emulate but failed. For a brief period, Rembrandt, too, came under a similar Flemish influence, that of Rubens, and those works were certainly not his best.

Here is a tantalizing thought: what if Lievens had not gone to England and then to Antwerp, before returning to Holland? Had he stayed in Holland, could Lievens have developed like Rembrandt? Clearly, two of Lievens' very late works not influenced by van Dyck, portraits of distinguished old men, are among the finest Dutch portraits ever.

As Professor W. Sumowski wrote:<sup>1</sup> "During his artistic decline Lievens still manages to surpass the greatest achievements of his early period in a portrait of Sir Robert Kerr (Fig. 1). This is a work that can be compared with Rembrandt's late portraits. Lievens here depicts the appearance and greatness of mind of an eminent old man. Everything that might distract from the face is absent. The dignity of the sitter is rooted in his person, not, as was customary, in his social status. The presentation is subtle with a very minimum of brush strokes. In color the miracle of Lievens' monochromatic Leiden period is repeated."

"In the portrait of Jacob Junius ... (on our cover) ... Lievens once again reaches this remarkable height."

In 1629, when he was the friend and emissary of Charles I, Sir Robert Kerr, the first Earl of Ancrum (Fig. 1) bought paintings from both Lievens and Rembrandt. When Lievens portrayed him in 1654, shortly before his death, in the painting now in the National Gallery of Scotland, the Earl was an unhappy exile, a dour and sad old man.

Jacob Junius (1608-1671) studied law in Leiden, made a fortune in Mazulipatnam in India, returned home and married late in life, in 1657. In 1667 he was elected regent of the Old and New Almshouse in Delft; perhaps this portrait was painted for that occasion. Junius was survived by his widow and three of their six children, and one wonders whether the loss of three children in infancy led to his dour appearance.

It must have been a combination of respect and sympathy for both sitters that led to Lievens' reaching such artistic heights.

(1) W. Sumowski, *Gemälde der Rembrandt-Schüler*, III, p 1769, describing paintings Nos. 1294 and 1295.



# Lab Notes

I wish to report two laboratory techniques which I have found helpful.

(1) Are you having problems labeling NMR tubes? Try using chart edging strip. The oval sprocket holes are just right for 5-mm tubes, and you can tear off the amount you need. Two examples are shown below in Figure 1. The samples are from different printers. One sample is a perforated edging strip, readily detachable from spectra, etc. The other has to be cut from a piece of waste chart paper, but one can choose its dimensions.

(2) Recently, I had to filter a reaction prod-

uct from its suspension in 50% hydrofluoric acid, and decided to use your polypropylene filter cloth (Z10,425-6) for the purpose. On inspection, this cloth appeared to be rather "wooly", and I suspected that it would be difficult to remove the solid product from it. However, a sheet of perforated polypropylene, cut to the same size and laid on top of the cloth, overcame the anticipated problem, *i.e.*, the solid material collected by filtration was easily removable. The perforated polypropylene came from a bread wrapper! That the material

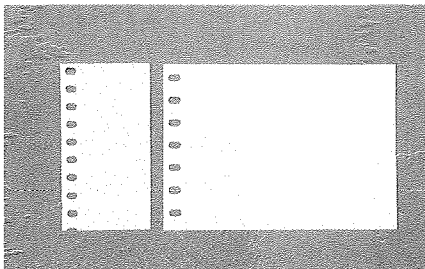


Fig. 1

was in fact polypropylene was rapidly established by comparing its IR spectrum with the Aldrich reference spectrum [FT-IR 1(2), 1158A]. Since then, I have also found this perforated polypropylene useful to cover samples being dried under vacuum at temperatures up to 100°C.

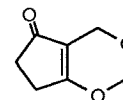
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## "Please Bother Us."

by  
*Amos B. Smith, III*

Professor Amos B. Smith, III, of the University of Pennsylvania kindly suggested that we offer this 1,3-dioxin vinyllogous ester, a versatile  $\beta$ -ketovinyl cation equivalent.<sup>1</sup> The



synthetic utility of this ester was demonstrated in Professor Smith's elegant syntheses of (-)-bertyadionol,<sup>2</sup> jatrophone<sup>3</sup> and the hydroxy-jatrophones.<sup>4</sup>

Naturally, we made this compound.

(1) Smith, A.B. III *et al.* *J. Org. Chem.* **1988**, *53*, 4314. (2) *Idem* *J. Am. Chem. Soc.* **1986**, *108*, 3110. (3) Smith, A.B. III *Strategies and Tactics In Organic Synthesis*; Linberg, T., Ed.; Academic Press: New York, 1984; Chapter 9, pp 224-274. (4) Smith, A.B. III *et al.* *J. Am. Chem. Soc.* **1989**, *111*, 6648.

# The Chiral Auxiliary $[(C_5H_5)Fe(CO)(PPh_3)]$ for Asymmetric Synthesis

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England

## 1. Introduction

There is an increasing demand for homo-chiral (enantiomerically pure) compounds. This demand arises primarily from the needs of the pharmaceutical industry but applications are also emerging from the electronics and polymer sectors. There are three fundamentally different approaches to the preparation of homochiral compounds: (i) resolution, (ii) the chiral pool and (iii) asymmetric synthesis.<sup>1-3</sup> The latter and most general approach involves the attachment of a chiral auxiliary to a prochiral group such as an olefin, carbonyl, enolate, and methylene; the chiral auxiliary then biases the formation from the prochiral group of any new chiral center towards one configuration. During the reaction which elaborates the new chiral centers, the chiral auxiliary may be attached either temporarily or permanently, giving rise in the former case to catalytic reactions and in the latter to stoichiometric reactions.

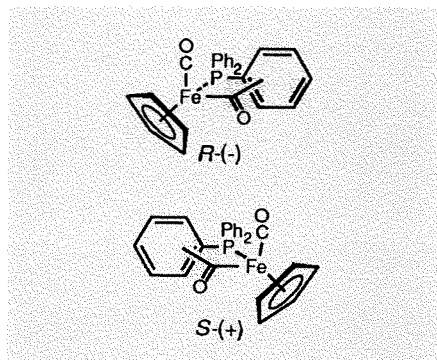
Over the past ten years at Oxford, we have been interested in developing the stoichiometric iron chiral auxiliary  $[(C_5H_5)Fe(CO)(PPh_3)]$  for controlling the stereochemistry during a variety of reactions associated with the carbonyl functional group.<sup>4-8</sup> Described below are some of the applications we have developed for asymmetric synthesis using the iron chiral auxiliary.

## 2. Alkylation Reactions

In 1982 we were the first to report that enolates could be generated from transition-metal acyl complexes.<sup>9</sup> Deprotonation of the orange chiral iron acetyl complex  $[(C_5H_5)Fe(CO)(PPh_3)COMe]$  (**1**) with butyllithium generated the blood-red enolate, which was quenched with methyl iodide to the corresponding propanoyl complex **2** in essentially quantitative yield (eq. 1).<sup>9,10</sup> An important feature of this and other enolates attached to the iron auxiliary is their smooth monoalkylation; no products from dialkylation are observed, which indicates that enolate exchange does not occur at a significant rate. The enolate derived from **1** is a good nucleophile reacting well with secondary iodides in good yield (e.g., isopropyl iodide, 86%) without significant competition from elimination.<sup>11</sup> Rather surprisingly, the enolate derived from **1** undergoes C- rather than O-silylation with

trimethylsilyl chloride to generate **3**.<sup>10</sup>

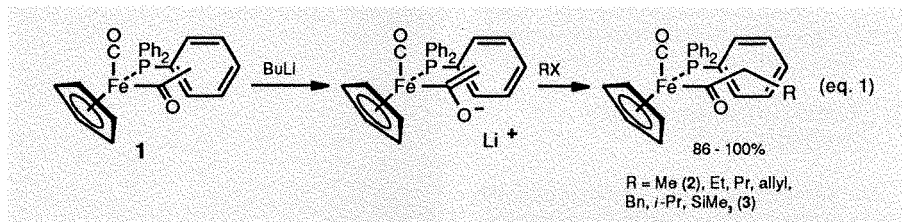
The acetyl complex **1** is octahedral in structure, with triphenylphosphine, carbon monoxide and the acetyl ligands each occupying one site, with the remaining three sites being taken by the cyclopentadienyl ligand. Complex **1** is chiral, existing as the *R*(-) and *S*(+) enantiomers,<sup>12</sup> and configurationally stable under nor-



mal conditions. The complex prefers to adopt a conformation which places the acetyl oxygen *anti* to the carbon monoxide ligand, with one of the triphenylphosphine phenyl groups approximately parallel to the plane of the acetyl ligand, thus shielding one face of the acetyl. There are no significant stereoelectronic factors influencing the conformation of the acetyl ligand; everything seems to be sterically driven.<sup>13-15</sup>

The acetyl carbonyl IR stretching frequency is  $1601\text{ cm}^{-1}$ , indicating a large charge separation ( $Fe^+, O^-$ ) in the ground state (Scheme 1). For this and other reasons, we draw the analogy between acetyl complex **1** and the enolate derived from ethyl acetoacetate, and between the enolate derived from **1** and the dianion from ethyl acetoacetate (Scheme 1). To emphasize the latter analogy, they both require a strong base such as butyllithium for their generation and both undergo C- not O-silylation.<sup>10</sup>

Deprotonation-methylation of the propanoyl complex **2** generates cleanly the elaborated



From right to left: Dr. Stephen Davies, recipient of the first Alfred Bader Award in the UK and Dr. Kay Davies; Prof. John Ward, President of the Royal Society of Chemistry; Mrs. Isabel Bader and Dr. Alfred Bader.

isobutyryl complex **4**. Further alkylations of the chiral iron acyl complexes **5** occur with essentially complete stereoselectivity (Scheme 2).<sup>16-18</sup> Some loss of stereocontrol is observed for small or very reactive electrophiles but, in these cases, small amounts of the minor diastereoisomer may be removed by a single crystallization. The configuration of the newly formed chiral center relative to the original iron center results from completely stereoselective generation of the *E*-enolates (Fe *trans* to R) and their reaction in the *anti* (O<sup>-</sup> to CO) conformation from the unshielded face with electrophiles (Scheme 2).<sup>16-19</sup> Further deprotonation of the dialkylated complexes **4** or **5** does not occur since the remaining  $\alpha$ -proton is buried in the chiral auxiliary and therefore inaccessible to base.

The absolute configuration of the new chiral center in these alkylation reactions is determined by which enantiomer of the chiral iron acetyl complex **1** is used as starting material, and by the order of addition of the alkyl groups in the sequential double-alkylation procedure. After elaboration of the  $\alpha$ -chiral center, the chiral auxiliary may be removed by one-electron oxidants such as bromine, *N*-bromosuccinimide (NBS), ceric ion, ferric ion, etc. Bromine is generally the preferred oxidant unless there are very acid-sensitive groups present, in which case NBS is generally satisfactory. Thus, oxidation of an iron acyl complex in the presence of water, alcohol or amine gives the corresponding carboxylic acid, ester or amide, respectively. Using bromine or NBS as the oxidant, the auxiliary is recovered as [(C<sub>5</sub>H<sub>5</sub>)Fe(CO)(PPh<sub>2</sub>)Br].<sup>11</sup>

The versatility of this alkylation procedure may be illustrated by the asymmetric synthesis of captopril and *epi*-captopril (Scheme 3).<sup>20</sup>

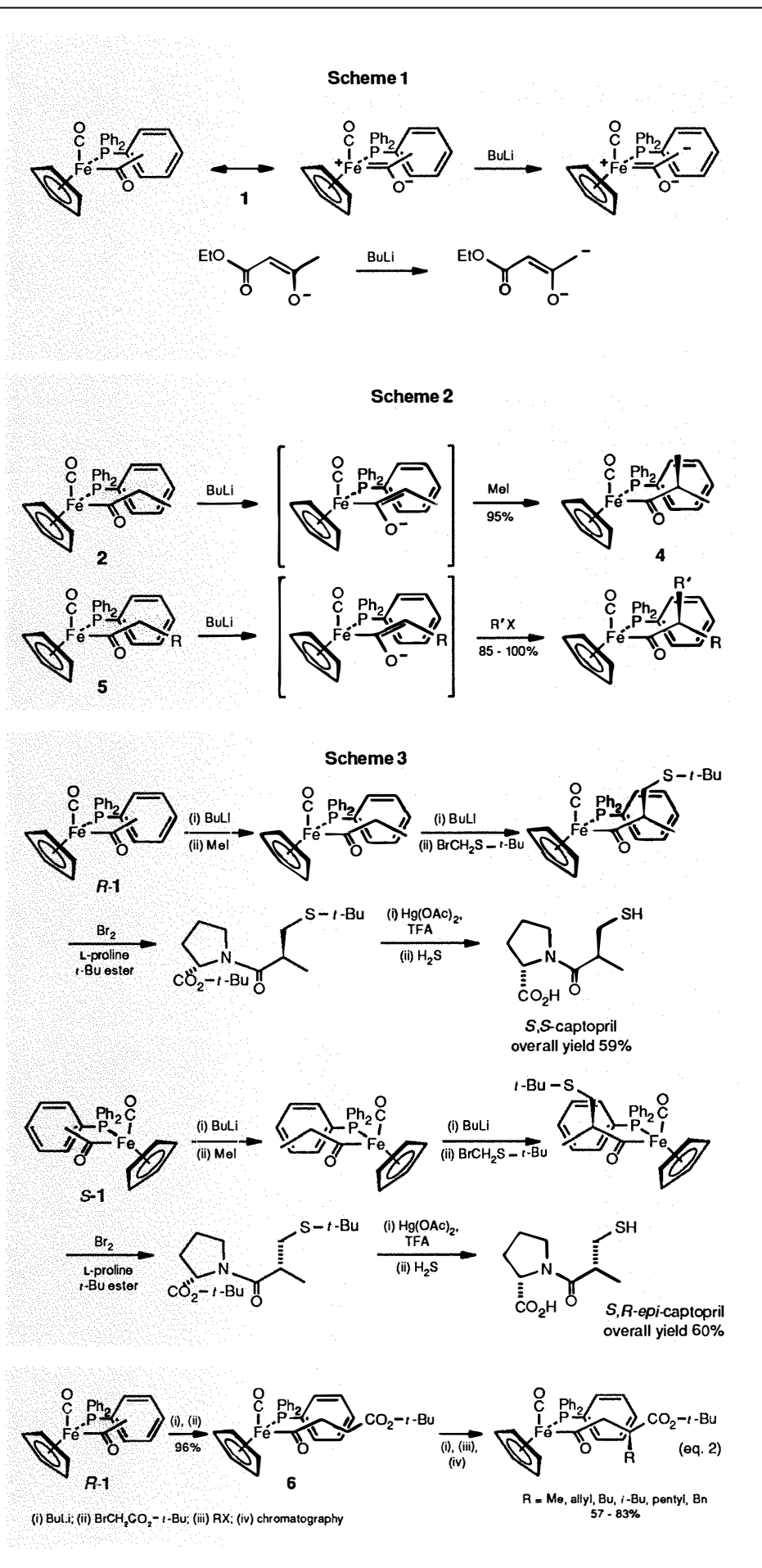
### 3. Homochiral Succinoyl Derivatives<sup>21,22</sup>

Alkylation of the enolate derived from the parent acetyl complex **1** with *tert*-butyl bromoacetate generates the succinoyl derivative **6**. As expected from the enolate chemistry described above, the succinoyl derivative **6** undergoes completely regioselective deprotonation  $\alpha$  to the ester rather than  $\alpha$  to the acyl carbonyl.<sup>22</sup> Good, although not complete, stereoselectivity is observed in the alkylation reactions of this succinoyl enolate with the major diastereoisomer being readily isolated by chromatography (eq. 2).

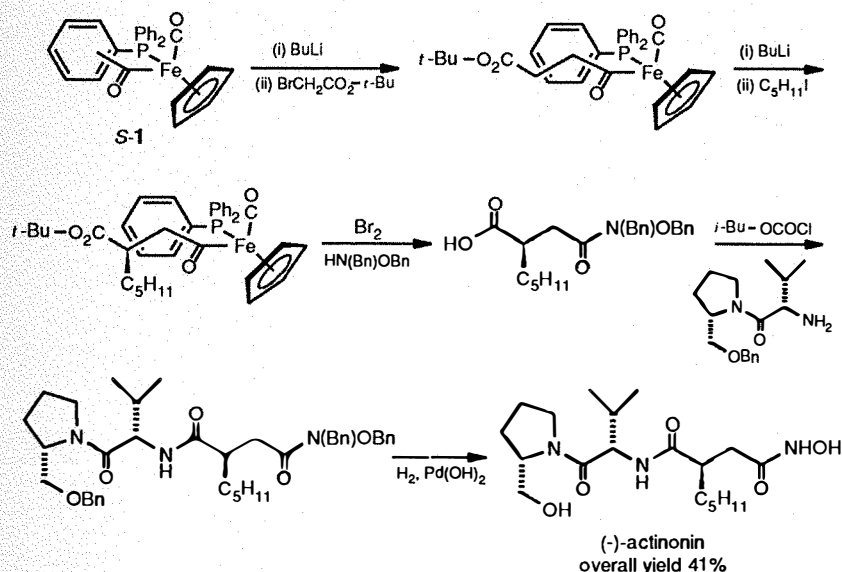
The chiral succinoyl derivatives have been used in the asymmetric synthesis of actinonin, (Scheme 4),<sup>23</sup> which has shown interesting anti-collagenase activity.

### 4. Asymmetric Aldol Reactions

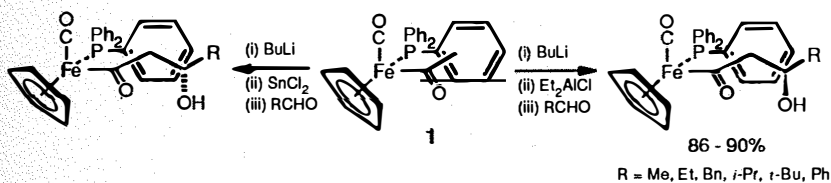
Addition of aldehydes to the lithium enolate derived from the parent acetyl complex **1** generates the corresponding  $\beta$ -hydroxy acyl complexes with essentially no stereocontrol. Transmetalation of the lithium enolate to the aluminum enolate by treatment with diethylaluminum chloride prior to addition of the



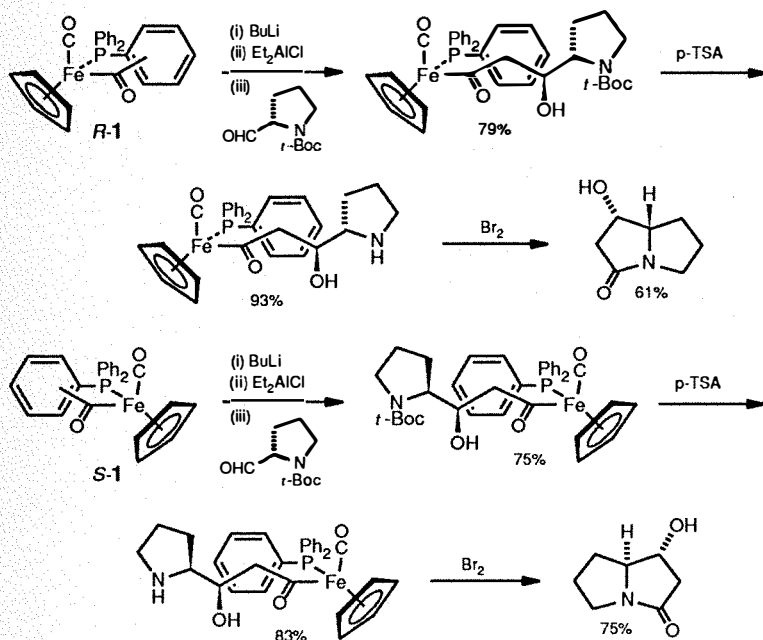
Scheme 4



Scheme 5



Scheme 6



aldehyde, leads to excellent stereocontrol in the formation of the  $\beta$ -hydroxy acyl complexes (Scheme 5).<sup>24,25</sup> Complementary stereoselectivity has been observed by Liebeskind *et al.* for the corresponding tin enolate.<sup>26</sup> The product  $\beta$ -hydroxy acyl complexes may be decomplexed to the corresponding  $\beta$ -hydroxy carboxylic acids, esters or amides, making the aluminum enolate a convenient chiral acetate enolate equivalent.

The usefulness of the above chiral acetate enolate equivalent is illustrated by synthesis of the bicyclic lactams derived from prolinal shown in Scheme 6.<sup>27</sup> In the synthesis of one of the lactam diastereoisomers, the iron auxiliary enhances the rather poor inherent stereoselectivity within the homochiral prolinal derivative while, for the other diastereoisomer, the control exerted by the auxiliary completely overwhelms this inherent stereocontrol. In both cases, therefore, the iron auxiliary predetermines the configuration of the alcohol produced in the aldol reaction.

Addition of aldehydes to the lithium enolate derived from the propanoyl complex **2** shows little stereoselectivity. However, as with the chiral acetate enolate equivalent, transmetalation leads to good stereocontrol.<sup>28,30</sup> Complementary stereoselectivities are observed for the aluminum and copper enolates in the formation of the  $\beta$ -hydroxy centers while the  $\alpha$ -center is formed with the stereocontrol expected from the simple alkylation reactions of enolates attached to the chiral auxiliary. Decomplexation of the products from the aluminum and copper enolates leads to homochiral *threo*- and *erythro*- $\alpha$ -methyl- $\beta$ -hydroxy acids, respectively (Scheme 7). In these reactions, the enantioselectivity is determined by the chirality at iron while the diastereoselectivity is determined by the counterion present.

The asymmetric synthesis of (*2R,3S*)-2-methyl-6-oxohepta-1,3-diacetate of known absolute configuration (Scheme 8),<sup>31</sup> using the chiral propionate enolate equivalent described above, allowed us to assign, by chemical correlation, the absolute configuration to a series of marine cyclic peroxides.

## 5. $\alpha,\beta$ -Unsaturated Iron Acyls

Alkylation of the enolate derived from the parent acetyl complex **1** with chloromethyl benzyl ether generates the  $\beta$ -benzyloxy complex which, on treatment with sodium hydride, produces the iron acryloyl complex (Scheme 9).<sup>32</sup> A mixture of *E*- and *Z*- $\alpha,\beta$ -unsaturated acyl complexes is produced in the Peterson reaction between the  $\alpha$ -trimethylsilyl acyl complex **3** and aldehydes.<sup>33,34</sup> The *E*- and *Z*-isomers may be readily separated by chromatography and this represents the best synthesis to date of the *Z*-isomers **8** (Scheme 9).<sup>33,34</sup> As indicated above, the aldol reaction between the enolate derived from **1** and aldehydes is non-selective. However, *O*-methylation (NaH/MeI) followed by elimination with sodium hydride of both  $\beta$ -hydroxyacyl diastereoisomers, either separately or as the mixture from the aldol reaction, stereoselectively

generates the *E*- $\alpha,\beta$ -unsaturated acyl complexes **7** (Scheme 9).<sup>33,34</sup>

## 6. Homochiral Dienolates

Treatment of *Z*- $\alpha,\beta$ -unsaturated acyl complexes possessing a  $\beta$ -methyl or methylene substituent with lithium alkyls or lithium amides generates the corresponding dienolates.<sup>35,36</sup> In contrast, under the same conditions, the *E*-isomers undergo smooth Michael addition (see below); however, this reaction is suppressed in the presence of HMPA or TMEDA, and dienolates are produced. These dienolates undergo ready alkylation in the  $\alpha$ -position to generate *E*- $\beta,\gamma$ -unsaturated iron acyl complexes (eq. 3), with both the  $\alpha$ -center and the double bond being formed completely stereoselectively.

## 7. Asymmetric Michael Additions

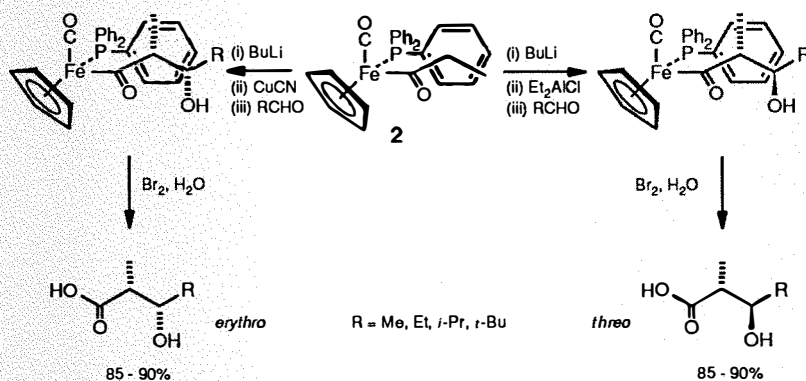
The chiral iron acryloyl complex undergoes Michael addition reactions with alkyllithium reagents to generate the corresponding *E*-enolates indicating that the acryloyl ligand is reacting in the *cisoid* conformation. Alkylation of the thus formed *E*-enolates is, as expected, highly stereoselective (Scheme 10).<sup>37-39</sup> Addition of alkyllithiums to the *E*- $\alpha,\beta$ -unsaturated acyl complexes **7** and trapping of the intermediate enolate by protonation generates acyl complexes with a new  $\beta$ -chiral center (Scheme 10). These reactions are completely stereoselective, with the configuration of the  $\beta$ -center being consistent with the nucleophile adding to the  $\alpha,\beta$ -unsaturated acyl ligand in its *cisoid* conformation from the unhindered face. In general, sequential addition of alkyllithiums and alkyl halides to *E*- $\alpha,\beta$ -unsaturated acyl complexes results in the highly stereoselective formation of two new chiral centers (Scheme 10). As mentioned above, *Z*- $\alpha,\beta$ -unsaturated acyl complexes bearing a  $\beta$ -methyl or methylene substituent undergo deprotonation rather than Michael addition reactions. If, however, the  $\beta$ -substituent is not deprotonatable (e.g., 1-alkenyl, aryl, furyl, etc.), then Michael additions occur very readily.

The asymmetric synthesis of (2*R*,3*R*)-(-)-*N*-benzyl-2,3-dimethylheptanamide from (*S*)-**1** (eq. 4)<sup>38,39</sup> serves to illustrate the power of this method. It is noteworthy that in the decomplexation, no sign of any epimerization at either the  $\alpha$ - or the  $\beta$ -center could be detected.

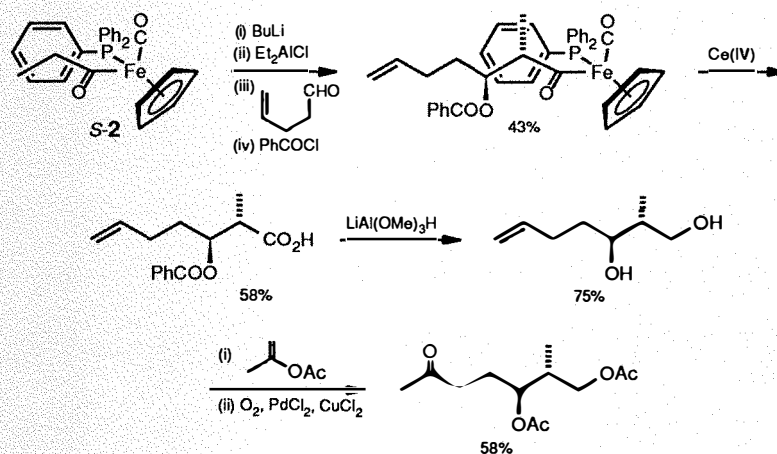
## 8. Asymmetric Synthesis of $\beta$ -Amino Acids and $\beta$ -Lactams

The iron acryloyl complex and the *E*- $\alpha,\beta$ -unsaturated acyl complexes **7** also undergo Michael additions in the presence of lithium amides. The resulting  $\beta$ -amino acyl ligands may be decomplexed either to  $\beta$ -amino acids or  $\beta$ -lactams. Sequential addition of lithium benzylamide and methyl iodide to the *E*-crotonyl complex generates completely stereoselectively the  $\alpha$ -methyl- $\beta$ -(benzylamino)-butanoyl complex which, on decomplexation

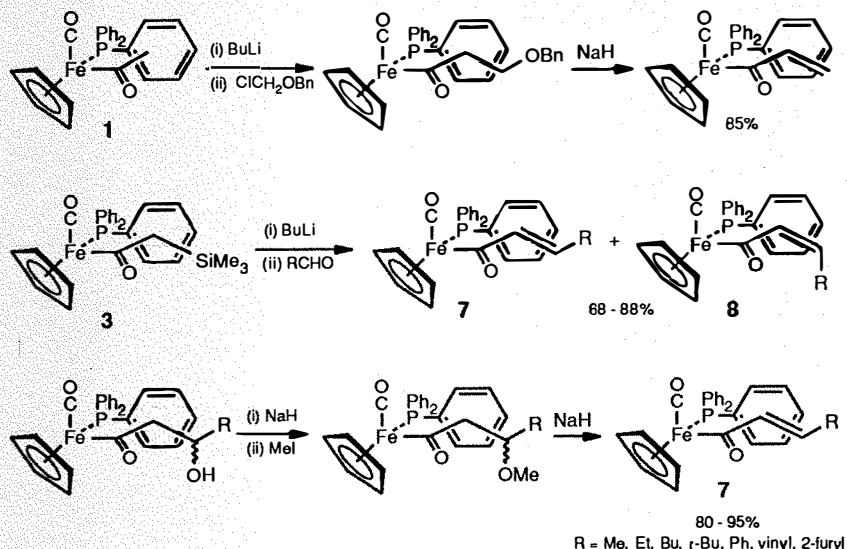
Scheme 7

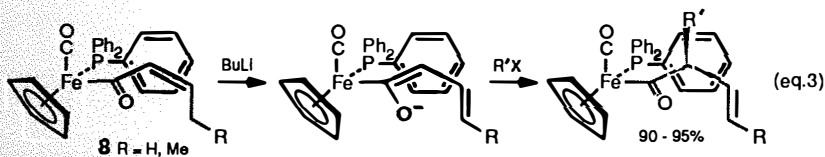


Scheme 8

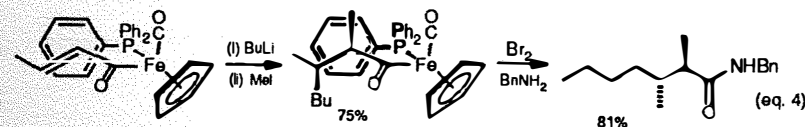
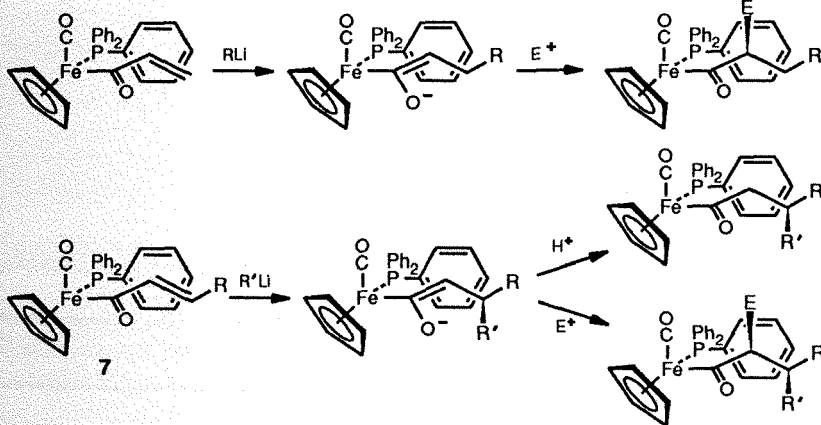


Scheme 9

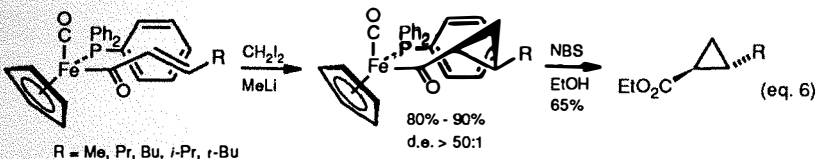
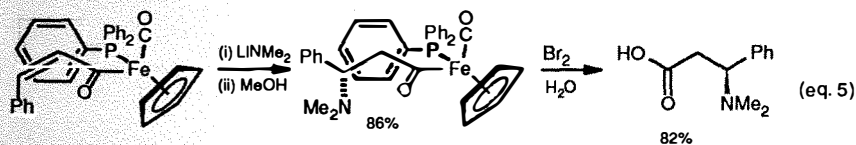
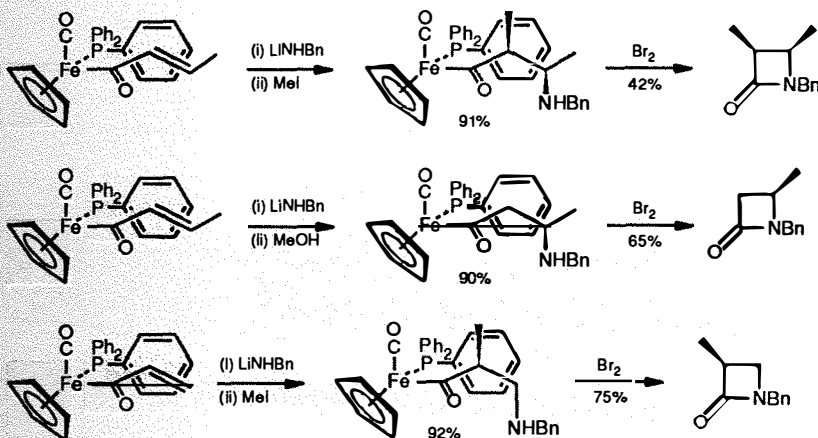




**Scheme 10**



**Scheme 11**



with bromine, generates diastereoisomerically pure homochiral *cis*-3,4-dimethyl- $\beta$ -lactam (Scheme 11).<sup>38,39</sup> Epimerization of the *cis*- $\beta$ -lactam with potassium *tert*-butoxide generates the thermodynamically more stable *trans* isomer. These results demonstrate that in the formation of the  $\beta$ -lactams neither chiral center is compromised. Addition of lithium benzylamide to the *E*-crotonyl complex followed by methanol generates, after decomplexation, homochiral 4-methyl- $\beta$ -lactam (Scheme 11). The final member of this series, 3-methyl- $\beta$ -lactam, was prepared in homochiral form by sequential addition of lithium benzylamide and methyl iodide to the acryloyl complex (Scheme 11).<sup>38,39</sup>

The absolute configuration has been assigned to the naturally occurring  $\beta$ -amino acid, Winterstein's acid, (*S*)-3-(dimethylamino)-3-phenylpropionic acid, by asymmetric synthesis of a homochiral sample of known configuration (eq. 5).<sup>40</sup>

## 9. Asymmetric Synthesis of Cyclopropanecarboxylic Acids

Nucleophilic methylene transfer to *E*- $\alpha,\beta$ -unsaturated chiral iron acyls is stereoselective (>50:1) leading, after decomplexation, to *trans*-substituted cyclopropanecarboxylic acid derivatives (eq. 6).<sup>41</sup> The corresponding *cis*-cyclopropanecarboxylic acid derivatives are available *via* electrophilic methylene transfer to *Z*- $\alpha,\beta$ -unsaturated chiral iron acyls (eq. 7).<sup>42</sup>

## 10. Asymmetric Synthesis of Sulfoxides *via* Pseudocatalysis

Stereoselective (16:1) trapping of the enolate derived from the propanoyl complex **2** with diphenyl disulfide allows the formation, after one crystallization, of pure complex **9** (Scheme 12).<sup>43</sup> *m*-Chloroperbenzoic acid oxidation of the sulfide **9** to the corresponding sulfoxide is quantitative and completely stereoselective. Oxidative decomplexation of this sulfoxide in the presence of benzylamine gave the homochiral  $\beta$ -sulfinyl amide whose enantiomeric purity was confirmed by <sup>1</sup>H-NMR analysis in the presence of the chiral shift reagent, 2,2,2-trifluoro-1-(9-anthryl)ethanol. Alternatively, addition of lithium dibutylcuprate to the sulfoxide complex generated, *via* inversion at sulfur, homochiral phenyl butyl sulfoxide while at the same time regenerating, essentially quantitatively, the homochiral starting propanoyl complex **2** which could be recycled.

## 11. Chirality Recognition for Homochiral Synthesis

In the synthesis of large molecules containing many chiral centers, strategies involving the combination of several chiral but racemic fragments is avoided since, in principle, this would lead to a mixture of all possible diastereoisomers. Each fragment is therefore generally prepared in homochiral form prior to coupling to the final product; in this way, one

homochiral diastereoisomer is assured. However, the same goal could be achieved from just one homochiral fragment with all the others being racemic if the level of chiral recognition (discrimination between the two enantiomers of a racemic substrate) in all the coupling steps is sufficiently high. Some useful chiral recognition processes involving the iron chiral auxiliary [(C<sub>5</sub>H<sub>5</sub>)Fe(CO)(PPh<sub>3</sub>)] are described in this section.

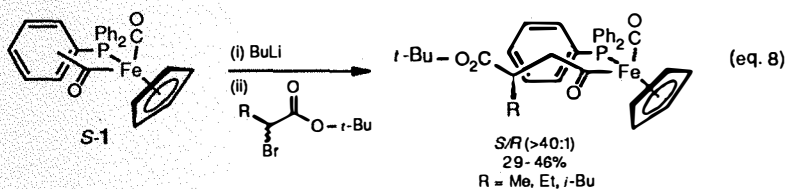
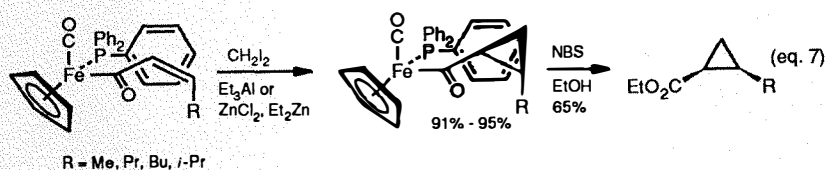
The enolate derived from the parent acetyl complex *S*-1 reacts in an S<sub>N</sub>2 fashion with the *R*-enantiomer of *tert*-butyl 2-bromopropionate greater than forty times as fast as with the *S*-enantiomer to form stereoselectively (d.e. >97.5%) the corresponding succinoyl derivative (eq. 8).<sup>44</sup> The reaction appears to be chelation-controlled with the lithium chelating to both the enolate and the ester. The reaction may not be used to kinetically resolve the  $\alpha$ -bromo ester due to racemization by the liberated bromide. This racemization, however, does allow all of the racemic  $\alpha$ -bromo ester to be converted to the same product diastereoisomer. The recognition process appears to be general for  $\alpha$ -bromo esters and the use of the product succinoyl derivatives in synthesis has been illustrated above.

Treatment of the lithium enolate from *S*-1 with racemic propylene oxide in the presence of diethylaluminum chloride leads to selective reaction with only one enantiomer to form the *S*,*R*- $\gamma$ -hydroxyacyl complex which, on oxidation, produces homochiral *R*-4-methylbutyrolactone (Scheme 13).<sup>45</sup> Transmetalation is not occurring under the reaction conditions: the diethylaluminum chloride is acting as a Lewis acid to increase the electrophilicity of the epoxide. The recognition process appears to be general for monosubstituted epoxides. Homochiral *S*-4-methylbutyrolactone was similarly prepared from racemic propylene oxide and *R*-1 (Scheme 13).

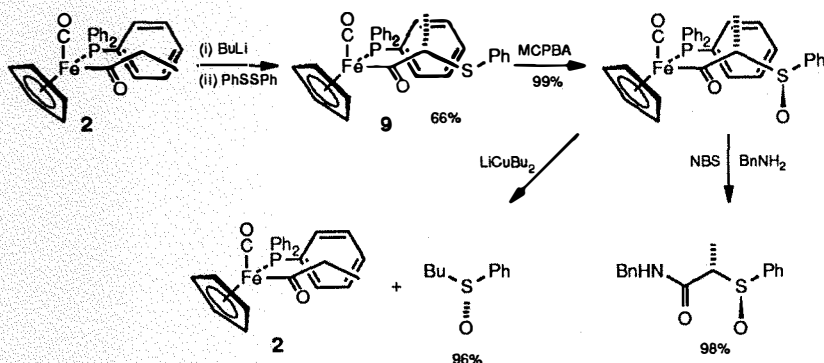
2,4-Disubstituted butyrolactones are also available in homochiral form *via* a chirality recognition process.<sup>46,48</sup> Thus, reaction of the enolate derived from *S*-2 with racemic styrene oxide in the presence of diethylaluminum chloride gave a single diastereoisomer of the intermediate hydroxy acyl which, on decomplexation, gave homochiral diastereoisomerically pure *S*,*S*-*cis*-2-methyl-4-phenylbutyrolactone (eq. 9). The epimeric homochiral lactone, *R*,*S*-*trans*-2-methyl-4-phenylbutyrolactone was prepared from homochiral *R*-2 and homochiral *R*-styrene oxide (eq. 10).<sup>48</sup>

## 12. Summary

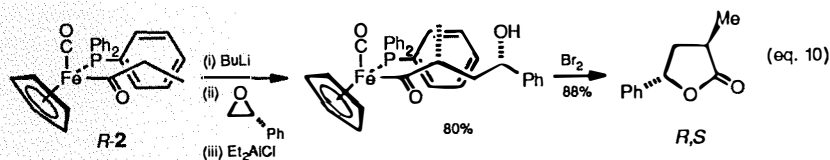
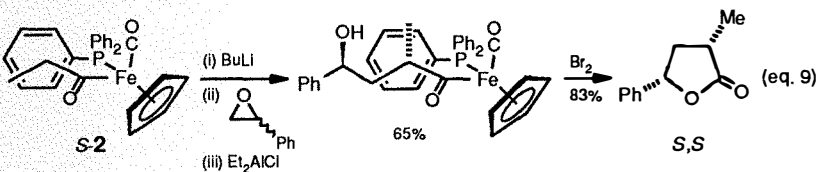
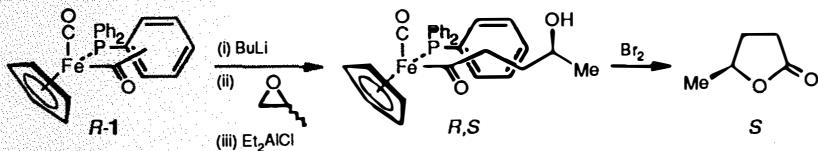
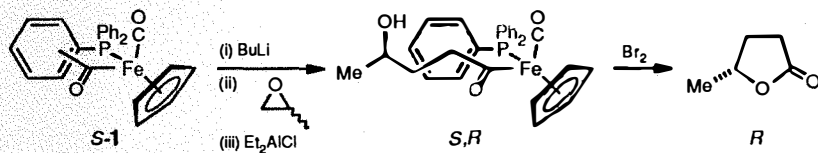
The above examples illustrate some of the applications we have developed at Oxford for the synthesis of homochiral materials using the iron chiral auxiliary [(C<sub>5</sub>H<sub>5</sub>)Fe(CO)(PPh<sub>3</sub>)] in asymmetric synthesis and chirality-recognition processes. All of the work described involves a common starting material, the parent acetyl complex, [(C<sub>5</sub>H<sub>5</sub>)Fe(CO)(PPh<sub>3</sub>)-COMe]. It should be stressed that these iron reagents are very easy to handle requiring no special apparatus. For example, the parent



Scheme 12



Scheme 13





complex is completely air stable (>10 years). The iron chiral auxiliary [(C<sub>5</sub>H<sub>5</sub>)Fe(CO)(PPh<sub>3</sub>)] is a very powerful and versatile tool for homo-chiral synthesis. Current work is focusing on extending the scope of chirality-recognition processes and pseudocatalytic reactions and in developing catalytic versions of these reagents.

### 13. Acknowledgements

I am deeply indebted to all those co-workers who are listed in the references. It has been only through their exceptional talents and hard work that we have been able to establish this exciting area of chemistry. I would also like to express my appreciation to BP International (for a Venture Research Award), British Biotechnology Ltd., Glaxo Group Research, ICI Pharmaceuticals, The Royal Society of Chemistry (for a Hickinbottom Fellowship) and the SERC for financial support.

### References:

- 1) Brown, J.M.; Davies, S.G.; Fleet, G.W.J.; Pratt, A.J. *Chem. Brit.* **1989**, 259.
- 2) Brown, J.M.; Davies, S.G. *Nature* **1989**, *342*, 631.
- 3) Morrison, J.D. *Asymmetric Synthesis*, Academic Press: New York; Vols 1-6, 1983-1985.
- 4) Davies, S.G.; Dordor-Hedgecock, I.M.; Easton, R.J.C.; Preston, S.C.; Sutton, K.H.; Walker, J.C. *Bull. Soc. Chim. Fr.* **1987**, 608.
- 5) Davies, S.G. *Pure Appl. Chem.* **1988**, *60*, 13.
- 6) Bashiardes, G.; Beckett, R.P.; Davies, S.G.; Coote, S.J.; Dordor-Hedgecock, I.M.; Goodfellow, C.L.; Gravatt, G.L.; McNally, J.P.; Whittaker, M. *Phil. Trans. Roy. Soc. London A* **1987**, *326*, 619.
- 7) Davies, S.G. *Chem. Brit.* **1989**, 268.
- 8) Davies, S.G.; Bashiardes, G.; Coote, S.J.; Goodfellow, C.L.; McNally, J.P. *New Aspects of Organic Chemistry*, Yoshida, Z.; Shiba, T.; Ohshiro, Y., Eds.; VCH: Basel; **1990**, Vol. 1, p81.
- 9) Aktogu, N.; Davies, S.G.; Felkin, H. *Chem. Commun.* **1982**, 1303.
- 10) Aktogu, N.; Davies, S.G.; Felkin, H.; Baird, G.J.; Watts, O. *J. Organomet. Chem.* **1984**, *262*, 49.
- 11) Davies, S.G., unpublished results.
- 12) Davies, S.G.; Dordor-Hedgecock, I.M.; Sutton, K.H.; Walker, J.C.; Boume, C.; Jones, R.H.; Prout, K. *Chem. Commun.* **1986**, 607.
- 13) Davies, S.G.; Seeman, J.I.; Williams, I.H. *Tetrahedron Lett.* **1986**, *27*, 619.
- 14) Blackburn, B.K.; Davies, S.G.; Sutton, K.H.; Whittaker, M. *Chem. Soc. Rev.* **1988**, *17*, 147.
- 15) Blackburn, B.K.; Davies, S.G.; Whittaker, M. *Stereochemistry of Organometallic and Inorganic Compounds*, Bernal, I., Ed.; Elsevier: Amsterdam, **1989**; Vol. 3, p141.
- 16) Baird, G.J.; Davies, S.G. *J. Organomet. Chem.* **1983**, *248*, C1.
- 17) Baird, G.J.; Bandy, J.A.; Davies, S.G.; Prout, K. *Chem. Commun.* **1983**, 1202.
- 18) Brown, S.L.; Davies, S.G.; Foster, D.F.; Seeman, J.I.; Warner, P. *Tetrahedron Lett.* **1986**, *27*, 623.
- 19) Davies, S.G.; Seeman, J.I. *ibid.* **1984**, *25*, 1845.
- 20) Bashiardes, G.; Davies, S.G. *ibid.* **1987**, *28*, 5563.
- 21) Bashiardes, G.; Collingwood, S.P.; Davies, S.G.; Preston, S.C. *J. Organomet. Chem.* **1989**, *364*, C29.
- 22) Bashiardes, G.; Collingwood, S.P.; Davies, S.G.; Preston, S.C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1162.
- 23) Bashiardes, G.; Davies, S.G. *Tetrahedron Lett.* **1988**, *29*, 6509.
- 24) Davies, S.G.; Dordor, I.M.; Warner, P. *Chem. Commun.* **1984**, 956.
- 25) Davies, S.G.; Dordor-Hedgecock, I.M.; Jones, R.H.; Prout, K.; Warner, P. *J. Organomet. Chem.* **1985**, *285*, 213.
- 26) Liebeskind, L.S.; Welker, M.E.; Fengl, R.W. *J. Am. Chem. Soc.* **1986**, *108*, 6328.
- 27) Beckett, R.P.; Davies, S.G. *Chem. Commun.* **1988**, 160.
- 28) Davies, S.G.; Dordor, I.M.; Walker, J.C.; Warner, P. *Tetrahedron Lett.* **1984**, *25*, 2709.
- 29) Davies, S.G.; Dordor-Hedgecock, I.M.; Warner, P. *ibid.* **1985**, *26*, 2125.
- 30) Ambler, P.W.; Davies, S.G. *ibid.* **1985**, *26*, 2129.
- 31) Capon, R.J.; MacLeod, J.K.; Coote, S.J.; Davies, S.G.; Gravatt, G.L.; Dordor-Hedgecock, I.M.; Whittaker, M. *Tetrahedron* **1988**, *44*, 1637.
- 32) Davies, S.G.; Walker, J.C. *Chem. Commun.* **1986**, 607.
- 33) Davies, S.G.; Easton, R.J.C.; Walker, J.C.; Warner, P. *J. Organomet. Chem.* **1985**, *296*, C40.
- 34) Davies, S.G.; Easton, R.J.C.; Walker, J.C.; Warner, P. *Tetrahedron* **1986**, *42*, 175.
- 35) Davies, S.G.; Easton, R.J.C.; Gonzalez, A.; Preston, S.C.; Sutton, K.H.; Walker, J.C. *ibid.* **1986**, *42*, 3987.
- 36) Davies, S.G.; Easton, R.J.C.; Sutton, K.H.; Walker, J.C.; Jones, R.H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 489.
- 37) Davies, S.G.; Walker, J.C. *Chem. Commun.* **1985**, 209.
- 38) Davies, S.G.; Dordor-Hedgecock, I.M.; Sutton, K.H.; Walker, J.C. *Tetrahedron Lett.* **1986**, *27*, 3787.
- 39) Davies, S.G.; Dordor-Hedgecock, I.M.; Sutton, K.H.; Walker, J.C.; Jones, R.H.; Prout, K. *Tetrahedron* **1986**, *42*, 5123.
- 40) Davies, S.G.; Dupont, J.; Easton, R.J.C. *Tetrahedron Asymmetry* **1990**, *1*, 279.
- 41) Ambler, P.W.; Davies, S.G. *Tetrahedron Lett.* **1988**, *29*, 6979.
- 42) Ambler, P.W.; Davies, S.G. *ibid.* **1988**, *29*, 6983.
- 43) Davies, S.G.; Gravatt, G.L. *Chem. Commun.* **1988**, 780.
- 44) Collingwood, S.P.; Davies, S.G.; Preston, S.C., submitted for publication.
- 45) Davies, S.G.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 4815.
- 46) Brown, S.L.; Davies, S.G.; Warner, P.; Jones, R.H.; Prout, K. *Chem. Commun.* **1985**, 1446.
- 47) Davies, S.G.; Middlemis, D.; Naylor, A.; Wills, M. *Tetrahedron Lett.* **1989**, *30*, 587.
- 48) Davies, S.G.; Polywka, R.; Warner, P. *Tetrahedron* **1990**, *46*, 4847.

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Dr. Stephen G. Davies received the B.A. in 1973 and the D.Phil (supervised by Dr. Gordon Whitham) in 1975 from Oxford. He subsequently held an ICI Postdoctoral Fellowship (1975-77, in collaboration with Professor Malcolm L.H. Green) at Oxford and a NATO Fellowship (1977-78, in collaboration with Professor Sir Derek H.R. Barton) at Gif-sur-Yvette, France. He then joined the CNRS at Gif-sur-Yvette, France, collaborating with Dr. Hugh Felkin before returning to Oxford in 1980 to a lectureship in Organic Chemistry and a Fellowship of New College. He received the Hickinbottom Fellowship in 1984, the Pfizer Award for Chemistry in 1985 and 1988, the Corday Morgan Medal in 1986, the Royal Society of Chemistry Award for Organometallic Chemistry in 1987 and most recently in 1989 the Royal Society of Chemistry Bader Award.

His major research interest involves the use of transition-metal chiral auxiliaries for stoichiometric, pseudocatalytic and catalytic asymmetric synthesis. Other research interests include the study of organometallic mechanisms, bimetallic catalysts, molecular switches, conformational analysis of transition-metal complexes and a study of molecular recognition phenomena related to kinetic resolutions.

# Carboxyolefination

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Carboxyolefination, that is the treatment of aldehydes and ketones with suitably substituted acetate carbanions followed by "dehydration", constitutes an important synthetic technique for the preparation of  $\alpha,\beta$ -unsaturated esters and their derivatives, often with high stereoselectivity. These compounds frequently serve as important intermediates in natural product synthesis.

Whereas the Knoevenagel condensation and the Reformatsky reaction are classical methods of carboxyolefination, the process can be achieved directly by the Wittig, Horner-Emmons-Wittig (HEW)<sup>1</sup> and Peterson Olefination reactions.<sup>2</sup> Other direct but less utilized techniques include the elimination of sulfonic<sup>3</sup> and seleninic acid<sup>4</sup> fragments from suitable precursors as well as the recent use of organotellurium ylides<sup>5</sup> and a haloboration-based method.<sup>6</sup> Of these methods, the Wittig reaction and its Horner-Emmons modification appear to be the most advantageous. Many of the required reagents are commercially available or easily made and a judicious choice of reagents and reaction conditions can lead to either olefinic isomer (*i.e.*, *E* or *Z*) with a surprisingly high degree of selectivity.

This article will thus focus on the utility of Wittig and HEW reagents with a brief discussion of other carboxyolefination reagents/methods.

## Carboxyolefination Employing Phosphoranes and Phosphonates

Reagents 1-10 represent the most frequently utilized ylides or their precursors.

Whereas preponderant formation of the *E*-olefinic product is usually the primary outcome of the reactions of stable ylides and phosphonocarboxylates, a number of variables may be applied to change this outcome to suit synthetic needs in certain situations.<sup>7a</sup> Many examples of strikingly high *E* or *Z* selectivity obtained by varying reagents and/or reaction conditions are encountered in the literature. For example, the *Z,Z* and *E,E* unsaturated esters required for the key cyclopropanation step during the synthesis of diastereomerically pure *cis*- and *trans*-hemitartronic aldehydes were prepared by Krief and co-workers employing 1 and 9, respectively (Scheme I). The two aldehydes are precursors to deltamethrin and *trans*-chrysanthemic acid,<sup>7b</sup> respectively.

Similarly, the *D*-mannitol-derived esters 15-18 have been prepared with a high degree of selectivity utilizing different conditions

(Scheme II).<sup>8</sup>

An interesting example of high *Z*-selectivity (>98%) is to be found in Kishi's work on monensin (eq. 1).<sup>9</sup>

As striking as the control of double-bond geometry appears to be from the above examples, one can hardly ignore the isomeric mixtures that are formed in a majority of the reactions. Furthermore, the use of simple acetates and propionates imposes limits on the synthetic utility of these reagents. Fortunately, many research groups have vigorously pursued solutions to these limitations resulting in the development of a number of new and specific reagents.<sup>10-18</sup>

Thus, the reagent 21 and its  $\alpha$ -methyl analog, developed by Still, exhibit very high *Z*-se-

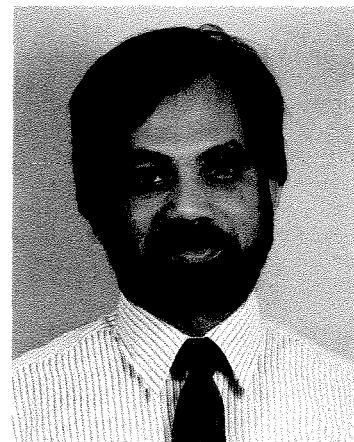
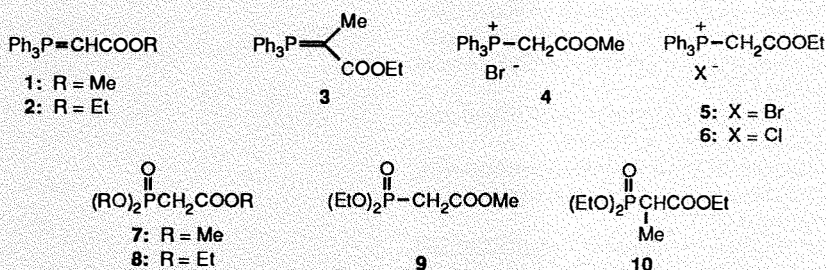
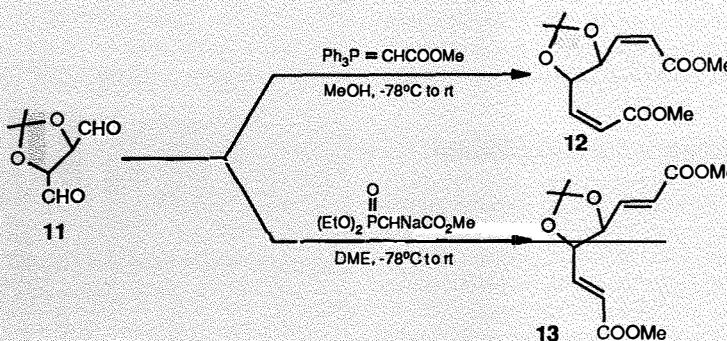


Table 1



Scheme I



lectivity<sup>10</sup> whereas Kishi's reagent **22** exhibits very high *E*-selectivity.<sup>11</sup>

The *t*-butyl esters **23**, **24** and **25** offer the convenience of acid-catalyzed ester hydrolysis for base-sensitive molecules.<sup>12</sup> Phosphonoacetate **23** also serves as a convenient raw material for the glycine phosphonate **31**. Compound **31** is a valuable reagent for the synthesis of fused  $\beta$ -lactams.<sup>13</sup>

The phosphonocrotonates **26** and **27** enable one to introduce a four/five-carbon unit in one step,<sup>14,15</sup> reagent **28** is a convenient precursor to the 5-methyl-3-methylene- $\gamma$ -butyrolactone *via* a propargylacrylate<sup>16</sup> and reagent **29** provides an entry into 3-substituted furans *via*  $\alpha$ -alkylidene butyrolactones.<sup>17</sup>

Recently, Boeckman and co-workers accomplished a stereocontrolled synthesis of (+)-ikarugamycin, where the allyl analog of **21** was used to introduce the *Z*-olefinic side chain and the masked  $\beta$ -acyl ketene derivative **32** prepared from **30** provided the right ingredient for an intramolecular macrocyclization (eq. 2).<sup>18</sup>

### Other Carboxyolefination Methods

The Peterson Olefination<sup>2</sup> which involves elimination of trialkylsilyl alkoxide provides an equally convenient route for the preparation of  $\alpha,\beta$ -unsaturated esters, lactones and acids. In fact, it becomes the method of choice for the olefination of readily enolizable ketones.<sup>19</sup> The formation of a strong Si-O bond provides sufficient driving force to promote elimination of silicon alkoxide over the elimination of phosphine oxide or phosphate (where such a choice is available) thus providing an important preparative method for vinyl phosphonates (Scheme III).<sup>20</sup>

Some of the commonly used silicon reagents are presented in Table 3.

The acid **38** and derivatives have been utilized in the synthesis of monic acid esters by Crimmin *et al.*<sup>21</sup>

Elimination of sulfoxide,<sup>3</sup> selenoxide<sup>4</sup> and telluroxide<sup>5</sup> from the corresponding  $\alpha$ -substituted esters, acids and lactones is yet another way of achieving carboxyolefination. However, unlike the HEW or silicon reagents, in a majority of the cases, the mercapto, seleno or telluro group is introduced in an independent step rather than being built into the reagent structure. This is particularly true with the selenium- and tellurium-based olefinations. Reagents such as **43-45** (Table 4) have been employed in the preparation of *E*-cinnamates,<sup>22</sup> substituted resorcinols<sup>23</sup> and other useful molecules.<sup>24</sup>

### New Directions in Carboxyolefination

In the recent past, several research groups have focused their efforts on the development of chiral reagents for achieving better *E/Z* selectivity through diastereofacial preference as well as for stereoselective syntheses.<sup>25-28</sup>

The formation of prostacyclin analogs with a high degree of *E/Z* selectivity during the HEW condensation of chiral phosphonoac-

Scheme II

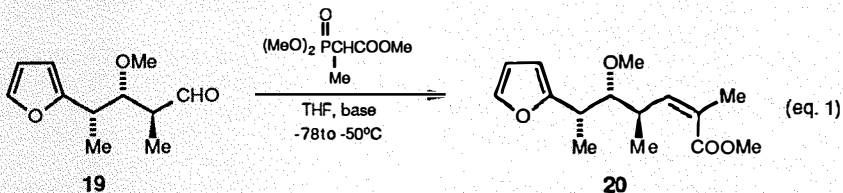
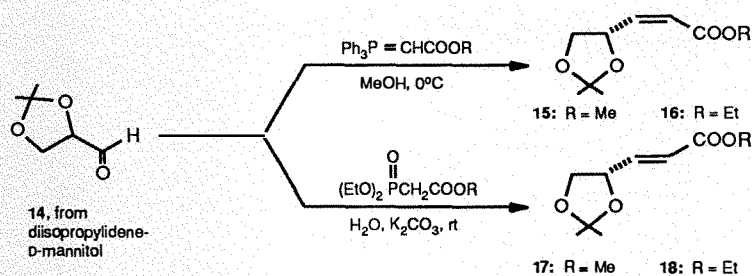
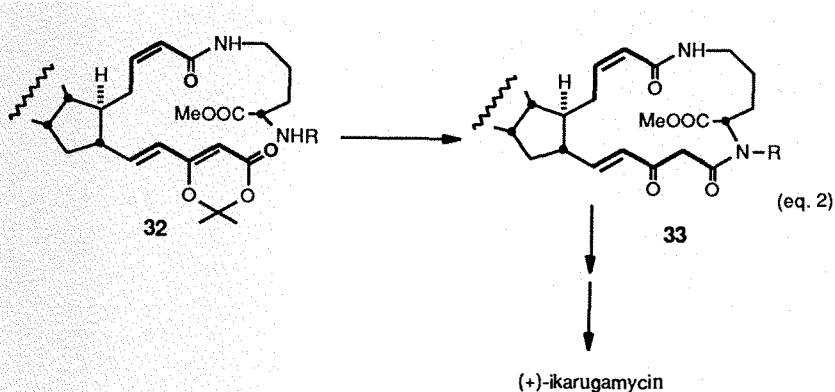
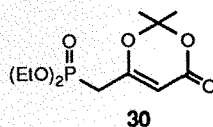
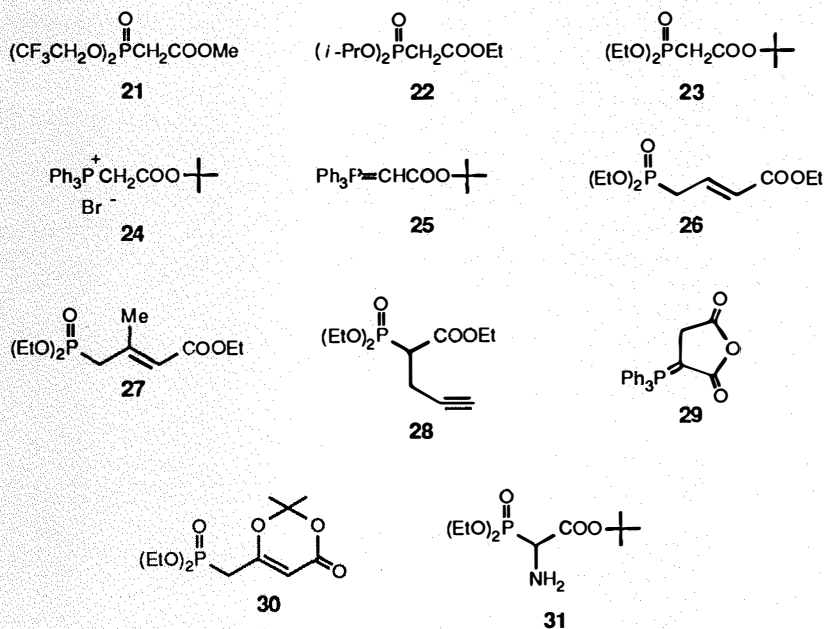
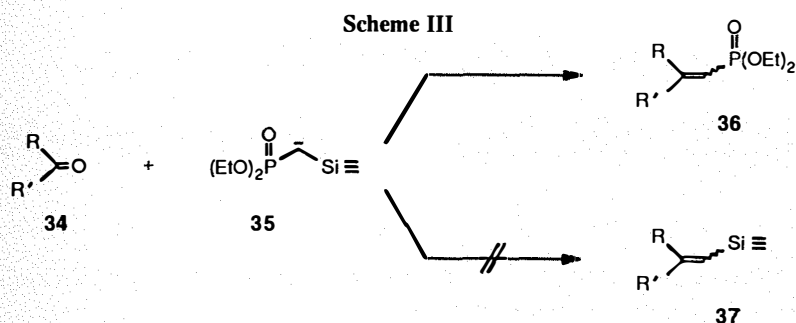
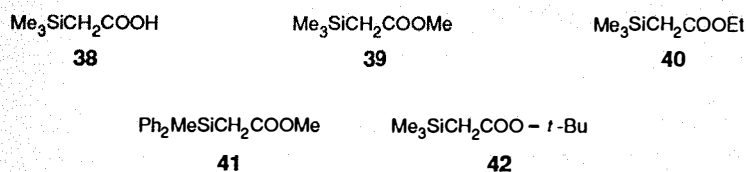


Table 2

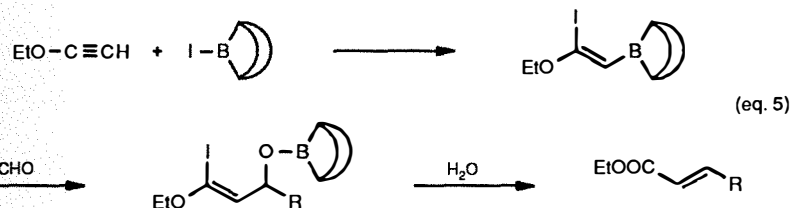
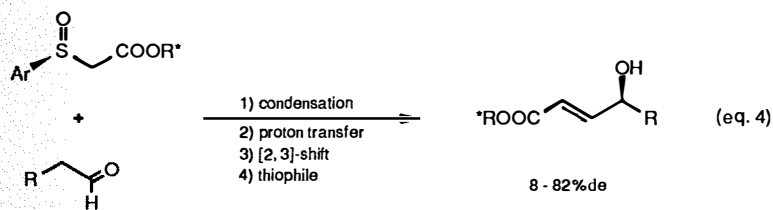
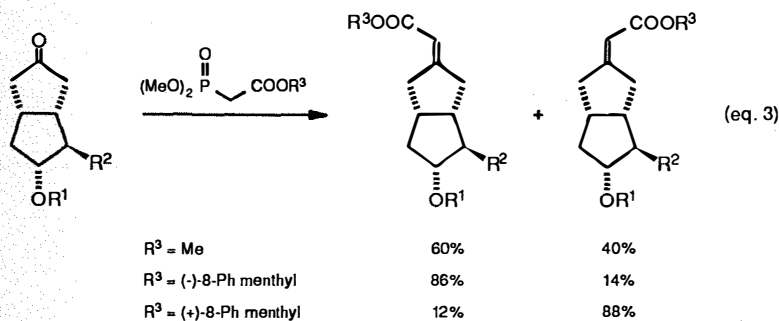
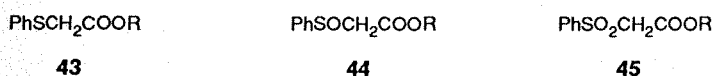




**Table 3**



**Table 4**



tates with chiral as well as achiral substrates, vividly demonstrates the power of diastereofacial interactions (eq. 3).<sup>25,26</sup> This area of research should prove to be even more interesting due to the ready availability of chiral phosphonoacetates via a simple ester exchange reaction<sup>29</sup> with commercially available chiral alcohols,<sup>30</sup> or via standard methods.

The stereoselective synthesis of  $\gamma$ -hydroxy- $\alpha,\beta$ -unsaturated esters which uses chiral sulfinyl acetate (eq. 4)<sup>31</sup> and the recently reported application of the haloboration reaction (eq. 5)<sup>6</sup> also provide a flavor of things to come.

## References

For selected reviews see refs. 1-4.

- 1) a) Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.* **1989**, *89*, 863. b) *Idem Phosphorus Sulfur* **1986**, *27*, 167. c) McEwen, W.E.; Beaver, B.D.; Cooney, J.V. *ibid.* **1985**, *25*, 255. d) Schlosser, M.; Oi, R.; Schaub, B. *ibid.* **1983**, *18*, 171. e) Wadsworth, W.S., Jr. *Org. React.* **1977**, *25*, 73.
- 2) Colvin, E.W. *Silicon in Organic Synthesis*; Butterworths: London, 1981.
- 3) Trost, B.M.; Melvin, L.S. *Sulfur Ylides*; Academic Press: New York, 1975.
- 4) a) Clive, D.L.J. *Tetrahedron* **1978**, *34*, 1049. b) Nicolaou, K.C.; Petasis, N. *Selenium in Natural Products Synthesis*; CIS Inc.: Philadelphia, 1984.
- 5) Huang, X.; Xie, L.; Wu, H. *J. Org. Chem.* **1988**, *53*, 4862.
- 6) Suzuki, A.; Satoh, Y.; Tayano, T.; Hara, S. *Tetrahedron Lett.* **1989**, *30*, 5153.
- 7) a) For a recent study of stereocontrol in HEW reactions, see Wiemer, D.F.; Hammond, G.B.; Cox, M.B. *J. Org. Chem.* **1990**, *55*, 128. b) Krief, A.; Dumont, W. *Tetrahedron Lett.* **1988**, *29*, 1083.
- 8) a) Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1985**, 403. b) Compounds **15**, **17** and **18** are available from Aldrich.
- 9) Kishi, Y.; Schmid, G.; Fukuyama, T.; Akasaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 259.
- 10) Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
- 11) Roush, W.R. *et al. J. Am. Chem. Soc.* **1989**, *111*, 2984.
- 12) Erion, M.D.; Walsh, C.T. *Biochemistry* **1987**, *26*, 3417.
- 13) Shirake, C. *et al. Synthesis* **1988**, 399.
- 14) Corey, E.J.; Magriotis, P.A. *J. Am. Chem. Soc.* **1987**, *109*, 287.
- 15) Vaezi, M.F. *et al. Org. Prep. Proced. Int.* **1987**, *19*, 187.
- 16) McMurry, J.E.; Donovan, S.F. *Tetrahedron Lett.* **1977**, 2869.
- 17) Ravikumar, V.T.; Swaminathan, S.; Rajgopalan, K. *Indian J. Chem., Sect. B* **1986**, *25B*, 292.
- 18) Boeckman, R.K., Jr.; Weidner, C.H.; Pemi, R.B.; Napier, J.J. *J. Am. Chem. Soc.* **1989**, *111*, 8036.
- 19) Boeckman, R.K., Jr.; Silver, S.M. *Tetrahedron Lett.* **1973**, 3497.
- 20) a) Gilman, H.; Tomasi, R.A. *J. Org. Chem.* **1962**, *27*, 3647. b) Carey, F.A.; Court, A.S. *ibid.* **1972**, *37*, 939.
- 21) Crimmin, M.J.; O'Hanlon, P.J.; Rogers, N.H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 541.
- 22) Chong-Ying, S.; Guang-jian, L.; Zhen, Z. *Synth. Commun.* **1987**, *17*, 1839.
- 23) Jaxa-Chamiec, A.A.; Sannes, P.G.; Kennewell, P.D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 170.
- 24) a) Raphael, R.A.; Ravenscroft, P. *J. Chem. Soc.* **1988**, 1823. b) Yoshida, T.; Saito, S. *Chem. Lett.* **1982**, 1587.
- 25) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754.
- 26) Gais, H.-J.; Erdelmeir, I.; Lindner, H.J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 935.
- 27) Rehwinkel, H.; Skupsch, J.; Vorbruggen, H. *Tetrahedron Lett.* **1988**, *29*, 1775.
- 28) Gais, H.-J. *et al. ibid.* **1988**, *29*, 1773.
- 29) Takano, S.; Hatakeyama, S.; Satoh, K.; Sakurai, K. *ibid.* **1987**, *28*, 2713.
- 30) (*S*)-8-Phenylmenthol and many other chiral alcohols are available from Aldrich.
- 31) Burgess, K.; Henderson, I. *Tetrahedron Lett.* **1989**, *30*, 4325.

### About the Author

After completing undergraduate education in Pune (India), Dr. Kulkarni did a short stint at the Ciba Geigy Research Center in India and then emigrated to the United States. He obtained his Ph.D. degree at the State University of New York at Buffalo with Al Padwa in 1982 and then did postdoctoral research with Art Schultz and Barry Snider. He joined the Aldrich R & D team in 1985 and is currently Supervisor of R & D. His major responsibilities are in the areas of development of new products and new product lines for the customers of Sigma-Aldrich Corporation, as well as contract research at Aldrich.

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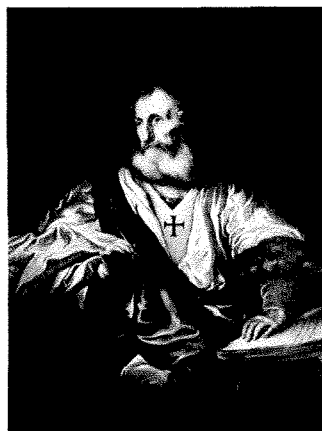


Fig. 1

Part of the story of this remarkable painting (oil on canvas, 51 x 38 inches) is told in *The Detective's Eye* (see below), the catalog of an exhibition where the painting was called *Father of the Church* (Fig. 1). However, the Maltese cross and Greek inscription disappeared during a cleaning which also revealed the turban and crown on the right. Hence this must be an oriental king, but who is this inspired figure?

Our chemist collector believes it is King David writing the Psalms, but in 17th century paintings King David as a psalmist is seldom depicted without his harp.

The painting on our cover is a masterpiece by one of Rembrandt's able students, Govaert Flinck, dating from the 1650's. It is surely fitting for the Acta dedicated to Professor Albert Eschenmoser on his 65th birthday, and containing papers by Professor Vladimir Prelog and Professor Nathan Kornblum. Professor Eschenmoser is one of Switzerland's ablest chemists, an inspiring teacher and a great man. When we asked Professor Prelog to write his paper, he said, "I cannot, but I must." Perhaps David felt like that when writing the Psalms.

### *The Detective's Eye: Investigating the Old Masters*

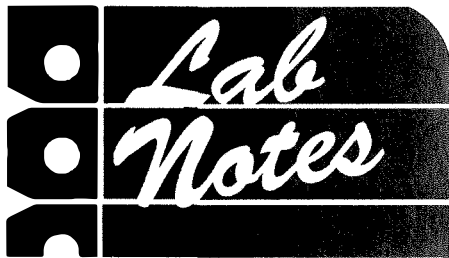
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Workers using your tetrafluoroboric acid-diethyl ether complex, 17,641-9, might be interested in a quick NMR method to determine the titer of small volume (microliter) samples conveniently dispensed with a microliter syringe. The method is based on the fast (on NMR time scale), quantitative, reversible protonation of *N,N*-dimethylaniline, D14,575-0, to give the corresponding anilinium ion. In acetone-*d*<sub>6</sub> the proton chemical shift of the *N*-Me groups is 873.8 Hz (at 25.0°C, 300.1 MHz vs. TMS). The *N*-Me groups of the anilinium ion are shifted considerably downfield to 1064.5 Hz. Assuming rapid exchange for a system containing both species, the chemical shift is

the weighted average, hence the mole fractions of *N,N*-dimethylaniline/*N,N*-dimethylanilinium tetrafluoroborate may be calculated. The advantage of the method is that the titer of very small aliquots may be determined. Equation 1 which reports mmol  $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ /microliter is derived from the above chemical shifts, the density, and molar mass of *N,N*-dimethylaniline.

$$[\text{HBF}_4] = (4.141 \times 10^{-5})(\text{N-Me}_{\text{ave}} - 873.8)R \quad (\text{eq. 1})$$

$\text{N-Me}_{\text{ave}}$  is the observed chemical shift of the *N*-Me groups (Hz) in acetone-*d*<sub>6</sub> and *R* is the ratio of microliters *N,N*-dimethylaniline/microliters  $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ . 5 microliter aliquots of *N,N*-dimethylaniline work well.

Professor C.R. Jablonski  
Department of Chemistry  
Memorial University of Newfoundland  
St. John's, Newfoundland A1B 3X7  
Canada

I have seen many people who have had a difficult time finding a Dewar flask which accommodates your cold traps Z10,310-1 and Z10,690-9. I have been using the perfect combination of the cold trap Z10,690-9 with Dewar flask Z12,078-2 since my Aldrich days over fifteen years ago.

It would be of great assistance to your customers if you would recommend the use of Dewar flask Z12,078-2 with the cold traps Z10,310-1 and Z10,690-9.

J.P. Li, Ph. D.  
Sandoz Crop Protection  
975 California Ave.  
Palo Alto, CA 94304

*Editors Note:* Here is more information on the Dewar flask recommended by Dr. Li.

*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) and if we publish it, you will receive, at no cost, a handsome Aldrich coffee mug as well as a copy of Pictures from the Age of Rembrandt. We reserve the right to retain all entries for consideration for future publication.*

## Steroid Reference Collection

A large collection of steroids for use as reference standards is maintained at the address below. The collection includes many steroids which are not available from any other source, including samples which have been donated by numerous eminent scientists for the benefit of others. As well as the steroid hormones and their metabolites, the collection contains synthetic intermediates, rare steroids of microbiological origin, bile acids, sterols, and some steroidal alkaloids and other plant products. Milligram or microgram quantities are supplied for use in clinical, biochemical or chemical studies, such as the identification of unknown steroids, the development and standardization of micro-assay techniques, chromatography and mass spectrometry. The Curator of the Collection is glad to provide advice on matters concerning steroids whenever possible.

Enquiries, requests for detailed information and a list of available steroids, or offers of samples for the Collection, should be addressed to:

Professor D.N. Kirk  
Curator of the Steroid Reference Collection  
Department of Chemistry  
Queen Mary and Westfield College  
London, E1 4NS  
U.K.

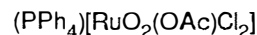
# "Please Bother Us."

by  
*Stephen Ley*

Professor Steven Ley and Dr. William Griffith at Imperial College, London, suggested we offer tetraphenylphosphonium acetatodichlorodioxoruthenate which, in the presence of *N*-methylmorpholine *N*-oxide (NMO), catalytically converts primary halides to aldehydes and secondary halides to ketones.<sup>1</sup> The catalyst oxidizes a variety of other functionalities and nicely complements tetrapropylammonium perruthenate, 33,074-4, another compound suggested by Professor Ley.

Naturally, we made it.

(1) Griffith, W.P.; Jolliffe, J.M.; Ley, S.V.; Williams, D.J., in preparation.



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

# Albert Eschenmoser

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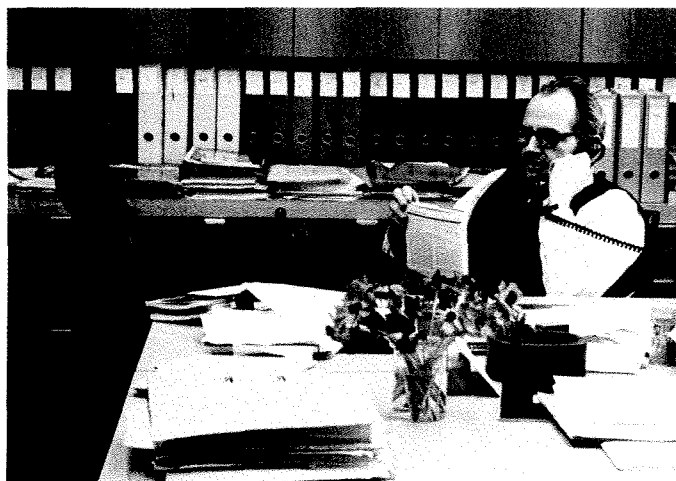


Fig. 1 - "Der Chef." (Photo: D. Felix)

Giving examinations is seldom one of the more enjoyable of a professor's tasks. One is only too happy to forget the many stressful hours spent with nervous, stuttering candidates; but there are also some pleasant exceptions. I still have with me the happy memory of Albert Eschenmoser's first undergraduate examination in organic chemistry, conducted more than forty years ago. In response to a somewhat general question, he proceeded to give me a comprehensive lecture, from which I learned much, both about chemistry and about the man. I have never had another student impress me to the same extent. He was so secure, his gifts and his extraordinary personality were so manifest, and it was already clear then how much came from within himself, and not from his teachers. On that occasion, there was no opportunity to ask him a second question!



Fig. 2 - Albert Eschenmoser as a young man.

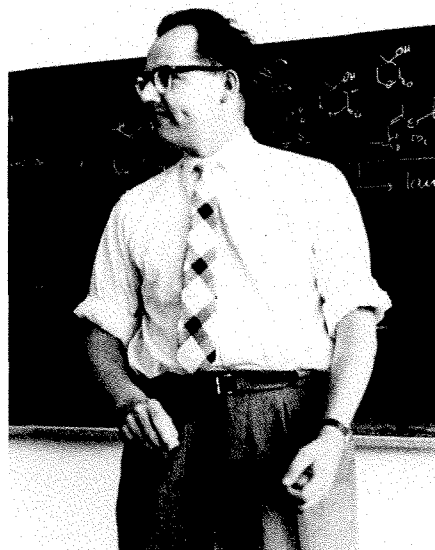


Fig. 3 - Albert Eschenmoser as Privatdozent.

Leopold Ruzicka, and his right-hand man, Placidus Plattner, both recognized Eschenmoser's exceptional talent and allowed him a free hand in his doctoral work, an unheard-of circumstance at that time. He completed this work in 1951, just two years after his undergraduate diploma. From then on, his academic career at the ETH proceeded swiftly. He completed his *Habilitation* and became a *Privatdozent* in 1956. He was appointed Associate Professor in 1960 and Professor of Organic Chemistry in 1965. It is worth noting that previously, since its founding in

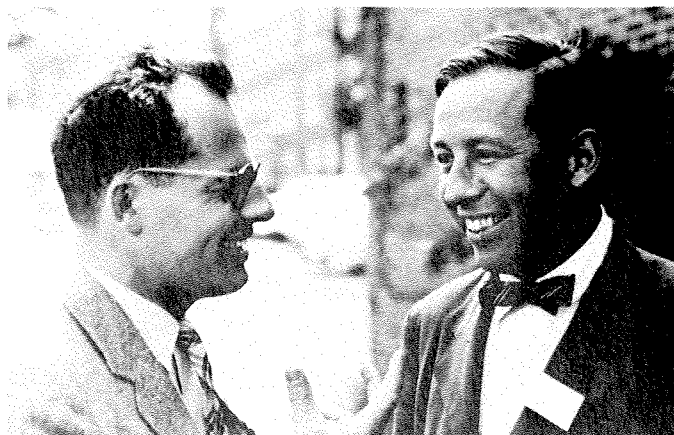


Fig. 4 - Good friends: Albert Eschenmoser and George Büchi.



Fig. 5 - At that time still a pipe smoker.

1855, the ETH had generally looked for its professors of chemistry, and especially of organic chemistry, beyond the borders of Switzerland, primarily in Germany (Städeler, Wislicenus, Victor Meyer, Hantzsch, Bamberger, Willstätter, Staudinger, Richard Kuhn, and Staudinger's student Ruzicka). Eschenmoser never studied abroad; on the other hand, his scientific development was self-generated to such a large extent that it cannot be cited as a paradigm for the quality of the Swiss chemical educational establishment.



Fig. 6 - Dr. Dorothee Felix - the "Good Angel" of the Eschenmoser Group.

Within the framework of this article it is not possible properly to assess, more than cursorily, the content and the richness of the ideas of Eschenmoser's 160 or so publications. Even a brief account of his major contributions to modern chemistry is a difficult task. As I attempted to come to grips with it, I found that the problem had already been nicely solved by Duilio Arigoni<sup>1</sup> in an article that I could only hope to paraphrase imperfectly. Therefore, I have asked Arigoni to allow me to use his *Laudatio*, and he has generously agreed.

"Eschenmoser used his early contributions to the area of acid catalyzed cyclization of aliphatic polyenes as mechanistic guidelines for the elucidation of new structures and for the critical evaluation of older structural proposals in the domain of the terpenes<sup>2</sup> (Figure A). The stereochemical elaboration of these ideas was the impetus

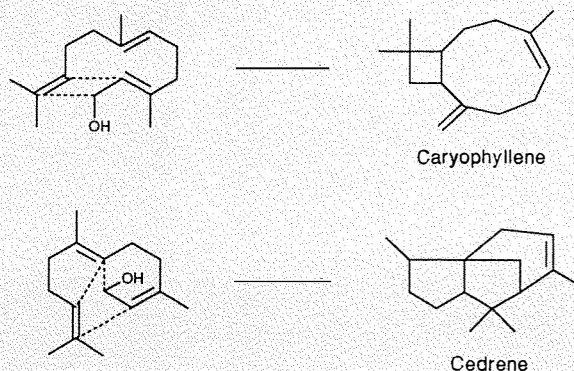


Fig. A - Eschenmoser's predictions for the correct structures of caryophyllene and cedrene.

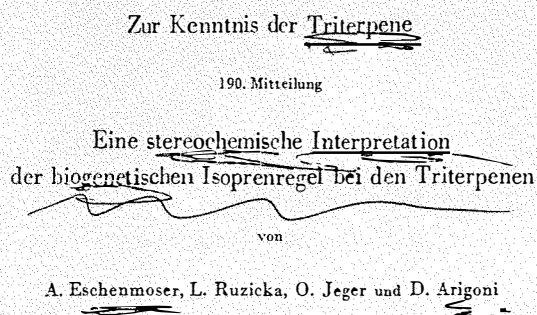


Fig. B - Ruzicka's personal copy of the 1955 paper on the biogenetic isoprene rule.<sup>4</sup>

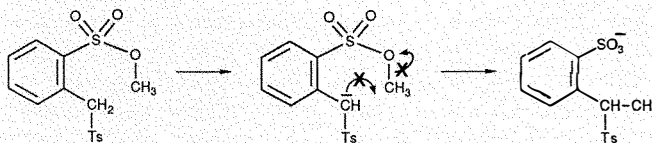


Fig. C - This reaction only occurs intermolecularly.

for the development of the final form of the biogenetic isoprene rule<sup>3</sup> (Figure B). At the same time, his work paved the way for the spectacular synthetic achievements of Johnson, van Tamelen and others.

"Over and over Eschenmoser has proved his uncanny ability to shed new light on fundamental problems in organic chemistry. Examples of his many-faceted interests are his study of the geometry of the transition state in the  $S_N2$  reaction at carbon centers<sup>5</sup> (Figure C), his clarification of important stereomechanistic aspects of the oxidation of alicyclic alcohols with chromium trioxide,<sup>6</sup> his preparation of organic molecules with a slowly inverting pyramidal nitrogen atom<sup>7</sup> (Figure D), and his manifold preparative use of fragmentation reactions<sup>8</sup> (Figure E), the nature and importance of which he had recognized ahead of others already at the start of his research career, and which appear throughout his work as a *Leitmotiv*, always in a subtle new form.

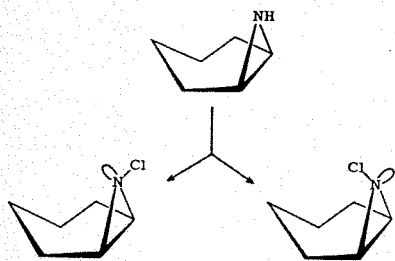


Fig. D - Two diastereomers exist as a result of slow inversion at pyramidal nitrogen.

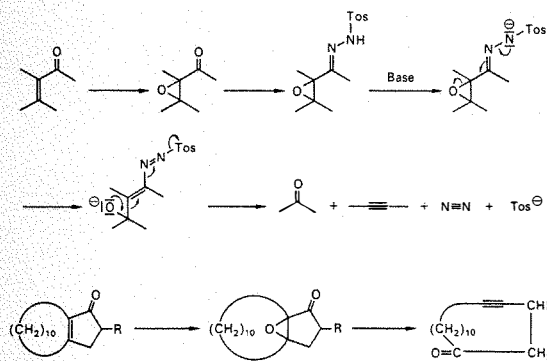


Fig. E - Eschenmoser fragmentation and one of its applications.

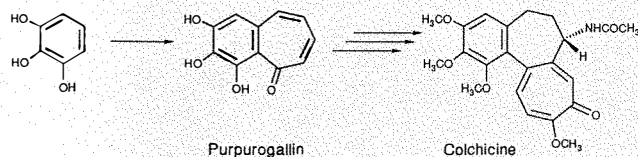


Fig. F - Synthesis of Colchicine.

"Eschenmoser is probably best known for his accomplishments in natural products synthesis. His singular command of strategy and tactics, already apparent in the total synthesis of the alkaloid colchicine<sup>9</sup> (Figure F), became more and more manifest in the course of his long and difficult investigations on the corrins, in part carried out in a competitive collaboration with the late R.B. Woodward, crowned with two quite distinct total syntheses of vitamin B<sub>12</sub><sup>10</sup> (Figure G). Their completion clearly confirmed the power of modern organic synthesis to achieve extraordinarily complex goals. In the course of this work Eschenmoser developed a multipronged set of synthetic routes to corrinoid and porphyrinoid compounds<sup>11</sup> (Figure H), enabling the first systematic investigation of the chemical properties of the corrinoids. He uncovered reaction paths entirely unsuspected before, which are central to an understanding of the biogenetic relationships within this biologically crucial class of pigments."

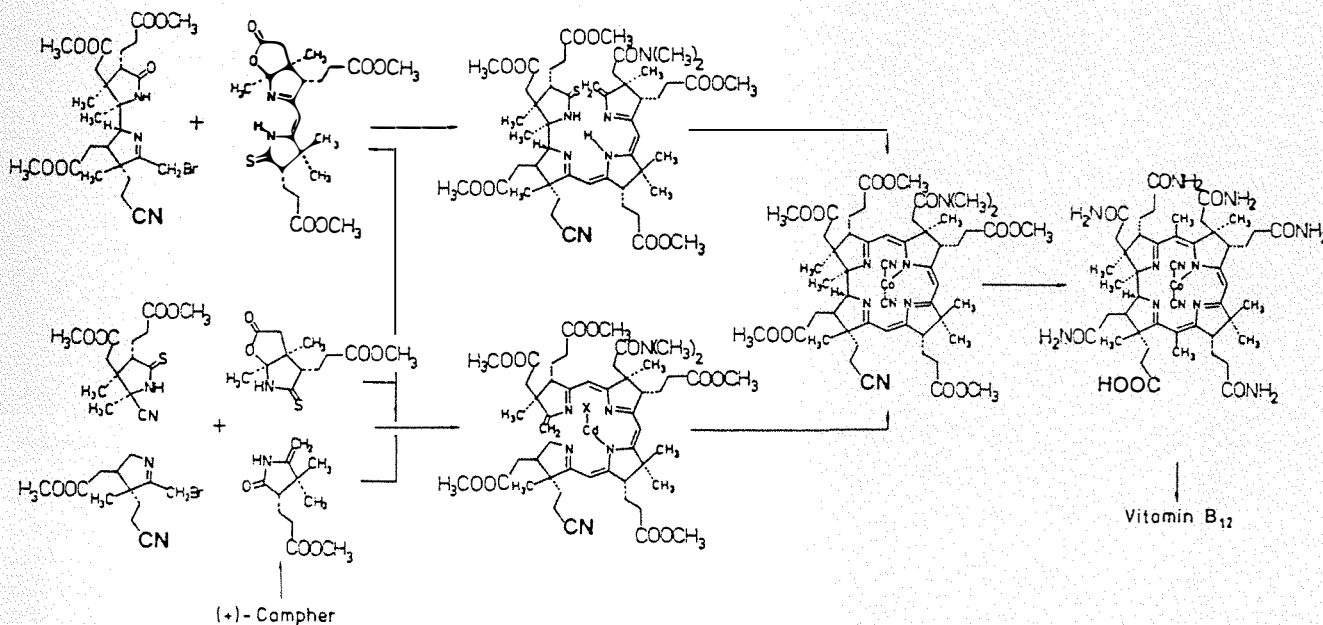


Fig. G - The two variants of the vitamin B<sub>12</sub> synthesis.



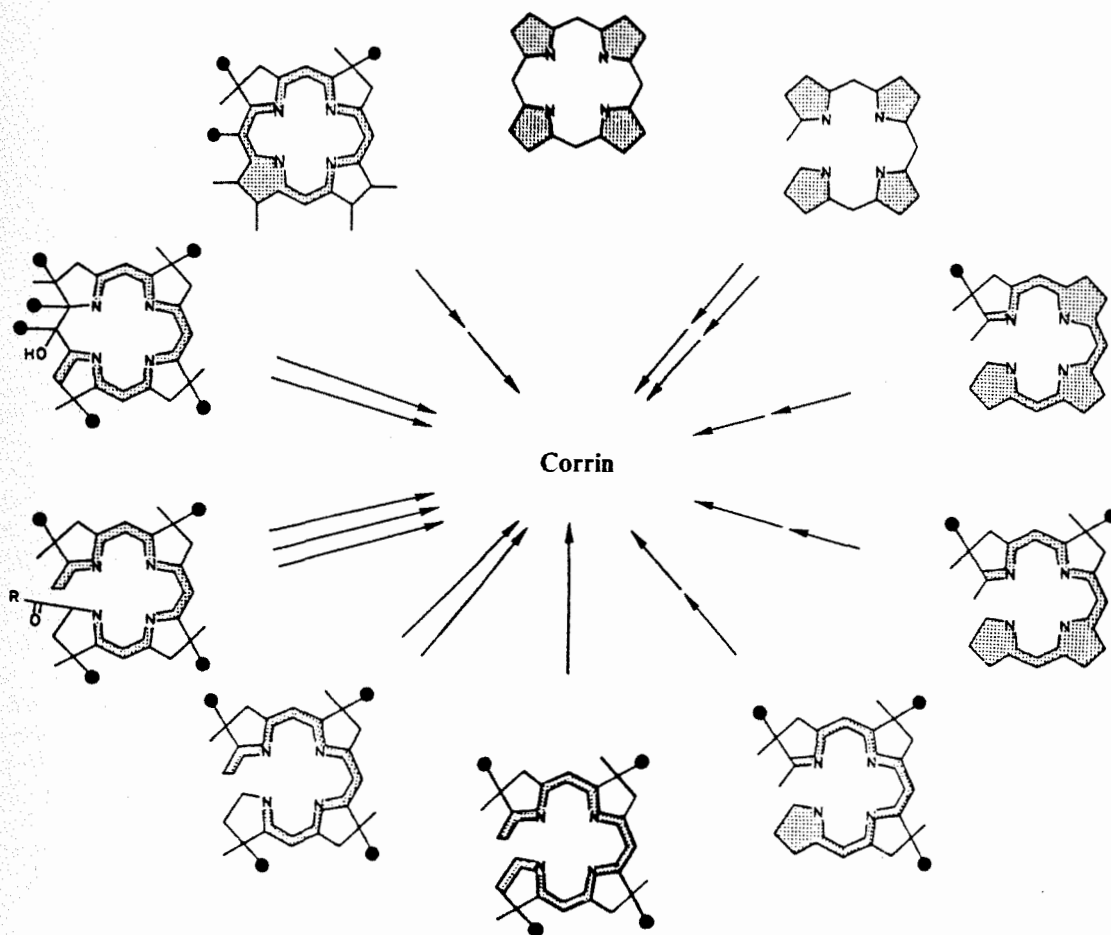


Fig. H - Cyclizations to corrinoids.

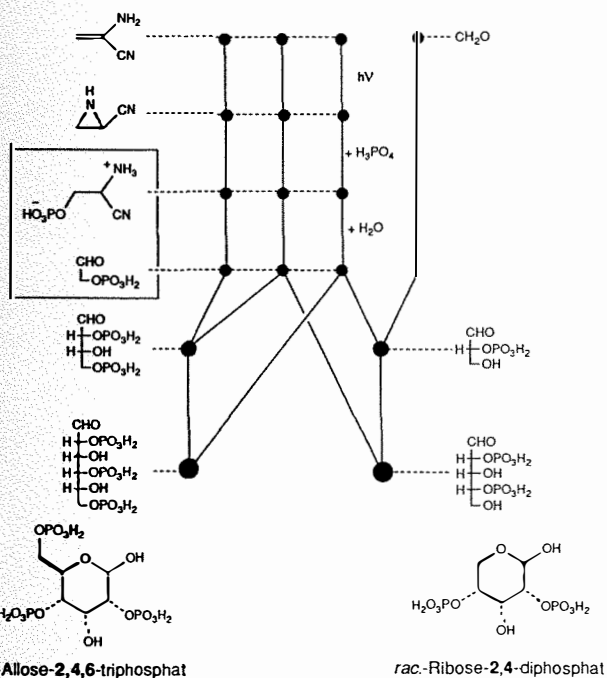


Fig. I - Racemic ribose-2,4-diphosphate is formed preferentially from potentially prebiotic starting materials.

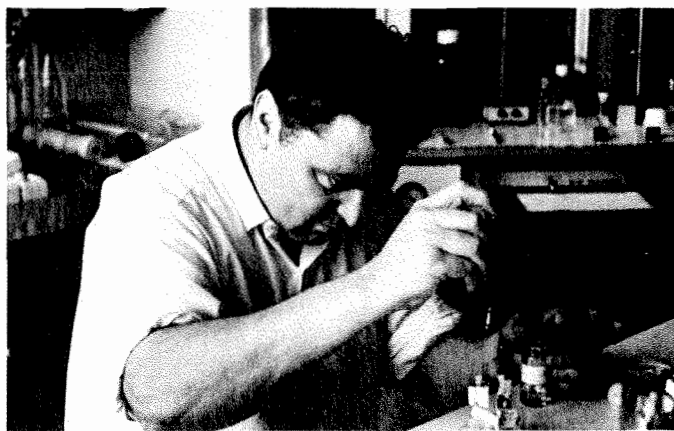


Fig. 7 - Dr. Jakob Schreiber - Albert Eschenmoser's first graduate student and lifelong friend.

Fascinated by the unbounded possibilities for constructing the most complex of molecules from elementary starting materials, Eschenmoser has more recently set himself the task of the demystification, through chemical rationalization, of the seeming structural complexity of the fundamental molecules of Nature. In seeking answers to the question, "Why have these molecules, in particular, been selected by biological evolution?" he is applying organic chemistry to probe the possibilities of the molecular self assembly of complex molecules from simple, potentially prebiological molecules<sup>12</sup> (Figure I).



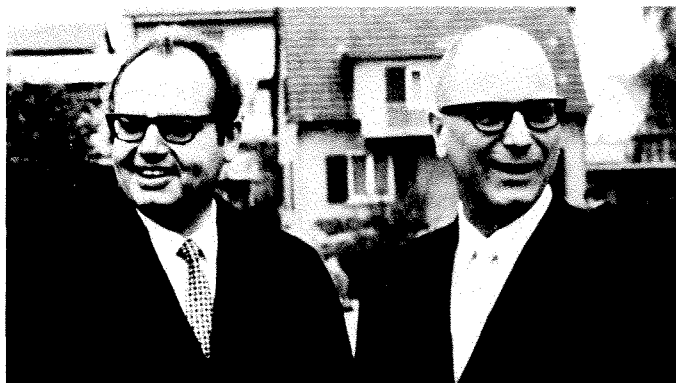


Fig. 8 - Albert Eschenmoser and Ernst Vogel, founder of Fluka.



Fig. 9 - Albert and Elisabeth Eschenmoser.



Fig. 10 - Duilio Arigoni and Albert Eschenmoser. (Photo: D. Felix)

*"Eschenmoser has received world-wide recognition for his contributions to chemical research, and has been the recipient of a long list of prizes and honors, among them the Marcel Benoist Prize, the R. A. Welch Award in Chemistry, The August Wilhelm von Hofmann Award, the Davy Medal, The Cope Award and the Wolf Prize, as well as a number of honorary degrees. As a teacher he carries a major responsibility for the not-so-conventional system of education in organic chemistry at the ETH Zürich. Doktorvater to some 140 students, he has also guided approximately the same number of postdoctoral fellows; his chemical progeny are in academic and industrial positions throughout the world."*



Fig. 11 - Dorothy Hodgkin and Albert Eschenmoser. (Photo: M. Bonetti)



Fig. 12 - R.B. Woodward, Albert Eschenmoser and the Vitamin B<sub>12</sub> Machine. ("Laufzeit nie länger als 2 Minuten, ansonst bildet sich B<sub>13</sub>")

The picture of Albert Eschenmoser's personality would be incomplete were one not to include the fact that he is a great perfectionist. If he considers a task to be important enough (and only then!) he spares no pain and no expenditure of time to carry it out optimally — whether he is writing a publication or organizing a symposium. Not only is he one of the most prominent organic chemists today, but also, as a result of his uncompromising standards, he has become the *arbiter elegantiarum* of contemporary organic chemistry, and he should be very proud of this. On this note, I would like to end with a small anecdote. Two of Eschenmoser's colleagues were discussing his personality in the corridor. One of them declared, "Deep down he's a very modest man." At that moment Eschenmoser appeared unexpectedly in the corridor, and the other colleague, somewhat embarrassed, said, "It's just been said of you that you're a very modest man." His immediate reaction: "Yes, but I can hide it very well!"

I thank Drs. Dorothee Felix and Jakob Schreiber and Profs. Duilio Arigoni and Claude Wintner (Haverford College) for their contributions to this article.



Fig. 13 - R.B. Woodward and Albert Eschenmoser. (Photo: L. Damm)

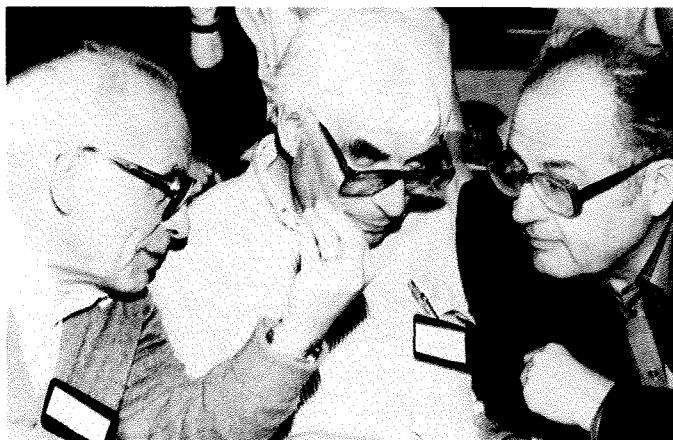
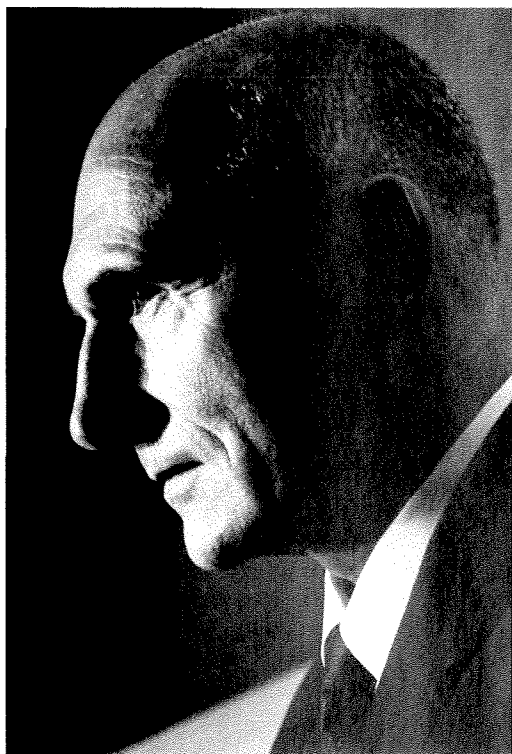


Fig. 14 - Oskar Jeger and Jack Dunitz with Albert Eschenmoser.

#### References:

- 1) Arigoni, D. *Chimia* **1985**, 39, 336. *Professor Albert Eschenmoser zum 60. Geburtstag.*
- 2) Eschenmoser, A. 1951 Thesis ETH Nr. 2018. *Zur säurekatalysierten Zyklisierung bei Mono- und Sesquiterpenverbindungen.*
- 3) *Idem* *Chimia* **1990**, 44, 1. *Leopold Ruzicka - From the Isoprene Rule to the Question of Life's Origin.*
- 4) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, 38, 1890. *Eine stereochemische Interpretation der biogenetischen Isoprenregel bei den Triterpenen.*
- 5) Tenu, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *ibid.* **1970**, 53, 2059. *Endocyclische  $S_N$ -Reaktionen am gesättigten Kohlenstoff?*
- 6) Schreiber, J.; Eschenmoser, A. *ibid.* **1955**, 38, 1529. *Über die relative Geschwindigkeit der Chromsäure-Oxidation sekundärer, alicyclischer Alkohole.*
- 7) Felix, D.; Eschenmoser, A. *Angew. Chem.* **1968**, 80, 197; *Int. Ed. Engl.* **7**, 224. *Slow Inversion at Pyramidal Nitrogen.*
- 8) Julia, S.A.; Eschenmoser, A.; Heusser, H.; Tarköy, N. *Helv. Chim. Acta* **1953**, 36, 1885. *Zur basenkatalysierten Spaltung von 1,5-Dicarbonyl-Verbindungen.* Eschenmoser, A.; Felix, D.; Ohloff, G. *ibid.* **1967**, 50, 708. *Eine neuartige Fragmentierung cyclischer  $\alpha,\beta$ -ungesättigter Carbonyl-systeme; Synthese von Exalton und rac-Muscon aus Cyclododecanon.* Felix, D.; Schreiber, J.; Ohloff, G.; Eschenmoser, A. *ibid.* **1971**, 54, 2896.  *$\alpha,\beta$ -Epoxyketon  $\rightarrow$  Alkinon-Fragmentierung I: Synthese von Exalton und rac-Muscon aus Cyclododecanon.*
- 9) Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Eschenmoser, A. *Angew. Chem.* **1959**, 71, 637. *Synthese des Colchicins.* Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Threlfall, T.; Eschenmoser, A. *Helv. Chim. Acta* **1961**, 44, 540. *Synthese des Colchicins.*
- 10) Eschenmoser, A.; Wintner, C.E. *Science* **1977**, 196, 1410. *Natural Product Synthesis and Vitamin  $B_{12}$ .* Eschenmoser, A. *Nova Acta Leopoldina* **1982**, N. F. 55 (247), 5. *Von der Synthese des Vitamin  $B_{12}$  zur Frage nach dem Ursprung der Corrinstruktur.*
- 11) Eschenmoser, A. *Angew. Chem.* **1988**, 100, 5; *Int. Ed. Engl.* **27**, 5. *Vitamin  $B_{12}$ : Experiments Concerning the Origin of Its Molecular Structure.*
- 12) Müller, D.; Pitsch, S.; Kittaka, A.; Wagner, E.; Wintner, C.E.; Eschenmoser, A. *Helv. Chim. Acta* **1990**, 73, 1940. *Chemie von  $\alpha$ -Aminonitrilen.*



#### About the Author

"Vladimir Prelog, born July 23, 1906 in Sarajevo, Yugoslavia. 1924-1929: Chemistry Department Czech Institute of Technology, Prague, CSSR; 1928: Dipl. Ing.-Chem.; 1929: Dr. Sc.Techn., Thesis under supervision of Professor E. Votocek; 1929-1935: Head of Laboratory of G.J. Driza, Prague; 1935-1940: "Dozent" at the Chemistry Department of the Technical University Zagreb, Yugoslavia; 1940-1941: Associate Professor, Zagreb; Since 1942: Swiss Federal Institute of Technology, Zürich, "Privatdozent"; 1947: Associate Professor; 1950: Full Professor; 1957-1965: Head of Laboratory of Organic Chemistry, Swiss Federal Institute of Technology (ETH), Zürich; 1976: retired."

Everyone who knows Professor Prelog will smile at the above curriculum vitae which he supplied. There it is — all correct — and yet so much is missing. Not just his many honors, including the Nobel Prize in 1975, but not a hint at what a humane person he is.

Some years ago he gave this old Chinese advice: "If you want to be happy for an evening, buy a bottle of wine; for a week, slaughter a pig; for a year, get married; but if you want to be happy throughout your life, enjoy your work." Some one who didn't know him once accused him of being misogynous, to which he replied that he drinks practically no wine, does not eat pork, and at 8 p.m. on April 1, 1927, met Kamila who has been his wife for 57 years.

The Bible says of Moses that at 120 his eyes were not dim nor his natural strength abated. To Professors Eschenmoser and Prelog we say: To 120 !

# Synthetic Aspects of Electron-Transfer Chemistry

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Our 1975 review of electron-transfer substitution reactions<sup>1</sup> dealt mainly with the basis for the then novel concept that nucleophilic substitution at a saturated carbon atom could proceed as a multi-stage sequence involving radical anions and free radicals as intermediates. In the intervening years, this concept has become widely accepted and applied, and as a consequence, there is now substantial literature concerned with the synthetic organic aspects of electron-transfer chemistry. It is clear that electron-transfer substitution processes are far more widespread and synthetically valuable than anyone envisioned fifteen years ago. These reactions provide novel means of synthesis: they occur readily under mild conditions, give excellent yields of pure products, and, in contrast to S<sub>N</sub>2 displacements, they are rather insensitive to steric hindrance. Many electron-transfer reactions result in carbon-carbon bond formation and this, coupled with the relative insensitivity of these reactions to steric hindrance, results in the facile synthesis of highly branched compounds. Especially noteworthy is a general synthesis of quaternary carbon compounds based on electron-transfer chemistry.<sup>2</sup>

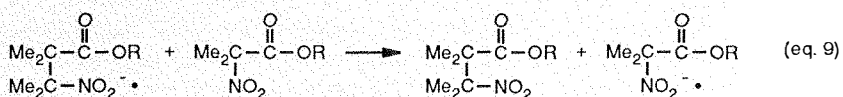
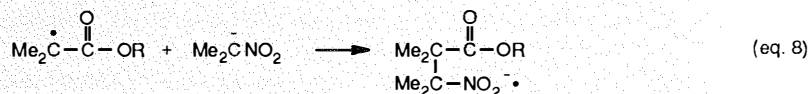
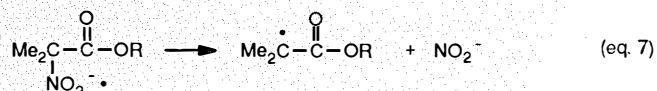
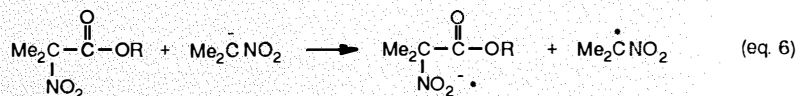
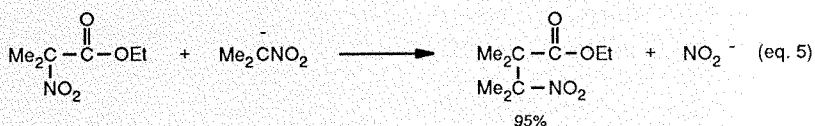
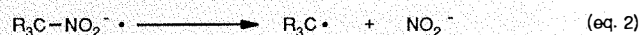
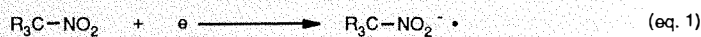
## 1. Introduction.

The various reactions described herein derive from two characteristics of aliphatic tertiary nitro compounds: (1) the ease with which the nitro group accepts one electron and (2) the facility with which the resulting nitro radical anion fragments (*i.e.*, eq. 1 and 2). The free radical thus formed is able to react in various ways. In electron-transfer substitution processes, the radical combines with the nucleophile A<sup>-</sup> (eq. 3) which is usually the source of the electron of eq. 1. The resulting radical anion then transfers an electron to a molecule of the tertiary nitro compound which readily accepts the electron (eq. 4).

It will be seen that the multi-step sequence (eq. 1-4) produces the substitution product in which A<sup>-</sup> has displaced NO<sub>2</sub><sup>-</sup>. The direct displacement of an aliphatic nitro group by a nucleophile has never been observed. Thus what cannot be accomplished directly in a single step is achieved by an indirect method

(eq. 1-4). Several important advantages accrue to this more complex reaction path: (1) a high degree of selectivity is observed; (2) chemical reactions which do not occur *via* the classical S<sub>N</sub>1-S<sub>N</sub>2 pattern take place readily, and; (3) a significant diminution in the importance of steric hindrance occurs.

The simple substitution of a nitro group by a nucleophile is not the invariant result of electron-transfer processes. Thus electron-transfer chemistry has made possible a new and very general synthesis of tetrasubstituted olefins. (See Section 3.)<sup>3</sup>



## 2. Replacement of the Nitro Groups of Tertiary Nitro Compounds.

The synthetic utility of tertiary nitro compounds derives from the ease with which they undergo electron-transfer substitution of the nitro group.

### 2.1. Replacement of the Nitro Group with Carbon-Carbon Bond Formation.

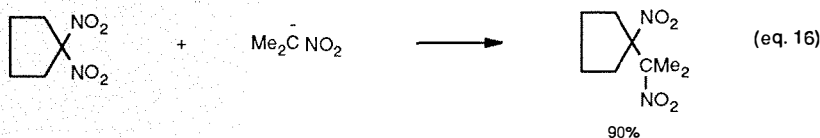
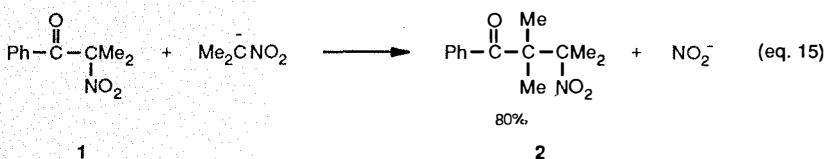
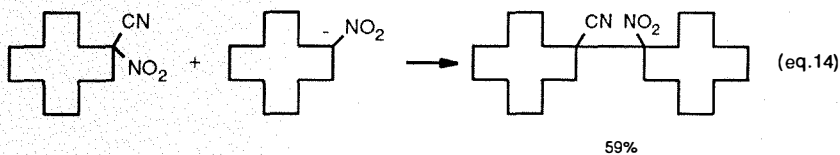
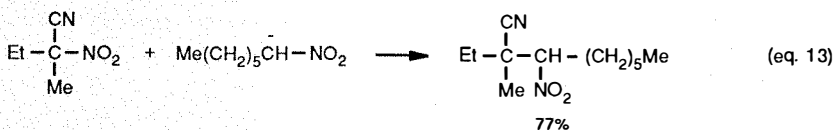
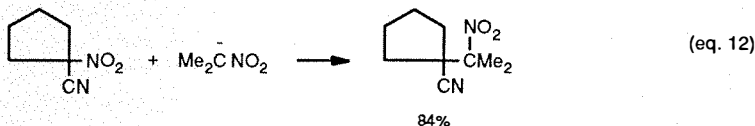
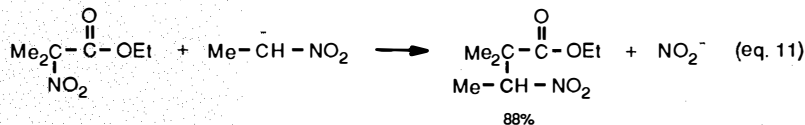
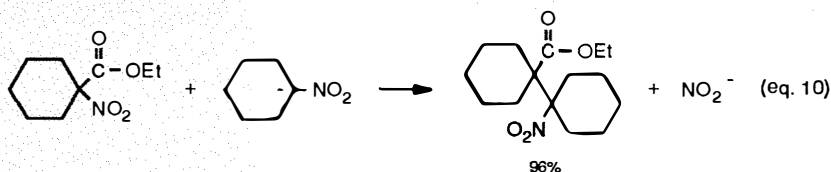
The conversion of ethyl  $\alpha$ -nitroisobutyrate to the  $\beta$ -nitroester takes place at room temperature and gives a 95% yield of pure product<sup>4</sup> (eq. 5). This reaction, which proceeds slowly in the dark, is accelerated by ordinary room light. For a discussion of this matter, see ref. 6. The chain mechanism of eq. 6-9 invokes both radical anions and free radicals; the intermediacy of radical anions is consonant with the ability of 5 mol% *p*-dinitrobenzene (*p*-DNB) to completely inhibit the reaction.<sup>5</sup> Support for the intermediacy of free radicals is provided by the observation that galvinoxyl,<sup>4</sup> at the 5 mol% level, also inhibits the reaction of eq. 5. Finally, the quantum yield for this reaction is 220;<sup>6</sup> thus, the average chain length is at least 220.

It will be seen from the mechanistic sequence of eq. 6-9 that replacement of a nitro group depends not only on the propensity of a nitro group for forming a radical-anion (eq. 6), but also, on the ease with which nitroaliphatic radical anions fragment (eq. 7).<sup>7</sup> Fragmentation (eq. 7), which is not observed with the radical-anions of nitroaromatics, provides a means of converting nitroparaffins into free radicals. These free radicals may then combine with nucleophiles to form radical-anions (eq. 8)<sup>8</sup> which perpetuate the chain by transferring an electron to a molecule of the starting nitro compound (eq. 9) and simultaneously generate the substitution product. (Later in this review, we reference the factors which govern the feasibility of the combination of a radical and an anion; *i.e.*, the reaction of eq. 8; see Scheme 2.)

The reaction of eq. 5 is a general reaction of  $\alpha$ -nitroesters with nitroparaffin salts;<sup>4</sup> for example: eq. 10. The salts of primary nitroparaffins may also be employed, and indeed, it is easy to isolate the product (eq. 11).

$\alpha$ -Nitro nitriles also undergo a general reaction<sup>9</sup> when treated with nitroparaffin salts. Here again, the nitro group of the  $\alpha$ -nitro nitrile is rapidly and cleanly replaced by the nitroparaffin anion *via* an electron-transfer chain sequence analogous to that of eq. 6-9 to give  $\beta$ -nitro nitriles (eq. 12-14).

The nitro group of an  $\alpha$ -nitroketone is also readily displaced:  $\alpha$ -nitroisobutyrophenone,

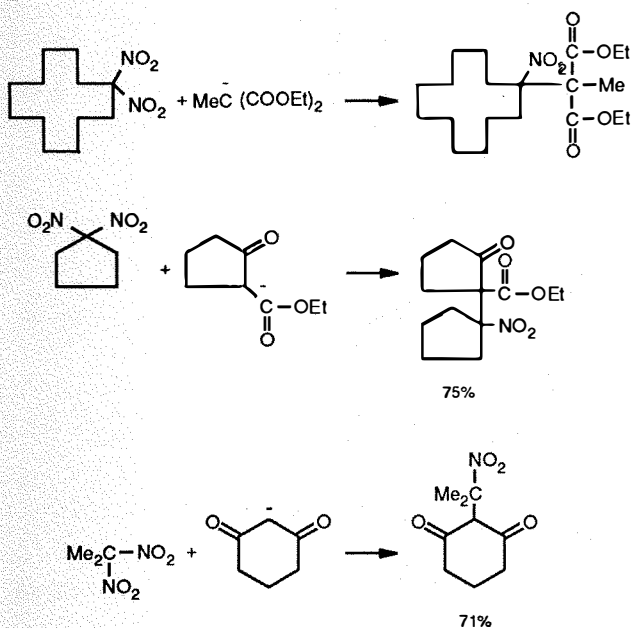


1, reacts with the anion of 2-nitropropane to give an 80% yield of the  $\beta$ -nitroketone 2 (eq. 15).<sup>4</sup>

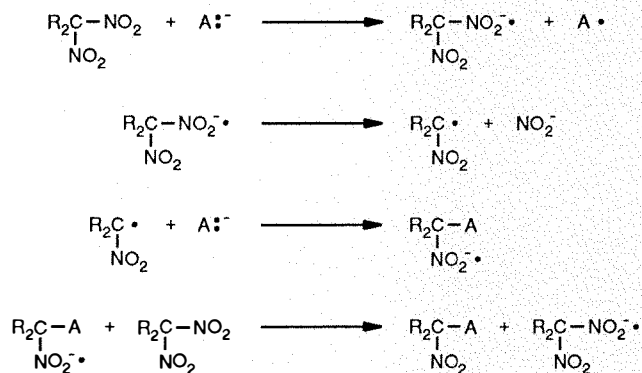
The reactions of  $\alpha,\alpha$ -dinitro compounds are of considerable synthetic value. They occur with great speed; the reaction of eq. 16 is complete in 15 minutes. And, whereas  $\alpha$ -nitroesters only react with nitroparaffin anions,  $\alpha,\alpha$ -dinitro compounds react with many other nucleophiles *via* the electron-transfer chain pathway. Thus, a variety of malonic ester

anions,  $\beta$ -diketone anions and  $\beta$ -ketoester anions displace a nitro group from  $\alpha,\alpha$ -dinitro compounds as the examples of Scheme 1 show.<sup>10</sup>

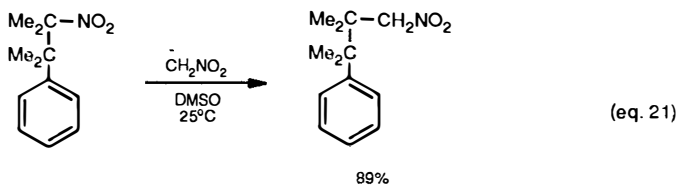
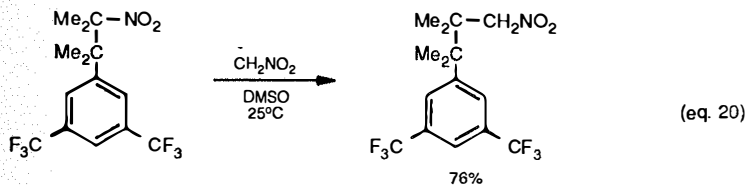
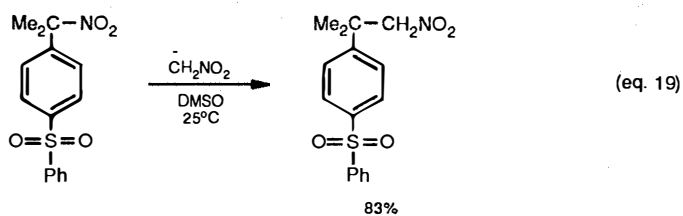
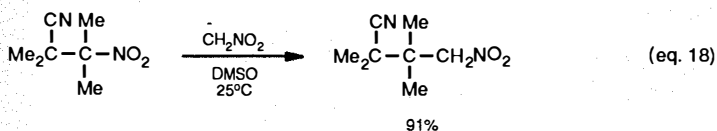
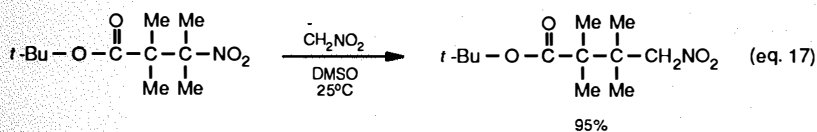
Aside from its synthetic utility, the great reactivity of  $\alpha,\alpha$ -dinitro compounds illustrates an important point.  $\alpha,\alpha$ -Dinitro compounds are uniquely reactive, because regardless of the nucleophile, there is always available a chain sequence which involves nitroparaffin radical anions — something that is



**Scheme 1** - Reactions of  $\alpha,\alpha$ -dinitro compounds.



**Scheme 2** - Chain sequence available for reactions of  $\alpha,\alpha$ -dinitro compounds with nucleophiles *A*.



not possible with  $\alpha$ -nitroesters (Scheme 2). [The factors which govern the feasibility of the combination of a radical and an anion (*i.e.*, the reaction of eq. 8) are further discussed in ref. 11.]

### 2.1.1. Replacement of the Nitro Group by the Sodium Salt of Nitromethane.

Tertiary nitro compounds react with the sodium salt of nitromethane (eq. 17-21). This provides a facile preparation of quaternary carbon compounds bearing a  $-\text{CH}_2\text{NO}_2$  on the quaternary carbon. Since a  $-\text{CH}_2\text{NO}_2$  is readily transformed into a number of other useful functional groups by well-established procedures (Scheme 3), this significantly extends the synthetic value of this reaction.

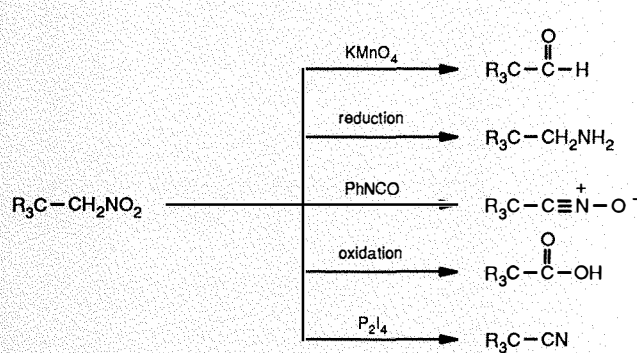
### 2.2. Replacement of the Nitro Group by Hydrogen.

The nitro group confers a unique capability for carbon-carbon bond formation. Clearly, once the desired carbon skeleton has been established, it is advantageous to have effective means for replacing the nitro group by hydrogen. Two procedures are now available.

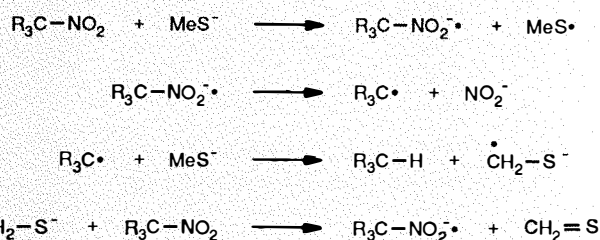
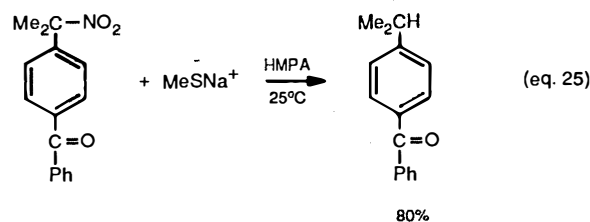
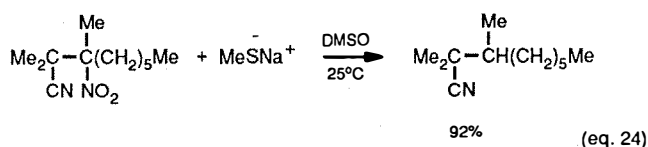
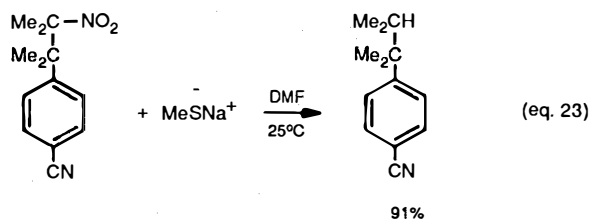
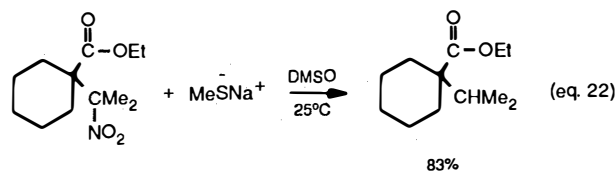
#### 2.2.1. By Sodium Mercaptide.

In 1972, it was found that a tertiary nitro group is replaced by hydrogen on treatment with the sodium salt of methyl mercaptan.<sup>14</sup> Equations 22-25 are illustrative.

These reactions exhibit the characteristics of electron-transfer chain processes; the accepted mechanism is given in Scheme 4.



**Scheme 3** - Some transformations of primary nitroparaffins:  $\text{KMnO}_4$ ,<sup>2</sup>  $\text{PhNCO}$ ,<sup>12</sup> and  $\text{P}_2\text{I}_4$ .<sup>13</sup>

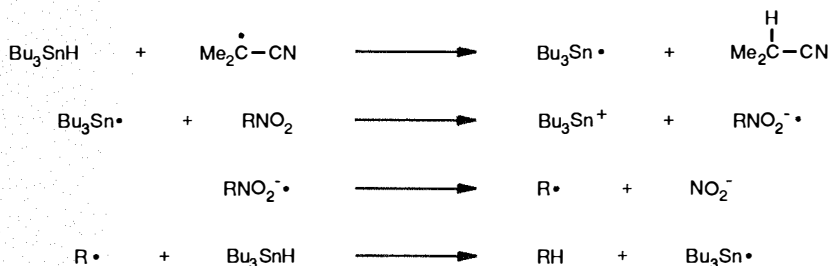
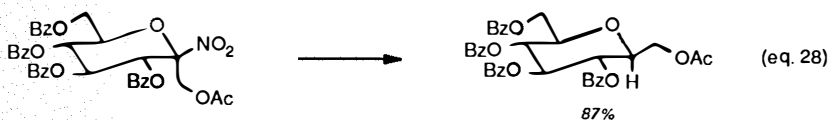
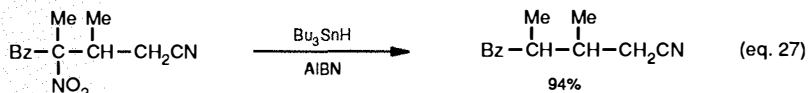
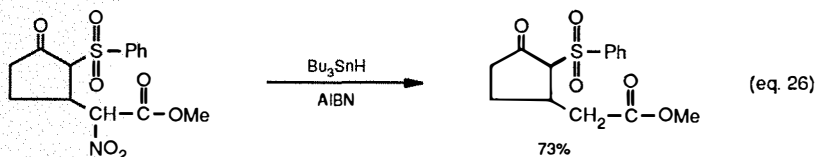


**Scheme 4** - Chain mechanism for replacing the nitro group by hydrogen by the action of the sodium salt of methyl mercaptan.

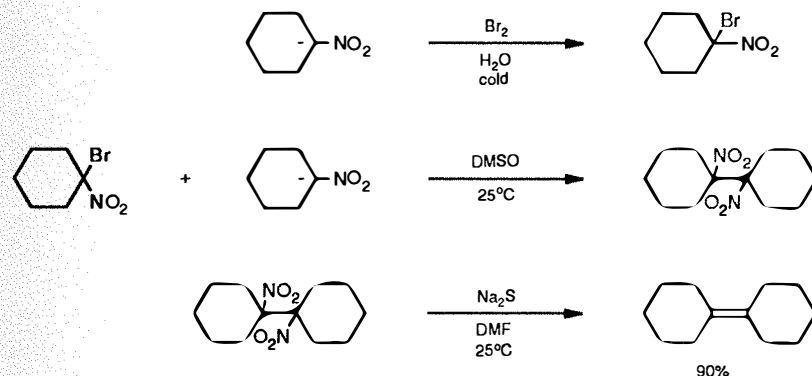
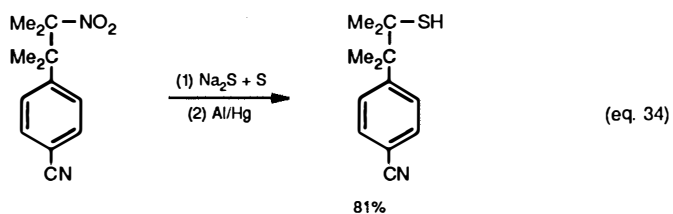
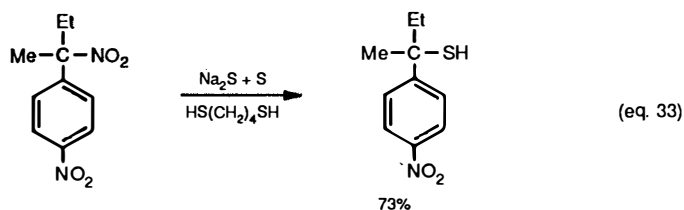
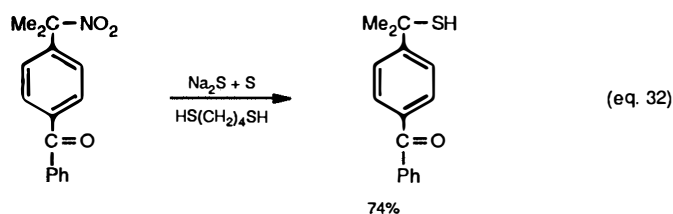
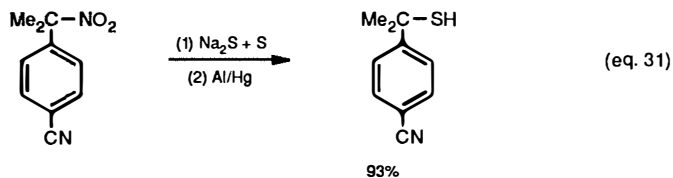
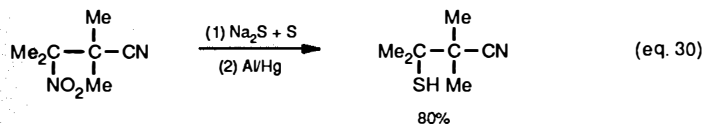
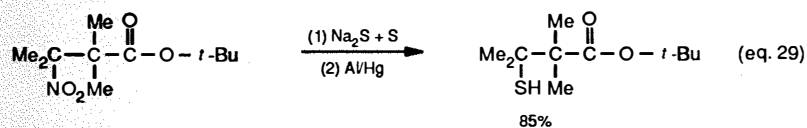
### 2.2.2. By Tri-*n*-butyltin Hydride ( $\text{Bu}_3\text{SnH}$ ).

In 1981, Tanner<sup>15</sup> and Ono<sup>16</sup> independently found that tri-*n*-butyltin hydride ( $\text{Bu}_3\text{SnH}$ ) also replaces a nitro group by hydrogen. The reaction is conducted in benzene at 80°C and is initiated by a catalytic amount of the free radical source azobisisobutyronitrile (AIBN). The reaction is quite general for tertiary nitro compounds, succeeds with some secondary nitro compounds, but fails with primary nitroparaffins. Compared to sodium mercaptide, tri-*n*-butyltin hydride possesses the valuable attribute that it is a neutral reagent and employs a poor ionizing solvent. This confers an advantage when nitro compounds which have been prepared by a Michael Addition are reduced. Ono<sup>17</sup> has exploited this advantage to good effect as can be seen from the examples of eq. 26 and 27.

Vasella<sup>18</sup> has shown that the  $\text{Bu}_3\text{SnH}$  reaction is valuable for the preparation of "C-glycosides" from nitro compounds derived from sugars (eq. 28). Support for a chain mechanism for the  $\text{Bu}_3\text{SnH}$  reaction<sup>15,16</sup> is derived from the observation that the reduction is initiated by catalytic amounts of AIBN and is inhibited by small amounts of *m*-dinitrobenzene (*m*-DNB) (Scheme 5). A more detailed description of this mechanism, based on ESR spectroscopy, has been published.<sup>19</sup>



**Scheme 5** - Chain mechanism for the  $\text{Bu}_3\text{SnH}$  reaction.



**Scheme 6** - The preparation of a symmetrical tetrasubstituted olefin.

### 2.3. Replacement of the Nitro Group by Thiol.

The direct conversion of a tertiary nitro group into a thiol was reported in 1978.<sup>20</sup> This important discovery provides a facile entry into the domain of organo-sulfur chemistry without destroying any other functional groups — even an aromatic nitro group comes through unscathed.

The transformation of nitro into thiol is accomplished by treating the tertiary nitro compound with a solution of sodium sulfide and sulfur in DMSO at 25°C, whereupon rapid conversion to a mixture of the corresponding thiol and dialkyl polysulfides occurs; on subjecting this mixture to the action of amalgamated aluminum, or 1,4-butanedithiol, the dialkyl polysulfides are cleaved to thiols. Some typical results are presented in eq. 29-34.

Precisely what reagent is responsible for this transformation is not clear. Sodium sulfide is ineffective, but when elemental sulfur is added to the sodium sulfide so that for each sulfide ion there is one sulfur atom (*i.e.*, the gross composition is Na<sub>2</sub>S<sub>2</sub>) the reaction proceeds smoothly. Further addition of sulfur is not beneficial; indeed, the rate of reaction is sharply decreased.

An electron-transfer chain mechanism has been proposed.<sup>20</sup> While it is probable that the reaction is an electron-transfer chain process, this has not been established. The difficulty in pinpointing the actual reducing agent in the sodium polysulfide reagent has served to discourage mechanistic studies.

### 3. The Synthesis of Tetrasubstituted Olefins.

A new and general synthesis of tetrasubstituted olefins, noteworthy for its simplicity and for providing pure products in excellent yields, has been reported.<sup>3</sup> Both symmetrical and unsymmetrical olefins are readily obtained (Table 1).

The elegance of this synthesis of tetrasubstituted olefins can be appreciated by comparison with the best previous synthesis of cyclohexylidencyclohexane described in *Organic Synthesis*.<sup>21</sup> When the salt of a secondary nitro compound is treated with bromine, it is rapidly and quantitatively converted to the α-bromonitro compound. This compound, without being purified, is treated with a second equivalent of the nitroparaffin salt, whereupon the pure *vicinal* dinitro compound is isolated in 89% yield (Scheme 6). As shown in Scheme 6, conversion of *vicinal* dinitro compounds into tetrasubstituted olefins occurs smoothly at room temperature when the dinitro compound is treated with sodium sulfide or sodium thiophenoxide. For preparative



purposes, sodium sulfide is preferred. For mechanistic studies, sodium thiophenoxide was employed. This synthesis is noteworthy for producing olefins free of isomers. Thus, even though a double bond exocyclic to a five-, six-, or seven-membered ring is prone to migrate into the ring,<sup>22</sup> this does not occur under the conditions employed.

The preparation of unsymmetrical *vicinal* dinitro compounds from  $\alpha$ -bromonitro compounds is not satisfactory, because in addition to the desired unsymmetrical compound, substantial amounts of the two symmetrical *vicinal* dinitro compounds are produced. This difficulty is easily circumvented by the use of  $\alpha,\alpha$ -dinitro compounds (eq. 35). In this way, 86-91% yields of pure unsymmetrical *vicinal* dinitro compounds are obtained.

The elimination of two nitro groups from *vicinal* dinitro compounds by the action of sodium sulfide, or sodium thiophenoxide, is not a simple ionic process. These reactions are accelerated by the light of an ordinary 20-watt fluorescent lamp, and they are inhibited by 5 mol% di-*tert*-butyl nitroxide or 5 mol% *m*-dinitrobenzene. Clearly, olefin formation is an electron-transfer chain process. Furthermore, during the initial phase of the reaction there is an unmistakable acceleration in rate. These facts have led to the mechanistic proposal of Scheme 7.<sup>23</sup>

It will be seen that the first four steps of Scheme 7 constitute a chain propagating sequence. Implicit in this mechanistic proposal is the reasonable assumption that the  $N_2O_4^{\cdot-}$  radical anion is a better one-electron transfer agent than thiophenoxide ion or sulfide ion.

Minor variations of this chain mechanism are readily envisioned; for example, the  $[C_6H_5S-NO_2]^{\cdot-}$  radical anion may well be involved instead of the  $N_2O_4^{\cdot-}$  radical anions.

### 3.1. The Synthesis of Functionalized Tetrasubstituted Olefins.

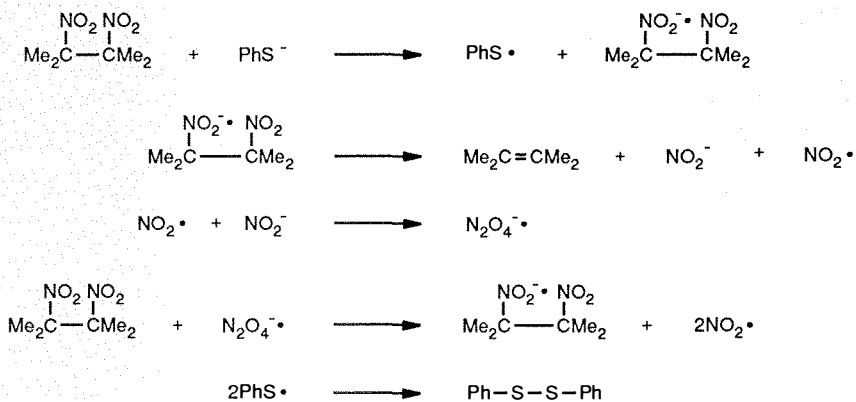
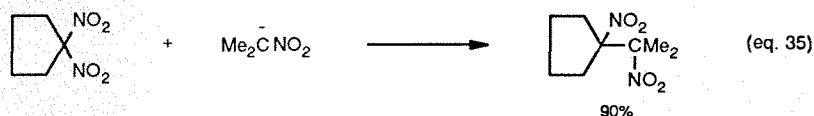
In 1977 a simple synthesis of symmetrical and unsymmetrical tetrasubstituted olefins bearing cyano, keto, ester and ether groups was described (Schemes 8 and 9).<sup>24</sup> Table 2 lists the olefins obtained; yields refer to pure isolated products which, when the possibility exists, contain both the *cis*- and *trans*- forms. The preparation of the requisite symmetrical dinitro compounds is illustrated by Scheme 8.

The success of this synthesis of functionalized olefins derives from the fact that of all the common functional groups the nitro group is the most readily induced to accept one electron. This, coupled with the use of a mild reducing agent, provides the observed selectivity. The salts of 2-nitropropane transform *vicinal* dinitro compounds into olefins. This preliminary result deserves further study.

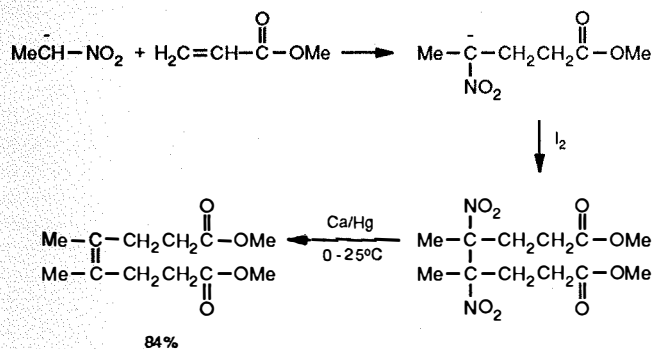
Table 1

Olefins Synthesized from Vicinal Dinitro Compounds

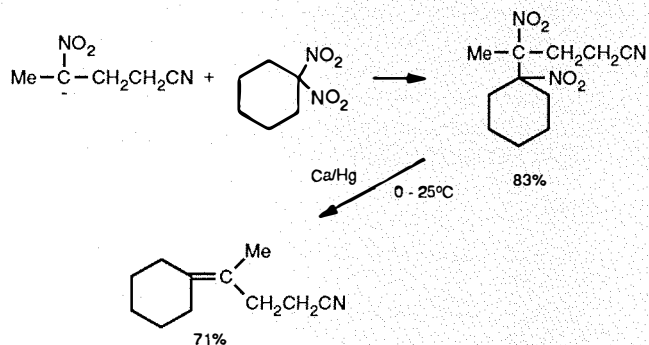
Olefin	% Yield
$\begin{array}{c} \text{Me} \quad \text{Me} \\   \quad   \\ \text{EtC}=\text{CEt} \end{array}$	82
$\begin{array}{c} \text{Pr} \\   \\ \text{EtC}=\text{CMe}_2 \end{array}$	88
$\begin{array}{c} \text{Me} \quad \text{Me} \\   \quad   \\ \text{PhC}=\text{CPh} \end{array}$	82
	89
	92
	90
	91
	90
	84



Scheme 7 - Chain mechanism for conversion of vicinal dinitro compounds to olefins.



**Scheme 8** - Preparation of symmetrical tetrasubstituted functionalized olefins.

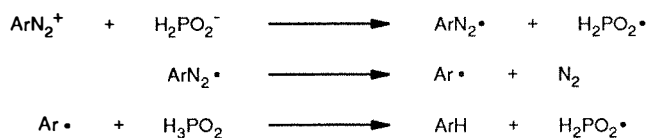


**Scheme 9** - Preparation of unsymmetrical tetrasubstituted functionalized olefins.

**Table 2**

Olefins Synthesized from Vicinal Dinitro Compounds

Olefin	% Yield
$\begin{array}{c} \text{Me-C-CH}_2\text{CH}_2\text{CN} \\ \parallel \\ \text{Me-C-CH}_2\text{CH}_2\text{CN} \end{array}$	87
$\begin{array}{c} \text{Me-C-CH}_2\text{CH}_2\text{C(=O)OMe} \\ \parallel \\ \text{Me-C-CH}_2\text{CH}_2\text{C(=O)OMe} \end{array}$	84
$\begin{array}{c} \text{Me-C-CH}_2\text{CH}_2\text{C(=O)Me} \\ \parallel \\ \text{Me-C-CH}_2\text{CH}_2\text{C(=O)Me} \end{array}$	77
$\begin{array}{c} \text{Et-C-CH}_2\text{OMe} \\ \parallel \\ \text{Et-C-CH}_2\text{OMe} \end{array}$	78
$\begin{array}{c} \text{Cyclohexane-C(Me)=CH-CH}_2\text{CH}_2\text{CN} \end{array}$	71
$\begin{array}{c} \text{Cyclohexane-C(Me)=CH-CH}_2\text{CH}_2\text{C(=O)OMe} \end{array}$	66
$\begin{array}{c} \text{Cyclohexane-C(Me)=CH-CH}_2\text{CH}_2\text{C(=O)Me} \end{array}$	68
$\begin{array}{c} \text{Cyclohexane-C(Et)=CH-CH}_2\text{OMe} \end{array}$	65



**Scheme 10** - Replacement of diazonium group by hydrogen.

## 4. Conclusion.

This discussion of synthetically useful electron-transfer chain processes would be incomplete without mention of the first example of such a reaction – replacement of the nitrogen of aryl diazonium salts by hydrogen. This transformation, discovered by Mai in 1902,<sup>25</sup> is brought about by treating a cold aqueous solution of the diazonium salt with hypophosphorous acid. The reaction is extremely reliable; indeed, it is one of the few truly general reactions of organic chemistry.

Not until 1949 was Mai's reaction shown to proceed *via* an electron-transfer chain sequence (Scheme 10).<sup>26</sup>

Since it is now clear that electron-transfer chain reactions are not restricted to aliphatic nitro compounds,\* one hopes that this review will serve to provide organic chemists with a rational basis for anticipating the possibility of electron-transfer transformations rather than requiring them to stumble upon such reactions in the dark.

\* Feiring, A.E.J. *Org. Chem.* **1983**, *48*, 347. Section 6.5, addendum.

## 5. Addendum.

For an addendum to this article, which describes more detailed syntheses of tertiary nitro compounds, etc., please contact our Technical Services Department at 800-231-8327.

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## References

- 1) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734.
- 2) Kornblum, N.; Erickson, A.S. *J. Org. Chem.* **1981**, *46*, 1037.
- 3) Kornblum, N.; Boyd, S.D.; Pinnick, H.W.; Smith, R.G. *J. Am. Chem. Soc.* **1971**, *93*, 4316.
- 4) Kornblum, N.; Boyd, S.D.; Stuchal, F.W. *ibid.* **1970**, *92*, 5783. Kornblum, N.; Boyd, S.D. *ibid.* **1970**, *92*, 5784.
- 5) See ref. 1 for a description of diagnostics for electron-transfer chain reactions.
- 6) Wade, P.A.; Morrison, H.A.; Kornblum, N. *J. Org. Chem.* **1987**, *52*, 3102.
- 7) Hoffmann, A.K.; Hodson, W.G.; Maricle, D.L.; Jura, W.H. *J. Am. Chem. Soc.* **1964**, *86*, 631.
- 8) Kornblum, N.; Singh, H.K.; Kelly, W.J. *J. Org. Chem.* **1983**, *48*, 332.
- 9) Kornblum, N.; Singh, H.K.; Boyd, S.D. *ibid.* **1984**, *49*, 358.
- 10) Kornblum, N.; Kelly, W.J.; Kestner, M.M. *ibid.* **1985**, *50*, 4720.
- 11) Kornblum, N. in *The Chemistry of Functional Groups, Supplement F: The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982, p 381.
- 12) Curran, D.P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.
- 13) Denis, J.N.; Krief, A. *Tetrahedron Lett.* **1979**, 3995.
- 14) Kornblum, N.; Carlson, S.C.; Smith, R.G. *J. Am. Chem. Soc.* **1978**, *100*, 289. *Idem ibid.* **1979**, *101*, 647.
- 15) Tanner, D.D.; Blackburn, E.V.; Diaz, G.E. *ibid.* **1981**, *103*, 1557.
- 16) Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, 1705.
- 17) Ono, N. *et al.* *J. Org. Chem.* **1985**, *50*, 3692. Ono, N. in Feuer, H.; Nielsen A. *Nitro Compounds*; VCH: New York, 1990, p 1.
- 18) Baumberger F.; Vasella A. *Helv. Chim. Acta* **1983**, *66*, 2210.
- 19) Dupuis, J.; Giese, B.; Hartung, J.; Leising M. *J. Am. Chem. Soc.* **1985**, *107*, 4332. Korth, H.; Sustmann, R.; Dupuis, J.; Giese, B. *Chem. Ber.* **1987**, *120*, 1197.
- 20) Kornblum, N.; Widmer, J. *J. Am. Chem. Soc.* **1978**, *100*, 7086; the use of amalgamated aluminum to cleave disulfides was first described by Kipnis, F.; Levy, I.; Ornfelt, J. *ibid.* **1949**, *71*, 2270.
- 21) *Organic Synthesis*, Collective Volume V; Baumgarten, H.E., Ed.; Wiley: New York, 1973, p 297.
- 22) Cope, A.C. *et al.* *J. Am. Chem. Soc.* **1950**, *82*, 1750.

- 23) Kornblum, N. *XXXIIIrd International Congress of Pure and Applied Chemistry*, 4; Butterworths: London, 1971, p 100.
- 24) Kornblum, N.; Cheng, L. *J. Org. Chem.* **1977**, *42*, 2944.
- 25) Mai, J. *Ber.* **1902**, *35*, 163.
- 26) Kornblum, N.; Cooper, G.D.; Taylor, J.E. *J. Am. Chem. Soc.* **1950**, *72*, 3013.

## About the Author

Professor Nathan Kornblum was born in New York City in 1914. He attended New York University, receiving the B.S. in 1935 and the M.S. in 1937. In September of that year he moved to the University of Illinois where he worked under Professor Roger Adams on the stereochemistry of large ring compounds. In June 1940 he was awarded the Ph.D.

In 1940 he went to Oberlin College as an instructor, and then in 1942 he took up the tenure of a National Research Council Fellowship at Harvard where he was associated with Professor Paul D. Bartlett. He was appointed an assistant professor at Purdue University in 1943 and became a full professor in 1952. From September 1952 until the end of May 1953 he was a Fulbright Senior Scholar at University College, London, after which he went, as a Guggenheim Fellow, to the Swiss Federal Institute of Technology in Zurich for the rest of his sabbatical year. He returned to Zurich as a National Science Foundation Senior Post-Doctoral Fellow in 1964 and spent twelve months at the Swiss Federal Institute of Technology. In 1973 and 1974 he again returned to Zürich for a year as a visiting professor of organic chemistry at the Swiss Federal Institute of Technology. From April to July of 1978 Dr. Kornblum was a visiting professor at the University of Marseille. In 1979, and again in 1984, he was a visiting professor at the University of Kyoto. He was a visiting professor for six months in 1988 at the University of Munich, a stay made possible by a Senior U.S. Scientist Award from the Alexander von Humboldt Foundation.

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# Aldrichimica Acta

Volume 23, Number 4, 1990



*Long-Range Electron Transfer in Proteins*

*Understanding and Controlling Diastereofacial  
Selectivity in Carbon-Carbon Bond-Forming Reactions*

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# Aldrichimica Acta

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## About Our Cover:



Fig. 1

There is a preparatory drawing (Fig. 1) for this painting (oil on canvas, 21½ x 25 inches), which shows how the artist began by wanting to depict King Solomon's idol worship; note that on the very right of the drawing is the foot of an idol. However, in the painting, done in the 1660's, the King seems to be praying with great devotion. Perhaps the artist changed his mind and finally depicted Solomon praying in the Temple.

This is one of the few paintings of the Rembrandt school portraying King Solomon. It is surely significant that Rembrandt and his students concerned themselves far more with the agonies of King Saul and the vicissitudes of King David than with the successes of Solomon. In his handling of light, Eeckhout comes close to works of his teacher and friend. He contrasts the simple architectural forms of the Temple with the splendor of Solomon's clothing and jewelry, achieving that effect by the use of white dots of light, a technique used by Rembrandt in his works of the 1630's.

### *From Dura to Rembrandt - Studies in the History of Art*

A collection of nineteen papers, seventeen in English and two in German, by Rachel Wischnitzer (1885-1989) ranging from synagogue architecture to the iconography of works by Rembrandt, together with this remarkable woman's life story, written by Prof. Bezalel Narkiss, the director of the Center for Jewish Art at the Hebrew University. A wonderful gift for any good friend.

### *The Detective's Eye: Investigating the Old Masters*

Twenty-three paintings that have been reproduced on our *Acta* covers and five that have been on our catalog covers were among some seventy works in an exhibit at the Milwaukee Art Museum (January 19 - March 19, 1989) for which Isabel and Alfred Bader were guest curators.

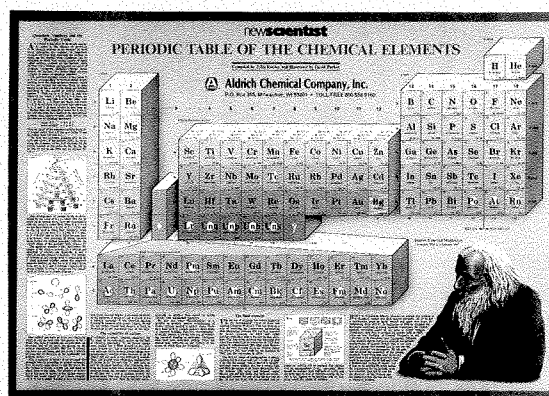
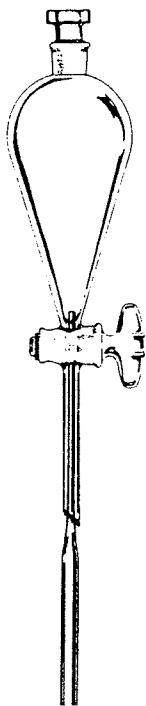
If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this fully illustrated catalog, and you will learn something about our chemist collector's interest in art and connoisseurship as well.

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# Lab Notes

No matter how careful laboratory technicians may be, once in a while ground glass stoppers jam in flask necks. This can be particularly annoying if it happens on a filled separatory funnel. We have solved this problem by passing a Pasteur pipette through the stopcock of the separatory funnel as shown in the figure. This allows air to come into the separatory funnel while the liquid comes out cleanly and without loss of material.

Ann Haestier  
Department of Chemistry  
Brandeis University  
Waltham, MA 02254-9110



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). For submitting your idea, you will receive, *at no cost*, a laminated periodic table poster (Z15,000-2 \$9.20, shown above). 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  
*Alfred Hassner*

Professor Alfred Hassner of Bar-Ilan University kindly suggested that we offer a polymeric quaternary ammonium azide reagent.<sup>1</sup> Alkyl, benzyl, and alpha-keto azides<sup>2</sup> are cleanly prepared from alkyl halides or sulfonates under mild conditions using this heterogenous reagent.

Naturally, we made it.

(1) Hassner, A.; Stern, M.; Gottlich, H.E. *J. Org. Chem.* **1990**, *55*, 2304. (2) Hassner, A.; Stern, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 478.

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

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# Long-Range Electron Transfer in Proteins

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Experiments in several laboratories over the last few years have established that electron transfer (ET) in modified proteins and protein-protein complexes can take place over long molecular distances ( $>10 \text{ \AA}$ ) at biologically significant rates.<sup>1-4</sup> The goal of our work in this field is elucidation of the factors that control the rates of these reactions.

## Ruthenated Proteins

The molecules we have employed are ones in which ruthenium amines are attached to surface histidines of structurally characterized redox proteins.<sup>5-7</sup> Surface modification of a protein is expected to be nonperturbative,<sup>8</sup> so it can be assumed that the structure of the modified protein is the same as that of the native protein. Hence, the distance and the intervening medium involved in electron transfer between the native and synthetic protein redox sites are known. Altering the site of attachment allows both the distance and the intervening medium for electron transfer to be varied. Changing the ligands in the ruthenium modification reagent also permits driving-force effects on the rate of the reaction to be studied.

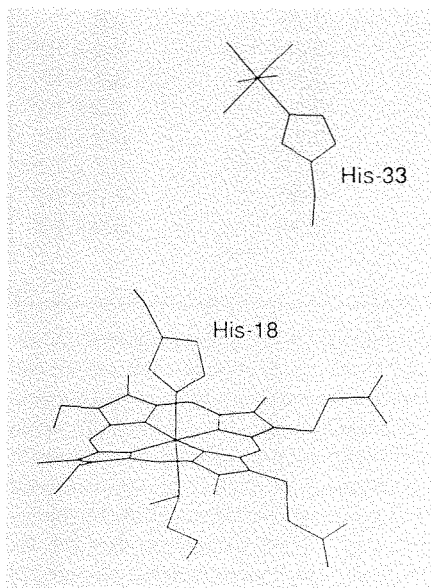


Fig. 1. Redox centers in  $\alpha$ -Ru(His33)cyt c. Edge-edge distances: His33 to His18, 11.7  $\text{\AA}$ ; His33 to the heme, 13.2  $\text{\AA}$ .

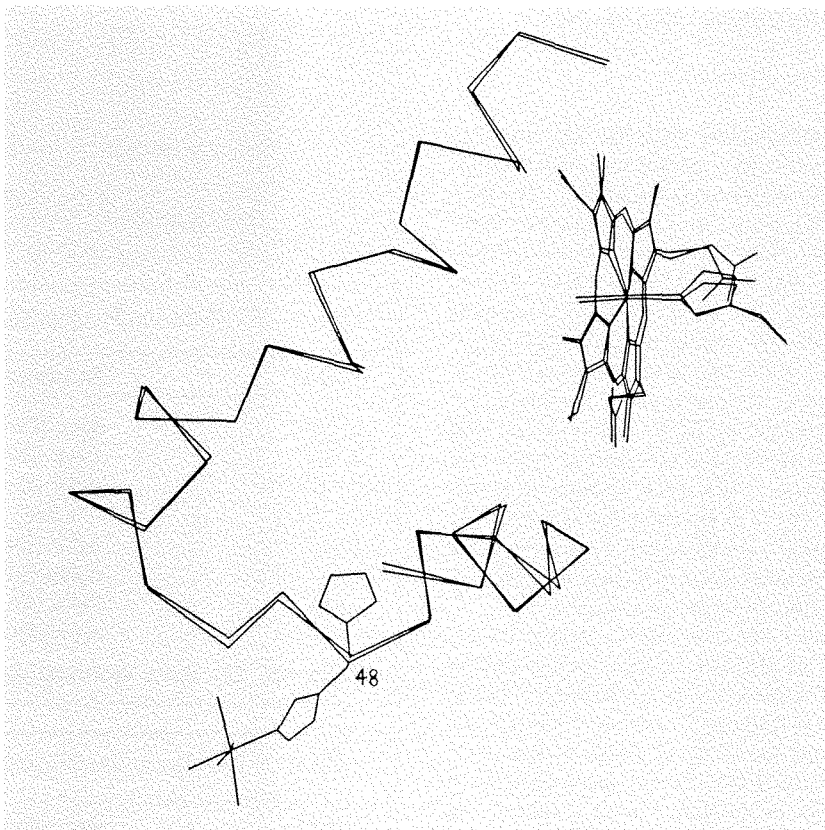


Fig. 2. Comparison of the structures of the His48 and heme regions of native and  $\alpha$ -Ru(His48)-modified myoglobin.



Professor Harry B. Gray (right) receiving the Alfred Bader Award in Bioinorganic or Bioorganic Chemistry from Dr. Alfred Bader.

Our modification procedure involves the reaction of aquopentaammine-ruthenium(II) ( $a_5Ru^{2+}$ ) with the imidazole of a surface histidine of a protein.<sup>6,7,9-13</sup> Importantly, the  $a_5Ru$ (histidine)-modified proteins are relatively robust in both the Ru(II) and Ru(III) oxidation states.<sup>14,15</sup> Modified proteins that have been studied extensively include  $a_5Ru$ (His33)cytochrome *c* (Fig. 1)<sup>6,9,15</sup> and  $a_5Ru$ (His48)myoglobin (Fig. 2).<sup>11,13</sup>

### Kinetics Methods

Flash photolysis and pulse radiolysis techniques have been employed to study electron transfer in ruthenated proteins.<sup>3,11</sup> The flash method used commonly to monitor  $Ru^{2+} \rightarrow Fe^{3+}$  and  $Ru^{2+} \rightarrow Cu^{2+}$  electron transfer is outlined in eq. 1-4 (illustrated for  $Ru^{2+} \rightarrow Fe^{3+}$  electron transfer). The electron transfer reaction is initiated by photogenerated  $Ru(bpy)_3^{2+*}$  ( $bpy = 2,2'$ -bipyridine), which rapidly reduces the surface ruthenium. The  $Ru(bpy)_3^{3+}$  is scavenged by EDTA before it can back react with the  $a_5Ru^{2+}$ (His) group. In the case of a heme (FeP), a fast increase in absorbance due to direct reduction of Fe(III)P by  $Ru(bpy)_3^{2+*}$  is followed by a slower increase in absorbance due to reduction of Fe(III)P by the Ru(II) on the protein surface.

Lieber has developed a method for the study of electron transfer from a protein metal center to a surface ruthenium.<sup>10</sup> In this method,  $Ru(bpy)_3^{2+*}$  acts as an oxidant, selectively removing an electron from a surface  $a_5Ru^{2+}$ (His). A Ni(II) macrocycle/alkyl bromide scavenger system oxidizes the  $Ru(bpy)_3^+$  before it can back react with  $a_5Ru^{3+}$ (His).

Electron transfer at high driving forces (values of  $-\Delta G^\circ$  in the  $\sim 1$  eV range) has been investigated in zinc-porphyrin (ZnP) derivatives of ruthenated cytochrome *c* and myoglobin.<sup>16,17</sup> Laser excitation generates the relatively long-lived excited triplet,  $^3ZnP^*$ , which is a powerful reducing agent. Both excited-state electron transfer ( $k_{ET}^*$ ) and thermal recombination ( $k_{ET}^b$ ) reactions can be monitored in favorable cases by transient absorption spectroscopy (eq. 5-7).

The rates of electron-transfer reactions in Ru(His33)cyt *c* (M) derivatives (M = Fe, Zn) range from  $3 \times 10^1$  to  $3.3 \times 10^6$  s<sup>-1</sup> (Table 1). The rates show a strong dependence on driving force ( $-\Delta G^\circ$ ), as predicted by Marcus.<sup>18</sup> Replacement of the heme in Ru(His48)Mb by several metalloporphyrins (MP: M = H<sub>2</sub>, Pd, Pt, Cd, Mg, Zn; P = mesoporphyrin IX diacid) yields Ru(His48)Mb(MP) species in which  $^3MP^* \rightarrow Ru^{3+}$  electron-transfer rates have been measured (Table 2). The electron-transfer rates again increase markedly as the driving force increases, following the same

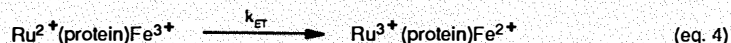
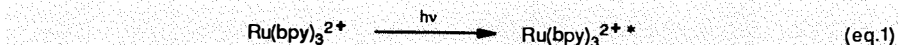


Table 1. ET Rates in Ru(His33)cyt *c* Derivatives<sup>a</sup>

Donor	Acceptor	$-\Delta G^\circ$ (eV)	$k_{ET}$ (s <sup>-1</sup> )
$a_5Ru^{2+}$	cyt <i>c</i> (Fe <sup>3+</sup> )	0.18	$3.0 \times 10^1$
$a_5Ru^{2+}$	cyt <i>c</i> (Zn <sup>+</sup> )	0.36	$2.4 \times 10^2$
$a_4(\text{isn})Ru^{2+}$	cyt <i>c</i> (Zn <sup>+</sup> )	0.66	$2.0 \times 10^5$
cyt <i>c</i> (Zn <sup>+</sup> )	$a_5Ru^{3+}$	0.70	$7.7 \times 10^5$
$a_4(\text{py})Ru^{2+}$	cyt <i>c</i> (Zn <sup>+</sup> )	0.74	$3.5 \times 10^5$
cyt <i>c</i> (Zn <sup>+</sup> )	$a_4(\text{py})Ru^{3+}$	0.97	$3.3 \times 10^6$
$a_5Ru^{2+}$	cyt <i>c</i> (Zn <sup>+</sup> )	1.01	$1.6 \times 10^6$
cyt <i>c</i> (Zn <sup>+</sup> )	$a_4(\text{isn})Ru^{3+}$	1.05	$1.9 \times 10^6$

<sup>a</sup> From ref. 17: isn = isonicotinamide; py = pyridine.

Table 2. ET Rates in Ru(His48)Mb Derivatives<sup>b</sup>

Donor	Acceptor	$-\Delta G^\circ$ (eV)	$k_{ET}$ (s <sup>-1</sup> )
FeP	$a_5Ru^{3+}$	0.02	0.04
FeP	$a_4(\text{py})Ru^{3+}$	0.28	2.5
H <sub>2</sub> P <sup>*</sup>	$a_5Ru^{3+}$	0.53	$7.6 \times 10^2$
PdP <sup>*</sup>	$a_5Ru^{3+}$	0.70	$9.1 \times 10^3$
PtP <sup>*</sup>	$a_5Ru^{3+}$	0.73	$1.2 \times 10^4$
CdP <sup>*</sup>	$a_5Ru^{3+}$	0.85	$6.3 \times 10^4$
MgP <sup>*</sup>	$a_5Ru^{3+}$	0.87	$5.7 \times 10^4$
ZnP <sup>*</sup>	$a_5Ru^{3+}$	0.88	$7.0 \times 10^4$
PdP <sup>*</sup>	$a_4(\text{py})Ru^{3+}$	0.96	$9.0 \times 10^4$

<sup>b</sup> From refs. 11 and 16.

pattern as observed for Ru(His33)cyt *c* (M) derivatives. In comparing data at the same driving force, however, it is clear that electron transfer in Ru(His48)Mb(MP) is not as facile as in the cytochrome *c* system.

### Reorganization Energies and Electronic Couplings

In semiclassical electron-transfer theory, three parameters govern the reaction rates: the electronic coupling between the donor and acceptor ( $\kappa_{ET}$ ); the free-energy change for

the reaction ( $\Delta G^\circ$ ); and a parameter ( $\lambda$ ) related to the extent of inner-shell and solvent nuclear reorganization accompanying the electron-transfer reaction.<sup>18</sup> Additionally, when intrinsic electron-transfer barriers are small, the dynamics of nuclear motion can limit electron-transfer rates through the frequency factor,  $\nu_N$ . These parameters describe the rate of electron transfer between a donor and acceptor held at a fixed distance and orientation (eq. 8), where  $R$  is the gas constant and  $T$  is the absolute temperature.

It is commonly assumed that for long-

$$k_{ET} = v_N \kappa_E \exp \left[ \frac{-(\Delta G + \lambda)^2}{4\lambda RT} \right] \quad (\text{eq. 8})$$

$$\kappa_E = \kappa_E^0 \exp[-\beta(d-d_0)] \quad (\text{eq. 9})$$

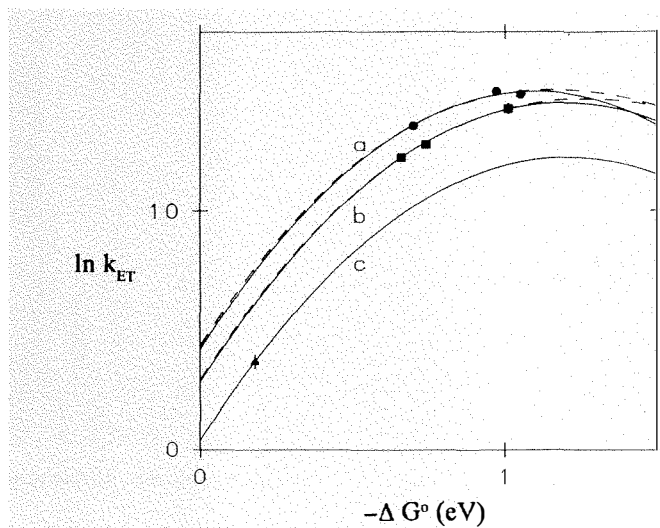


Fig. 3.  $\ln k_{ET}/\Delta G^\circ$  plots for Ru(His33)cyt c derivatives.

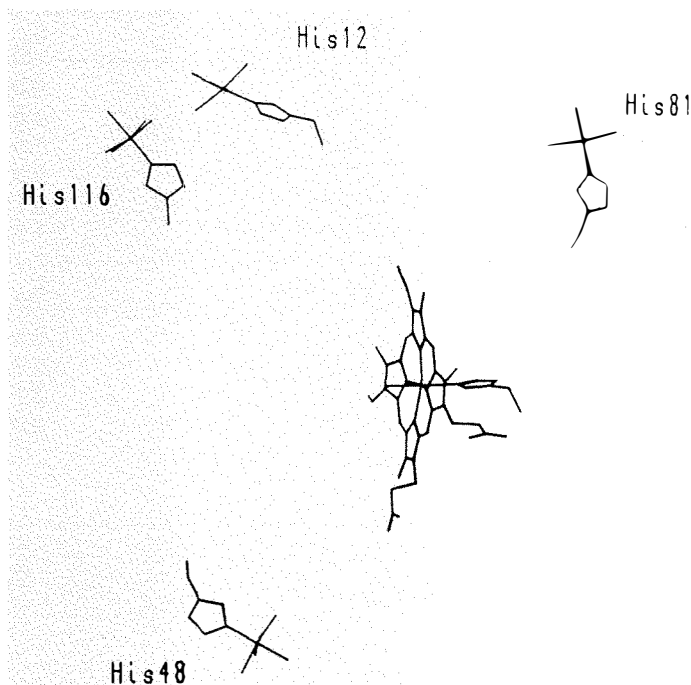


Fig. 4. Relative positions of four surface histidines and the heme in ruthenated myoglobin.

Table 3. ET Distances and Rates for  $a_5$ Ru(HisX)Mb(ZnP) Derivatives

X	Distance ( $\text{\AA}$ ) <sup>c</sup>	$k_{ET}$ ( $\text{s}^{-1}$ ) <sup>d</sup>
48	11.8 - 16.6 (12.7)	$7.2 \times 10^4$
81	18.8 - 19.3 (19.3)	$1.5 \times 10^2$
116	19.8 - 20.4 (20.1)	$3.0 \times 10^1$
12	21.5 - 22.3 (22.0)	$1.4 \times 10^2$

<sup>c</sup> Edge-edge distances (d) from ref. 11; estimated d(eq) values in parentheses.

<sup>d</sup>  ${}^3\text{ZnP}^* \rightarrow \text{Ru}^{3+}$  rates from refs. 16 and 21.

range electron transfer the electronic factor ( $\kappa_E$ ) will decrease exponentially with the donor-acceptor edge-edge distance, d (eq. 9).<sup>18</sup> The closest contact distance,  $d_0$ , is normally taken to be 3  $\text{\AA}$  (van der Waals contact of the edges of the donor and acceptor). The value of  $\beta$  is a measure of the effectiveness of the intervening medium in coupling the donor and acceptor (eq. 9).

Analysis of electron-transfer rate data for  $a_5$ Ru(His48)Mb(MP) derivatives gives  $\lambda \sim 1.4$  eV.<sup>1</sup> The maximum electron-transfer rate,  $v_N \kappa_E \sim 3.5 \times 10^5 \text{ s}^{-1}$ , is proportional to the square of the matrix element,  $H_{AB}$ , that describes the electronic coupling between  $a_5$ Ru(His48) and the metalloporphyrin. In the nonadiabatic limit ( $H_{AB} \ll k_B T$ ), the proportionality constant is  $(\pi/\hbar^2 2\lambda RT)^{1/2}$ ,<sup>18</sup> which gives an  $H_{AB}$  of roughly 0.05  $\text{cm}^{-1}$  for the  $a_5$ Ru(His48)Mb(MP) system.

In an analysis of Ru(His33)cyt c, plots of  $\ln k_{ET}$  vs.  $-\Delta G^\circ$  for (a)  ${}^3\text{ZnP}^* \rightarrow \text{Ru}^{3+}$ , (b)  $\text{Ru}^{2+} \rightarrow \text{ZnP}^+$ , and (c)  $\text{Ru}^{2+} \rightarrow \text{Fe}^{3+}$  reactions were fit separately to eq. 8 (Fig. 3).<sup>17</sup> The values of  $\lambda$  range from 1.15 to 1.25 eV, which are slightly smaller than the  $\lambda$  for myoglobin.  $H_{AB}$  values are  $\sim 0.03$  (FeP) and  $\sim 0.12$   $\text{cm}^{-1}$  (ZnP) for the electron-transfer reactions. It is interesting that the ZnP:Ru(His) electronic coupling is better for His33-modified cytochrome c than for His48-modified myoglobin.

#### Experiments at Different Fixed Distances

The distance dependence of electron-transfer rates in proteins has been studied in ruthenated sperm whale myoglobin, where there are four surface histidines at different edge-edge distances, d, from the metal porphyrin (Fig. 4).<sup>16,19,21</sup> Analysis of the rates of photoinduced electron transfer in derivatives in which the iron porphyrin is replaced by zinc mesoporphyrin IX diacid (ZnP) (Table 3) gives  $\beta$  values in the 0.8-1.0  $\text{\AA}^{-1}$  range. It is of interest that the rates of related electron-transfer reactions in  $a_5$ Ru(His33)cytochrome c<sup>17</sup> and Zn,Fe-hybrid hemoglobin<sup>22</sup> fall near the lines in Fig. 5. It also has been found that the  $\text{Ru}(\text{bpy})_3^{2+} \rightarrow \text{Fe}^{3+}$  and  $\text{Fe}^{2+} \rightarrow \text{Ru}(\text{bpy})_3^{3+}$  electron-transfer rates in  $\text{Ru}(\text{bpy})_3$ (lysine) derivatives of horse heart cytochrome c scale roughly with edge-edge distance.<sup>23</sup>

One notable observation is that  ${}^3\text{ZnP}^* \rightarrow a_5\text{Ru}(\text{His}12)^{3+}$  electron transfer is faster than expected based on edge-edge distance. Since Trp14 lies directly between His12 and the porphyrin, it may play a role in enhancing the electron-transfer rate.<sup>16,19,20</sup> One possibility is that  $\beta$  is approximately 0.1  $\text{\AA}^{-1}$  less for  $a_5$ Ru(His12)Mb than for the other myoglobin derivatives.<sup>16</sup> However,

the rate of electron transfer from  $a_5\text{Ru}(\text{His62})^{2+}$  to  $\text{Fe}^{3+}$  in a yeast iso-1-cytochrome *c* mutant (produced by site-directed mutagenesis) apparently is not enhanced even though polarizable Trp59 and Met64 side chains reside in the intervening medium.<sup>24</sup>

Several unusually slow electron-transfer rates at short edge-edge separation distances have been reported for ruthenium-modified proteins.<sup>14,25-28</sup> The most striking examples have come from experiments involving plastocyanins modified with  $a_3\text{Ru}^{3+}$  at His59.<sup>27,28</sup> The electron-transfer rates in these proteins ( $k_{\text{ET}} < 0.3\text{s}^{-1}$ ) are much lower than would be expected for edge-edge distances in the 10-12 Å range. The inner-sphere reorganization energy for blue copper proteins should be small, since the geometry at the copper site is intermediate between Cu(I) and Cu(II).<sup>29</sup> The outer-sphere reorganization energy is expected to be small as well, since the Cu site is buried (and no solvent molecules are proximal to the metal). In addition, the ruthenium-labeled histidine is thought to be similar in structure to that of the modified histidines in other proteins. Thus, it is likely that the slow rates are attributable to very poor Cu-Ru electronic coupling, although it will require additional experimental and theoretical work to settle the matter.

In recent work, the kinetics of long-range electron transfer have been measured in  $a_4\text{LRu}(\text{His39})$  derivatives (L =  $\text{NH}_3$ , pyridine, isonicotinamide) of Zn-substituted *Candida krusei* cytochrome *c*<sup>30</sup> and  $a_4\text{LRu}(\text{His62})$  derivatives (L =  $\text{NH}_3$ , pyridine) of Zn-substituted *Saccharomyces cerevisiae* cytochrome *c*.<sup>31</sup> Electron-transfer rates are set out in Table 4. The rates of both excited-state electron transfer ( ${}^3\text{ZnP}^* \rightarrow \text{Ru}^{3+}$ ) and thermal recombination ( $\text{Ru}^{2+} \rightarrow \text{ZnP}^+$ ) are approximately three times greater in Ru(His39)cyt *c* than the rates of the corresponding reactions in Ru(His33)cyt *c*, but analogous electron-transfer reactions in Ru(His62)cyt *c* are roughly two orders of magnitude slower than in the His33-modified protein.

Plots of the Ru(HisX)cyt *c* (X = 33, 39, 62) data are shown in Fig. 6. Although the reorganization parameter  $\lambda$  is nearly the same for the electron-transfer reactions in the three proteins (~1.2 eV), the  $H_{\text{AB}}$  value for Ru(His39)cyt *c* (0.21  $\text{cm}^{-1}$ ) is almost twice as large as that for Ru(His33)cyt *c* (0.12  $\text{cm}^{-1}$ ) and over twenty times larger than  $H_{\text{AB}}$  for Ru(His62)cyt *c* (0.01  $\text{cm}^{-1}$ ). Since virtually the same donor and acceptor electronic states are found in the three proteins, the differences in  $H_{\text{AB}}$  must arise from the manner in which the intervening atoms couple the two states. If a homogeneous medium of constant tunneling-barrier height separated the

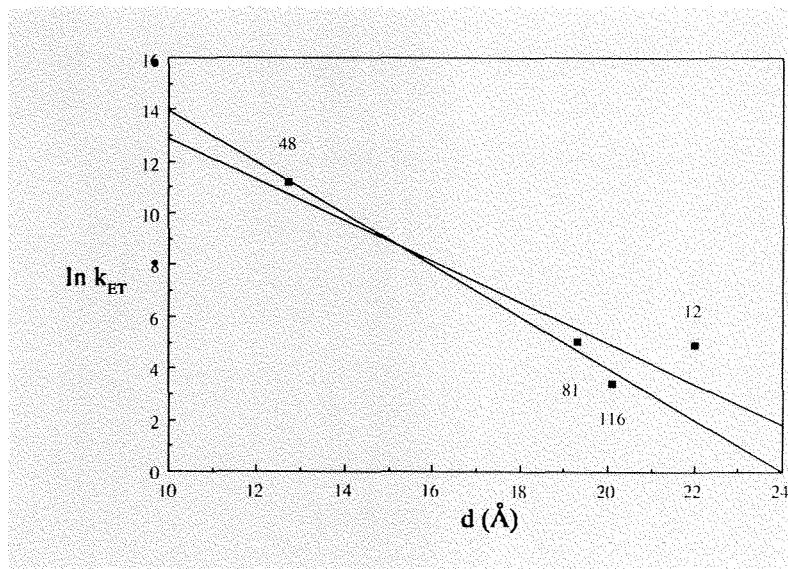


Fig. 5.  $\ln k_{\text{ET}}$  vs. distance for  ${}^3\text{ZnP}^* \rightarrow a_5\text{Ru}^{3+}$  ET reactions in ruthenated myoglobin. All four points give  $\beta = 0.79 \text{Å}^{-1}$ ; exclusion of His12 gives  $\beta = 1.0 \text{Å}^{-1}$ .

Table 4. ET in Ru(His39) and Ru(His62) Cytochromes *c*

Ru(His39)cyt <i>c</i> <sup>e</sup>	$-\Delta G^\circ$ (eV)	$k_{\text{ET}}$ ( $\text{s}^{-1}$ )
$a_4(\text{isn})\text{Ru}^{2+} \rightarrow \text{ZnP}^+$	0.66	$6.5 \times 10^5$
${}^3\text{ZnP}^* \rightarrow a_5\text{Ru}^{3+}$	0.70	$1.5 \times 10^6$
$a_4(\text{py})\text{Ru}^{2+} \rightarrow \text{ZnP}^+$	0.74	$1.5 \times 10^6$
${}^3\text{ZnP}^* \rightarrow a_4(\text{py})\text{Ru}^{3+}$	0.97	$8.9 \times 10^6$
$a_5\text{Ru}^{2+} \rightarrow \text{ZnP}^+$	1.01	$5.7 \times 10^6$
${}^3\text{ZnP}^* \rightarrow a_4(\text{isn})\text{Ru}^{3+}$	1.05	$1.0 \times 10^7$
Ru(His62)cyt <i>c</i> <sup>f</sup>	$-\Delta G^\circ$ (eV)	$k_{\text{ET}}$ ( $\text{s}^{-1}$ )
${}^3\text{ZnP}^* \rightarrow a_5\text{Ru}^{3+}$	0.70	$6.5 \times 10^3$
$a_4(\text{py})\text{Ru}^{2+} \rightarrow \text{ZnP}^+$	0.74	$2.6 \times 10^3$
${}^3\text{ZnP}^* \rightarrow a_4(\text{py})\text{Ru}^{3+}$	0.97	$2.7 \times 10^4$
$a_5\text{Ru}^{2+} \rightarrow \text{ZnP}^+$	1.01	$2.0 \times 10^4$

<sup>e</sup> From ref. 30.  
<sup>f</sup> From ref. 31.

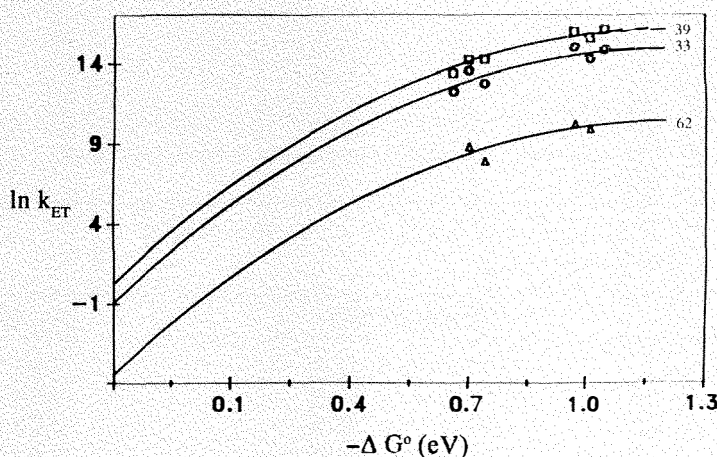


Fig. 6. Plots of  $\ln k_{\text{ET}}$  vs.  $-\Delta G^\circ$  for Ru(HisX)cytochrome *c* ET reactions: boxes (X=39); circles (X=33); triangles (X=62).

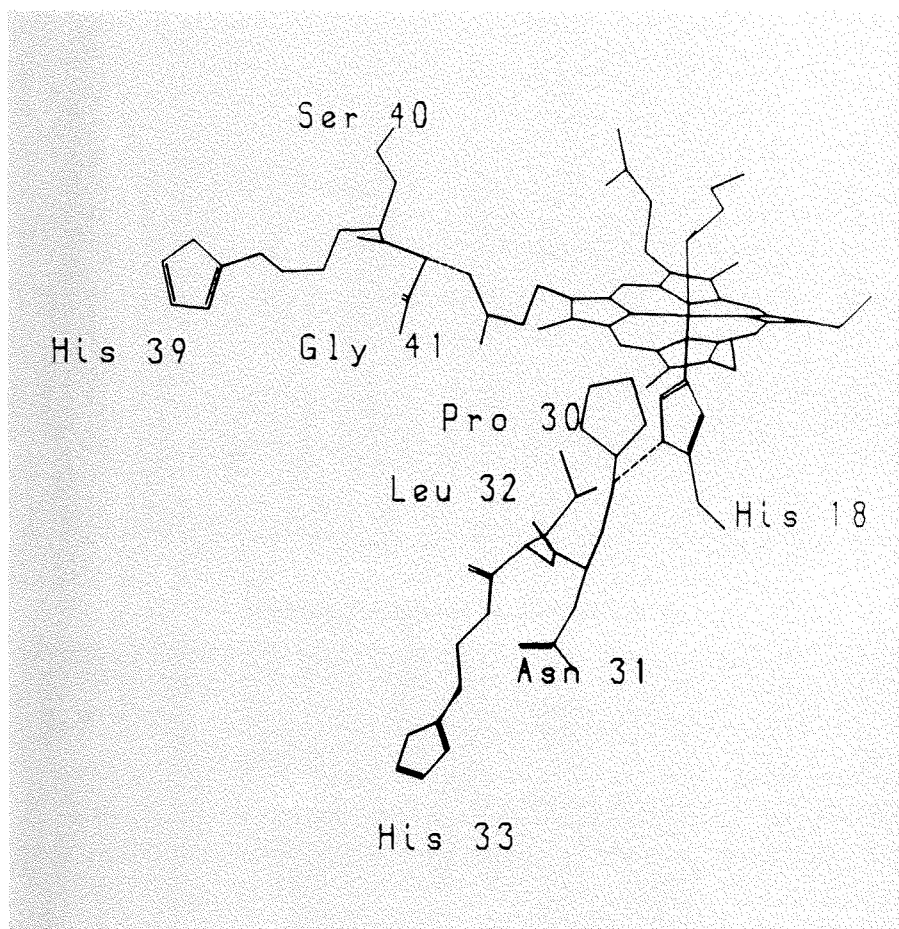


Fig. 7. ET pathways from His33 and His39 ( $d=13.0 \text{ \AA}$ ) to the heme in cytochrome *c*.

$$\epsilon_B = \text{const} \times \exp[-\beta_0(R-R_{eq}^B)] \quad (\text{eq. 10})$$

$$\epsilon_H = \sigma_H \bar{\epsilon}_B^2 \exp[-\beta_2(R-R_{eq}^H)] \quad (\text{eq. 11})$$

$$\epsilon_S = \sigma_S \bar{\epsilon}_B \exp[-\beta_1(R-R_{eq}^S)] \quad (\text{eq. 12})$$

donor and the acceptor in the three systems, then  $H_{AB}$  would depend primarily on the edge-edge distance and would be nearly the same for Ru(His33)cyt *c* and Ru(His39)cyt *c* and decrease only slightly for Ru(His62)cyt *c* relative to Ru(His39)cyt *c*.<sup>30,31</sup> Clearly, this prediction is not borne out by experiment. The evidence suggests that the chemical nature of the polypeptide medium separating the Ru-ammine and metalloporphyrin sites is responsible for the differential electronic coupling in these Ru-Zn-cyt *c* derivatives. We will return to this matter shortly.

It has been shown in studies of Os- and Ru-ammines bridged by polyproline spacers that the distance dependence of  $\lambda$  can be greater than that of  $H_{AB}$ .<sup>32</sup> Dielectric continuum models of solvent reorganization predict that  $\lambda_0$  will increase with donor-acceptor separation. Models that describe charge

transfer within low-dielectric spheres or ellipsoids embedded in dielectric continua exhibit a dependence upon electron-transfer distance as well as upon the positions of the redox sites inside the sphere or ellipsoid.<sup>33</sup> Modeling the Ru-Zn-cyt *c* systems as single spheres suggests, however, that variations in  $\lambda_0$  for the Ru(His33)cyt *c*, Ru(His39)cyt *c*, and Ru(His62)cyt *c* electron-transfer reactions will not be significant (0.57, 0.60, and 0.63 eV, respectively).<sup>31</sup>

Winkler has examined the maximum variation in  $\lambda_0$  predicted by the single-sphere continuum model.<sup>31,34</sup> The cyt *c* molecule can be taken as a 34 Å radius sphere with its metal center 5.8 Å from the origin. The Ru-ammine complex is taken as a 6 Å sphere centered on the Ru atom that is assumed to be fixed 16 Å from the center of the cyt *c* sphere. The small sphere can occupy any position on the large sphere with values of the electron-transfer distance varying from 10.2 to 21.8 Å. A third sphere then encloses the two other spheres and  $\lambda_0$  for electron transfer between the two metals is calculated by treating the solvent as a dielectric continuum. The magnitude of  $\lambda_0$  varies from 0.38 to 0.63 eV almost linearly as the electron-transfer distance increases from 10.2 to 21.8

Å. The total variation of 0.25 eV is only slightly larger than the uncertainty range in the estimates of  $\lambda$  ( $\pm 0.1 \text{ eV}$ ). The invariance of  $\lambda$  found for the electron-transfer reactions of the three modified cytochromes is, therefore, consistent with theoretical considerations.

### Electron-Tunneling Pathways

In covalently-coupled donor (spacer) acceptor molecules, the evidence now available suggests that electron-transfer rates depend upon the number of covalent bonds separating the donor and the acceptor, rather than upon their direct separation distance.<sup>35-40</sup> Several investigators have begun to examine potential electron-tunneling pathways in proteins.<sup>41-47</sup> Interestingly, the through-peptide routes generally involve so many bonds that they cannot possibly account for the observed rates.<sup>16,17</sup> Beratan and Onuchic have developed a simple model to describe the contribution of the polypeptide bridge to the donor-acceptor electronic coupling in protein systems.<sup>41</sup> The essence of the model is that  $H_{AB}$  decreases from its maximal value (at van der Waals contact of donor and acceptor) by a constant factor for each covalent bond in the electron-transfer pathway ( $\epsilon_B = 0.6$ ). Ionic contacts (H-bonds and salt bridges) and through-space jumps decrease  $H_{AB}$  by somewhat larger factors ( $\epsilon_H$  is the H-bond coupling;  $\epsilon_S$  is the through-space coupling). The decay factors are described in eq. 10-12. The  $\beta$ 's specify the distance dependence of the interactions, and the  $\sigma$ 's give their orientation dependences. A computer program has been written employing these interactions to search for electron-tunneling pathways through proteins.<sup>46</sup> In its simplest version, the parameters are as follows:  $\epsilon_B = \bar{\epsilon}_B$ ,  $\sigma_H = 1.0$ ,  $\sigma_S = 1.0$ ,  $\beta_0 = \beta_1 = \beta_2 = 1.7 \text{ \AA}^{-1}$ , and  $\text{const} = 0.6$ .

Calculated electron-transfer pathways in Ru(His33)cyt *c* and Ru(His39)cyt *c* are shown in Fig. 7. The best pathway from His33 to the metalloporphyrin is a 15-bond route to the metal atom through His18 that includes a 1.85 Å hydrogen bond between the Pro30 carboxyloxygen and the proton on the His18 nitrogen. The shortest pathway from His39 is a 12-bond route that includes a 2.4 Å H-bond between the  $\alpha$ -amino hydrogen atom of Gly41 and the carboxyl oxygen of a propionate side chain on the porphyrin. The key difference between these two pathways is the number of covalent bonds; the His39 pathway is built from 11 covalent bonds and 1 H-bond, while the His33 pathway has 15 covalent bonds and 1 H-bond. Hence, the experimental observation that the electronic coupling is stronger in the His39 derivative

than in the His33-modified protein (even though the edge-edge distances in the two modified proteins are roughly the same) is consistent with the Beratan-Onuchic pathway analysis.

Two tunneling pathways for Ru(His62)cyt *c* that emerge from the analysis are shown in Fig. 8. One is a 17-bond route with 14 covalent bonds and 3 H-bonds (the third of which connects the Trp59 nitrogen atom to the carbonyl oxygen of a heme propionate side chain); the other is a 13-bond route with 12 covalent bonds and a through-space interaction between the sulfur atom of Met64 and the heme edge. The sharply lower electronic coupling in the His62 protein, relative to both the His33 and His39 systems, indicates that the Met64-heme through-space interaction is a poor shortcut in the His62-Met64 electron-transfer pathway. As pathway analyses are made on other structurally engineered proteins, it will be interesting to see if examples can be found in which through-space contacts are much better shortcuts. It is possible that the nature of the interacting groups and their relative orientation will greatly influence the strength of coupling.

There has been a good deal of interest in the donor-acceptor electronic couplings that have been extracted for the four ruthenated myoglobins. Employing molecular orbital methods, three groups independently have obtained theoretical results in good agreement with the experimentally derived values.<sup>43-45</sup> All three calculations show that the electron-transfer rate constant decreases with distance roughly as predicted by eq. 9, with  $\beta$  values from theory ( $\sim 0.8 \text{ \AA}^{-1}$ ) in accord with experiment. The rate/distance scaling apparently is much more predictable for myoglobin than for cytochrome *c*, owing to a lack of dominant pathways in the former case. Indeed, there are many more pathways (with comparable couplings) for myoglobin [ $\sim 200$  for Ru(His48)Mb] than for any protein studied to date.<sup>46</sup>

Many of the Ru(His48)Mb electron-transfer pathways feature a through-space jump between Phe43 and the heme (Fig. 9). This raises the question of enhanced electronic coupling attributable to phenyl-porphyrin interactions, a coupling that in a  $\pi$ - $\pi$  superexchange model might be stronger in the  $\text{Ru}^{2+} \rightarrow \text{ZnP}^+$  direction than for  ${}^3\text{ZnP}^+ \rightarrow \text{Ru}^{3+}$  electron transfer. Analysis of extensive kinetics experiments on Ru(His48)Mb(ZnP) derivatives shows that the electronic coupling is not significantly different for the two processes, thereby adding to the results that point to  $\sigma$ -hole tunneling as the dominant mechanism for long-range interactions.<sup>48</sup>

Finally, we look once again at Ru(His12)Mb, where there is both theoreti-

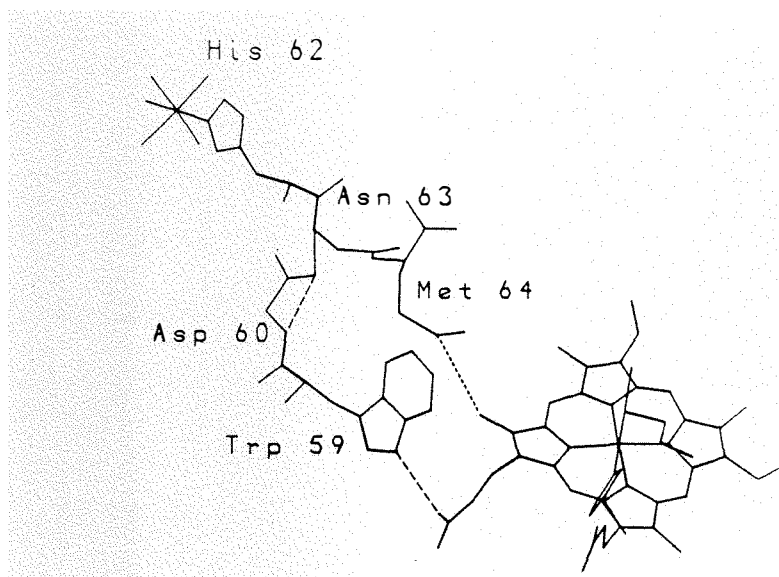


Fig. 8. ET pathways for Ru(His62)cyt *c* ( $d=15.6 \text{ \AA}$ ).

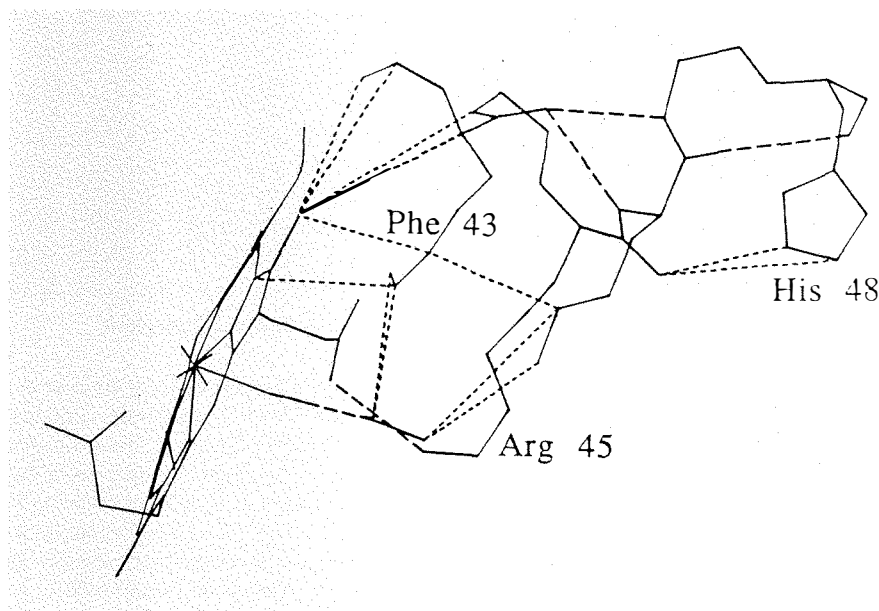


Fig. 9. ET pathways for Ru(His48)Mb.

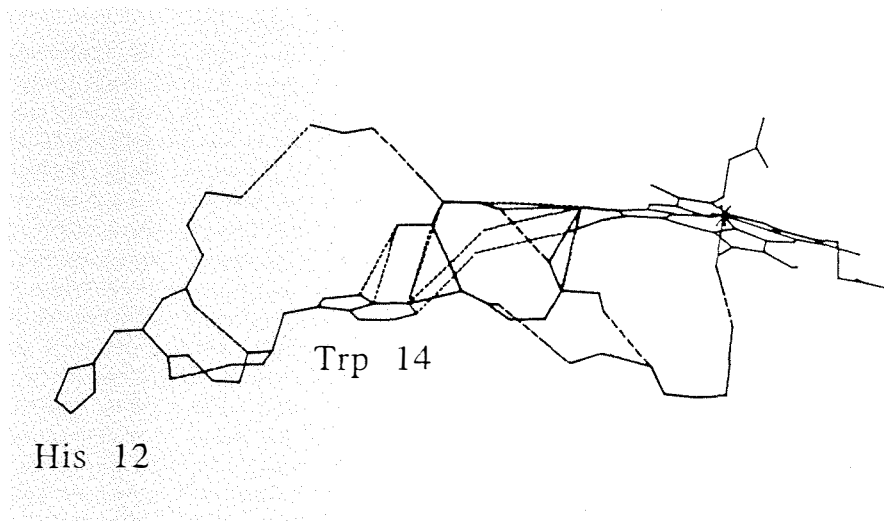


Fig. 10. ET pathways for Ru(His12)Mb.



cal<sup>43,45</sup> and experimental<sup>19,20</sup> evidence for electron-transfer rate enhancement by an intervening aromatic group. In the His12-modified protein, the important pathways involve residues in two  $\alpha$ -helices linked through space by Trp14 or Leu76(Fig. 10).<sup>46</sup> In the  $\sigma$ -hole tunneling model, the calculated  $H_{AB}$  for His12-heme interactions falls well below the experimentally estimated value, thereby hinting at a special role for Trp14 in the through-space connections.<sup>46</sup> Experiments aimed at evaluating donor-acceptor couplings in myoglobin mutants in which Trp14 is replaced by other amino acids could help resolve this matter. Indeed, there is much left to be done before we can claim to have a good understanding of the ways in which the intervening medium manipulates the rates of long-range electron transfer through proteins.

### Acknowledgments

I am greatly indebted to the dedicated graduate students, postdoctoral fellows and visiting associates in my group. The names of many of my co-workers appear in the references. I especially thank Jay Winkler, David Beratan, Jose Onuchic, Rudy Marcus, Bo Malmström, Mike Therien, Adrienne Raphael, Bruce Bowler, Jeff Chang, Brad Jacobs, Debbie Wuttke, John Brewer and Ramy Farid for helpful discussions in connection with the Bader Award Lecture. Our work on metalloprotein electron transfer has been supported by the National Science Foundation and the National Institutes of Health. This is contribution no. 8200 from the Chemistry Department of the California Institute of Technology.

### References:

- Gray, H.B.; Malmström, B.G. *Biochemistry* **1989**, *28*, 7499.
- McLendon, G. *Acc. Chem. Res.* **1988**, *21*, 160.
- Bowler, B.E.; Raphael, A.L.; Gray, H.B. *Prog. Inorg. Chem.*, in press.
- McGourty, J.L.; Peterson-Kennedy, S.E.; Ruo, W.Y.; Hoffman, B.M. *Biochemistry* **1987**, *26*, 8302.
- Mayo, S.L.; Ellis, W.R., Jr.; Crutchley, R.J.; Gray, H.B. *Science* **1986**, *233*, 948.
- Yocom, K.M.; Shelton, J.B.; Schroeder, W.A.; Worosila, G.; Isied, S.S.; Bordignon, E.; Gray, H.B. *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 7052.
- Gray, H.B. *Chem. Soc. Rev.* **1986**, *15*, 17.
- Baldwin, R.L.; Eisenberg, D. *Protein Engineering*; Oxender, D.L.; Fox, C.F., Eds.; Alan R. Liss: New York, 1987; pp 127-148.
- Therien, M.J.; Chang, I.-J.; Raphael, A.L.; Bowler, B.E.; Gray, H.B. *Structure and Bonding*, in press.
- Lieber, C.M.; Karas, J.L.; Gray, H.B. *J. Am. Chem. Soc.* **1987**, *109*, 3778.
- Lieber, C.M.; Karas, J.L.; Mayo, S.L.; Albin, M.; Gray, H.B. *Proceedings of the Robert A. Welch Conference on Chemical Research. Design of Enzymes and Enzyme Models*, Robert A. Welch Foundation, Houston, TX, Nov. 2-4, 1987; pp 9-33.
- Margalit, R.; Kostic, N.M.; Che, C.-M.; Blair, D.F.; Chiang, H.-J.; Pecht, I.; Shelton, J.B.; Shelton, J.R.; Schroeder, W.A.; Gray, H.B. *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 6554.
- Crutchley, R.J.; Ellis, W.R., Jr.; Gray, H.B. *Frontiers in Bioinorganic Chemistry*; Xavier, A.V., Ed.; VCH: Weinheim, FRG, 1986; pp 679-693.
- Osvath, P.; Salmon, G.A.; Sykes, A.G. *J. Am. Chem. Soc.* **1988**, *110*, 7114.
- Yocom, K.M.; Winkler, J.R.; Nocera, D.G.; Bordignon, E.; Gray, H.B. *Chemica Scripta* **1983**, *21*, 29.
- Cowan, J.A.; Upmacis, R.K.; Beratan, D.N.; Onuchic, J.N.; Gray, H.B. *Ann. New York Acad. Sci.* **1988**, *550*, 68.
- Meade, T.J.; Gray, H.B.; Winkler, J.R. *J. Am. Chem. Soc.* **1989**, *111*, 4353.
- Marcus, R.A.; Sutin, N. *Biochim. Biophys. Acta* **1985**, *811*, 265.
- Axup, A.W.; Albin, M.; Mayo, S.L.; Crutchley, R.J.; Gray, H.B. *J. Am. Chem. Soc.* **1988**, *110*, 435.
- Cowan, J.A.; Gray, H.B. *Chemica Scripta* **1988**, *28A*, 21.
- Upmacis, R.K.; Gray, H.B., unpublished results.
- Peterson-Kennedy, S.E.; McGourty, J.L.; Kalweit, J.A.; Hoffman, B.M. *J. Am. Chem. Soc.* **1986**, *108*, 1739.
- Durham, B.; Pan, L.P.; Long, J.E.; Millett, F. *Biochemistry* **1989**, *28*, 8659.
- Bowler, B.E.; Meade, T.J.; Mayo, S.L.; Richards, J.H.; Gray, H.B. *J. Am. Chem. Soc.* **1989**, *111*, 8757.
- Jackman, M.P.; Lim, M.-C.; Salmon, G.A.; Sykes, A.G. *J. Chem. Soc., Chem. Commun.* **1988**, 179.
- Idem. J. Chem. Soc., Dalton Trans.* **1988**, 2843.
- Jackman, M.P.; McGinnis, J.; Powls, R.; Salmon, G.A.; Sykes, A.G. *J. Am. Chem. Soc.* **1988**, *110*, 5880.
- Jackman, M.P.; Sykes, A.G.; Salmon, G.A. *J. Chem. Soc., Chem. Commun.* **1987**, 65.
- Gray, H.B.; Malmström, B.G. *Comments Inorg. Chem.* **1983**, *2*, 203.
- Therien, M.J.; Selman, M.A.; Gray, H.B.; Chang, I.-J.; Winkler, J.R. *J. Am. Chem. Soc.* **1990**, *112*, 2420.
- Therien, M.J.; Bowler, B.E.; Selman, M.A.; Gray, H.B.; Chang, I.-J.; Winkler, J.R. *ACS Symp. Ser.*, in press.
- Isied, S.S.; Vassilian, A.; Wishart, J.W.; Creutz, C.; Schwarz, H.; Sutin, N. *J. Am. Chem. Soc.* **1988**, *111*, 635.
- Brunschwig, B.S.; Ehrenson, S.; Sutin, N. *J. Phys. Chem.* **1986**, *90*, 3657.
- Winkler, J.R., unpublished results.
- Closs, G.L.; Calcaterra, L.T.; Green, N.J.; Penfield, K.W.; Miller, J.R. *J. Phys. Chem.* **1986**, *90*, 3673.
- Schmidt, J.A.; McIntosh, A.R.; Weedon, A.C.; Bolton, J.R.; Connolly, J.S.; Hurley, J.K.; Wasielewski, M.R. *J. Am. Chem. Soc.* **1988**, *110*, 1733.
- Heitele, H.; Michel-Beyerle, M.E.; Finckh, P. *Chem. Phys. Lett.* **1987**, *134*, 273.
- Balaji, V.; Ng, L.; Jordan, K.D.; Paddon-Row, M.N.; Patney, H.K. *J. Am. Chem. Soc.* **1987**, *109*, 6957.
- Oliver, A.M.; Craig, D.C.; Paddon-Row, M.N.; Kroon, J.; Verhoeven, J.W. *Chem. Phys. Lett.* **1988**, *150*, 366.
- Oevering, H.; Paddon-Row, M.N.; Heppener, M.; Oliver, A.M.; Cotsaris, E.; Verhoeven, J.W.; Hush, N.S. *J. Am. Chem. Soc.* **1987**, *109*, 3258.
- Beratan, D.N.; Onuchic, J.N. *Photosynthesis Research* **1989**, *22*, 173.
- Kuki, A.; Wolynes, P.G. *Science* **1987**, *236*, 1647.
- Broo, A.; Larsson, S. *Int. J. Quant. Chem.: Quant. Biol. Symp.* **1989**, *16*, 185.
- Siddarth, P.; Marcus, R.A. *J. Phys. Chem.* **1990**, *94*, 2985.
- Goldman, C., unpublished results.
- Beratan, D.N.; Onuchic, J.N.; Betts, J.N.; Bowler, B.E.; Gray, H.B. *J. Am. Chem. Soc.* **1990**, *112*, 7915.
- Christensen, H.E.M.; Conrad, L.S.; Mikkelsen, K.V.; Nielsen, M.K.; Ulstrup, J. *Inorg. Chem.* **1990**, *29*, 2808.
- Karas, J.L.; Winkler, J.R., unpublished results.

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Professor Harry Gray is Director of the Beckman Institute and Arnold O. Beckman Professor of Chemistry at the California Institute of Technology. Professor Gray began his research in inorganic chemistry at Northwestern University, where he earned his Ph.D. in 1960. After completing a postdoctoral year at the University of Copenhagen, he went to Columbia University, where he became a full professor in 1965. He joined the faculty at Caltech in 1966. In 1971, he was elected to the National Academy of Sciences, and he has served both on the NAS Council and the Governing Board of the National Research Council. For his work in bioinorganic chemistry and inorganic photochemistry, he has received the Alfred Bader Award in Bioorganic or Bioinorganic Chemistry and the National Medal of Science. In 1991, he will receive the Priestley Medal of the American Chemical Society.



# Understanding and Controlling Diastereofacial Selectivity in Carbon-Carbon Bond-Forming Reactions

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“Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations...”<sup>1</sup>

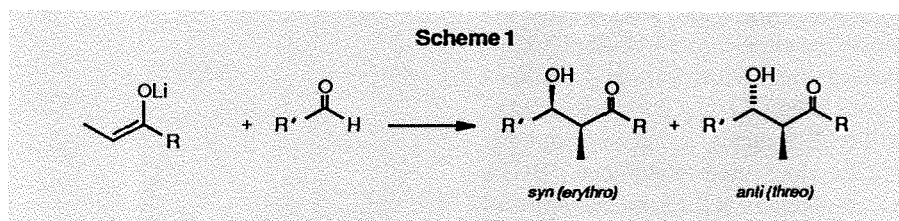
The last two decades have witnessed a renaissance in the aldol reaction, one of the most venerable of organic reactions. This torrent of research activity was made possible by two main developments: the discovery of methods for the formation and use of preformed enolates, particularly those of lithium; and the advent of powerful analytical methods that are well suited for the analysis of diastereomeric mixtures, especially <sup>13</sup>C NMR spectrometry. The principal factor that was responsible for the rebirth of the aldol reaction as a modern method of synthesis was probably the discovery that its stereochemistry can be controlled quite effectively through the use of preformed enolates.<sup>2</sup> In this article, I highlight the research on stereoselective C-C bond constructions that has been carried out since 1976 by my research group at Berkeley. This research had its origin in an investigation of simple stereoselection (*syn/anti* stereoselection) in the reactions of preformed lithium enolates with aldehydes. From this topic, we moved to a study of diastereofacial selectivity in the aldol reactions of chiral enolates and chiral aldehydes. In recent years, we have extended these investigations to include reactions of electrophiles analogous to aldehydes (oxonium ions, thionium ions, immonium ions). This article provides a broad overview of these studies. Although I focus on work carried out in my research group at Berkeley, there is no intention to slight the important contributions from many other research groups, notably those of David Evans, Satoru Masamune, Teruaki Mukaiyama, Dieter

Seebach, Manfred Reetz, Cesare Genari, Manfred Braun and Ian Paterson.

The reaction between a prochiral enolate and an aldehyde can give two diastereomeric  $\beta$ -hydroxy ketones, sometimes referred to as *syn* (*erythro*) and *anti* (*threo*) (Scheme 1).<sup>3</sup> In our earliest work on the aldol reaction, we found that the relative stereochemistry of an aldol is related to that of the enolate from which it comes; *Z* enolates give *syn* aldols, and *E* enolates give *anti* aldols, provided the group attached to the oxygen-bearing carbon of the enolate is bulky.<sup>4</sup> This relationship was capitalized upon by the creation of several

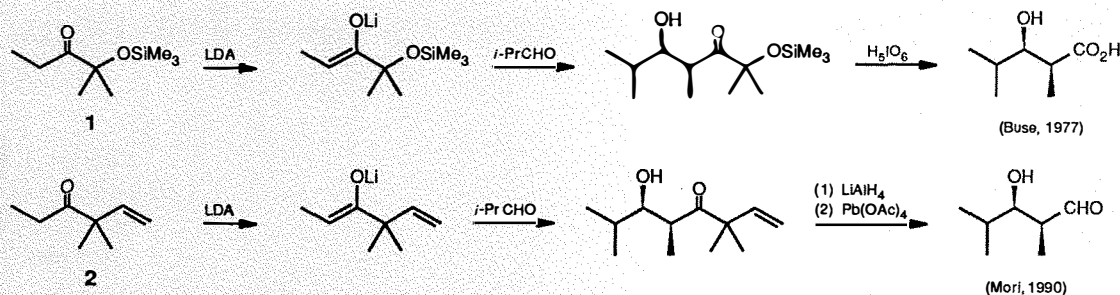
reagents that can be used to prepare *syn* or *anti*  $\alpha$ -alkyl- $\beta$ -hydroxy carboxylic acids. The useful  $\alpha$ -trimethylsilyloxy ketone **1** (Buse's reagent)<sup>5</sup> and  $\beta,\gamma$ -unsaturated ketone **2** (Mori's reagent)<sup>6</sup> both give *Z* enolates that react with aldehydes to give only *syn* aldols (Scheme 2). The aldols derived from **1** are cleaved with periodic acid to obtain *syn*  $\alpha$ -alkyl- $\beta$ -hydroxycarboxylic acids;<sup>7</sup> those derived from ketone **2** are reduced and the resulting homoallylic alcohols cleaved with lead tetraacetate to acquire  $\alpha$ -alkyl- $\beta$ -hydroxy carboxaldehydes.

On the other hand, esters tend to give *E* enolates upon deprotonation with LDA

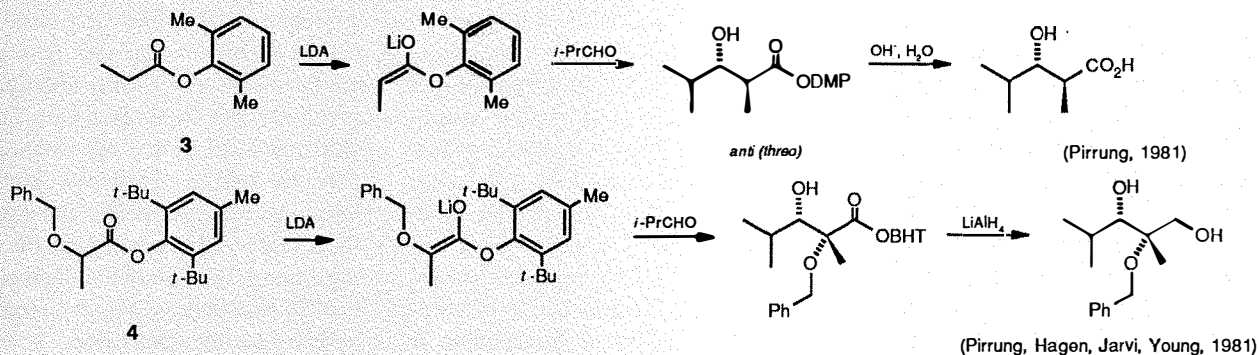


Professor Clayton H. Heathcock (right) receiving the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry from Dr. Alfred Bader.

### Scheme 2



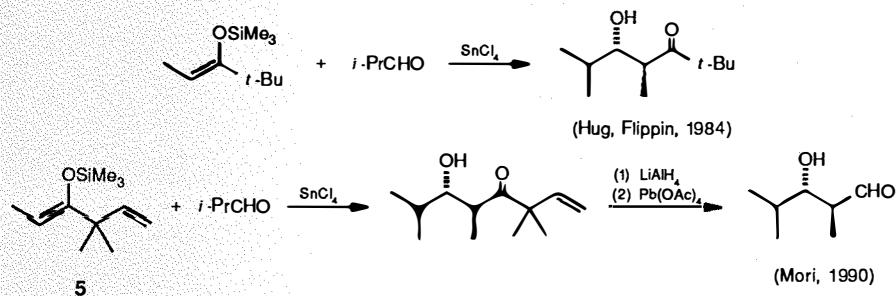
### Scheme 3



and other lithium amide bases, but the enolates of normal alkyl esters show essentially no simple stereoselection in their aldol reactions. However, the *E* enolates derived from esters of 2,6-dimethylphenol (DMP), 4-methyl-2,6-di-*tert*-butylphenol ('butylated hydroxytoluene', BHT), and 4-methoxy-2,6-di-*tert*-butylphenol ('dibutylated hydroxyanisole', DBHA) give  $\alpha$ -alkyl- $\beta$ -hydroxy esters with quite useful stereoselectivity.<sup>8</sup> One example is the reaction of ester **3** (Pirring's reagent) with isobutyraldehyde (Scheme 3).<sup>9</sup> Remarkably, the high stereoselectivity of these hindered aryl esters carries over to the esters of  $\alpha$ -alkoxy carboxylic acids. Thus, as shown in Scheme 3, the BHT ester of *O*-benzylsuccinic acid, **4**, gives an enolate that reacts with isobutyraldehyde to give a single aldol.<sup>10</sup> Reagent **4** and its analogs therefore serve as useful synthetic equivalents for the lactaldehyde enolate.

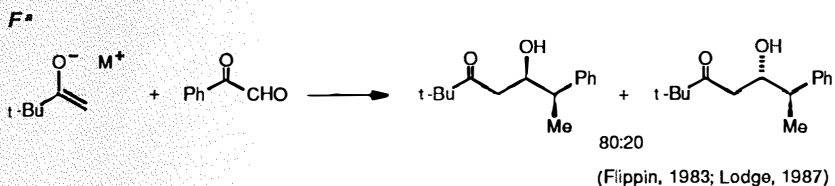
Parallel investigations of Lewis acid mediated aldol reactions also led to synthetically useful reagents. Although most silyl enol ethers do not show exceptional simple stereoselection in their Lewis acid mediated reactions with aldehydes,<sup>11</sup> those derived from *tert*-alkyl ketones do give

### Scheme 4



### Scheme 5

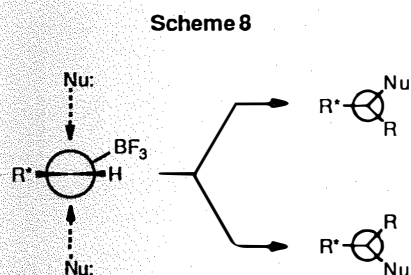
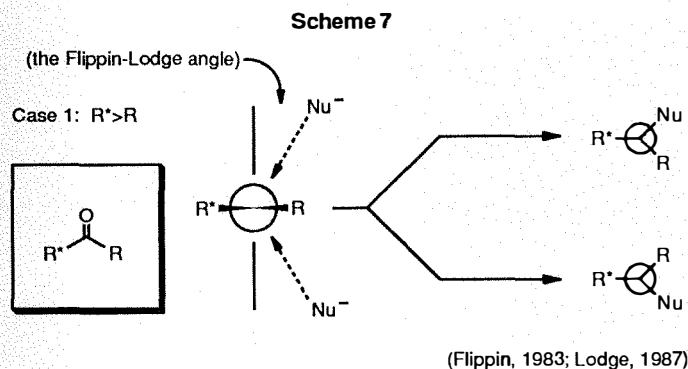
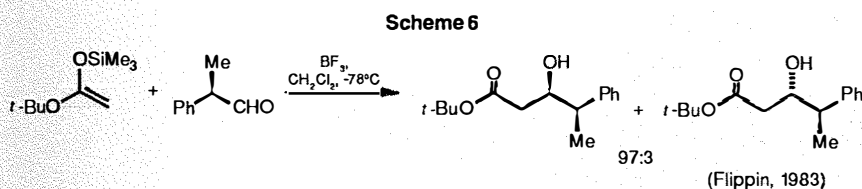
#### Facial Diastereoselectivity (One Reactant Chiral)



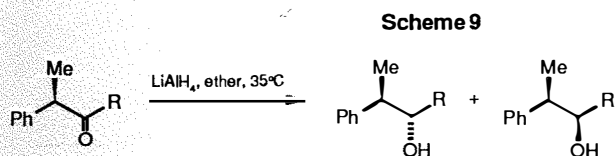
*anti*  $\alpha$ -alkyl- $\beta$ -hydroxy ketones with good stereoselectivity (Scheme 4).<sup>12</sup> Compound **5**, prepared from the Mori reagent, **2**, provides a useful complement to the corresponding *syn*-selective lithium enolate.<sup>13</sup>

When one of the two reaction partners

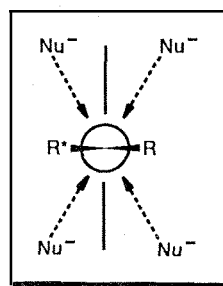
in an aldol reaction is chiral, there exists the possibility of a fundamentally different kind of stereoselection. In this instance, the two faces of the carbonyl acceptor or enolate donor are diastereotopic, and there exist two



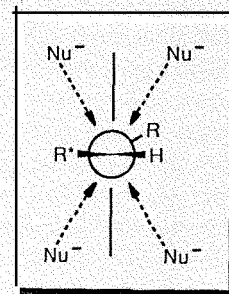
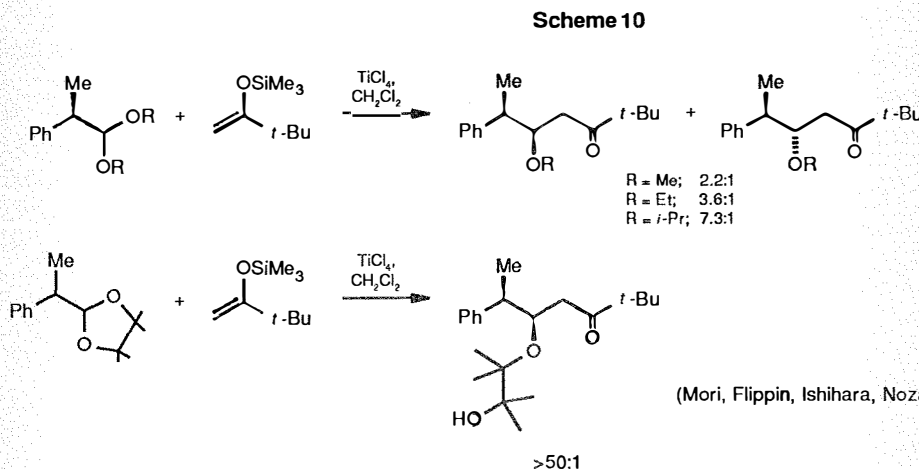
diastereomeric transition states (Scheme 5). For additions of lithium enolates to chiral aldehydes in which the stereogenic center is adjacent to the carbonyl group, the intrinsic diastereofacial preference ( $F^a$ ) is usually relatively low – on the order of 2:1 to 6:1.<sup>14</sup>



R	Diastereoselectivity
Me	3:1
Et	3:1
<i>i</i> -Pr	5:1
<i>t</i> -Bu	50:1



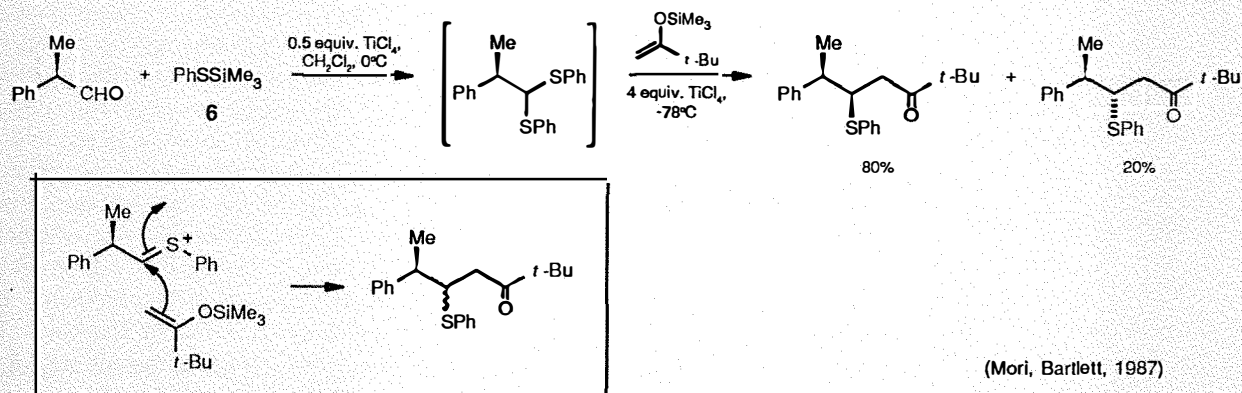
(Cherest, Felkin, Prudent, 1968)



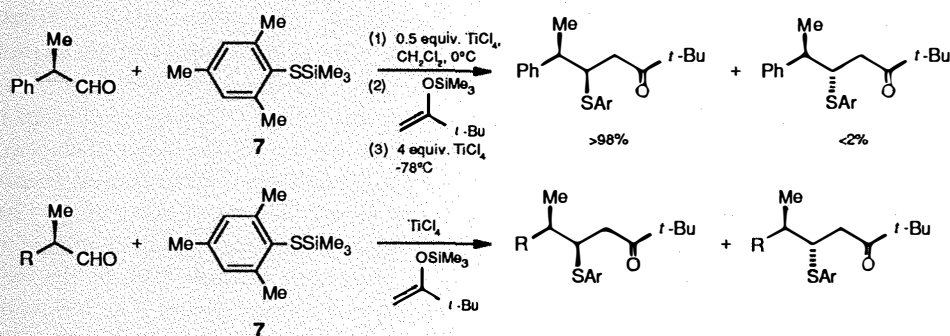
(Mori, Flippin, Ishihara, Nozaki, Yamamoto, Bartlett, 1990)

Following a lead discovered by Danishefsky and co-workers in their study of Lewis acid mediated hetero-Diels-Alder reactions of 2-silyloxy-1,3-butadienes,<sup>15</sup> we found that the  $\text{BF}_3$ -mediated reactions of silyl enol ethers and silyl ketene acetals with chiral aldehydes proceed with high stereoselectivity relative to the corresponding lithium enolate additions (Scheme 6).<sup>16</sup> The theory that was advanced to explain the extraordinary diastereofacial preferences of  $\text{BF}_3$ -coordinated chiral aldehydes is shown in Scheme 7. If the two carbonyl group ligands are the same (*i.e.*, as in formaldehyde or a symmetrical ketone like acetone), then the attacking nucleophile will approach along the Burgi-Dunitz angle in the plane that bisects the compound, the 'normal plane'. However, if the two carbonyl ligands are not the same, then it is likely that the nucleophile will follow a trajectory that keeps it further away from the larger of the two carbonyl ligands. The amount of distortion away from the normal plane (the 'Flippin-Lodge angle') will be related to the difference in steric bulk on the two sides of the normal plane. If  $R^* > R$ , as in the case of a chiral aldehyde, then the path traversed by the incoming nucleophile will tend to be away from the stereogenic center, thus minimizing the intrinsic diastereofacial preference. However, it is known that Lewis acids coordinate aldehydes *cis* to the hydrogen and *trans* to the alkyl group.<sup>17</sup> Thus, the bulky  $\text{BF}_3$  group is on the same side of the normal plane as the hydrogen and will tend to counteract the normal steric bias of the addition reaction (Scheme 8). This distortion of the Flippin-Lodge angle will

### Scheme 11



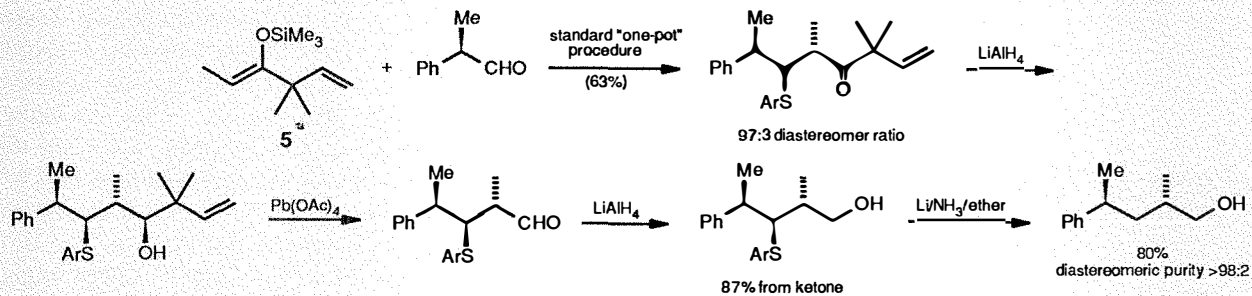
### Scheme 12



R	% syn	% anti
cyclohexyl	>98	<2
benzyl	>98	<2
ethyl	83	17

(Mori, Bartlett, 1987)

### Scheme 13



amplify the diastereofacial preference, relative to that of the uncoordinated aldehyde, leading to higher stereoselectivity.

If 'trajectory analysis' is a valid concept, it should be applicable in other situations as well. In fact, the hypothesis is in excellent accord with a set of data reported by Felkin and his co-workers for the reduction of chiral ketones (Scheme 9).<sup>18</sup> We wondered if it could also be important in additions to chiral oxonium ions. As shown in Scheme 10, this is indeed the case; the diastereoselectivity seen in nucleophilic substitution of one of

the two alkoxy groups in an acetal of 2-phenylpropanal ranges from 2.2:1 for the dimethyl acetal to more than 50:1 for the pinacol acetal.<sup>19</sup>

Scheme 11 illustrates a new procedure for the generation and trapping of thionium ions. Thus, if 2-phenylpropanal is treated sequentially with trimethylsilyl phenyl sulfide, 6, titanium tetrachloride, and a silyl enol ether, two diastereomeric  $\beta$ -phenylthio ketones are produced. The mechanism of this reaction presumably involves addition to the thionium ion as shown in the insert in Scheme 11. However,

if sulfide 7 is used in the same process, the diastereoselectivity increases to >50:1; only a single  $\beta$ -mesitylthio ketone is obtained from 2-phenylpropanal (Scheme 12).<sup>20</sup> The phenomenon is applicable to other chiral aldehydes as shown. With 2-methyl-3-phenylpropanal, a single isomer is produced even though the stereodifferentiation in this case is between methyl and a primary alkyl group. More impressive is the 6:1 ratio observed with 2-phenylbutanal; typical diastereofacial selectivities seen with this aldehyde in nucleophilic addition reactions are 55:45.

Use of the thionium ion methodology as an iterative tool is illustrated in Scheme 13.<sup>21</sup>

In one of the earliest cases in which the intrinsic diastereofacial preference of a chiral enolate ( $F^d$ ) was determined, the kinetically-formed lithium enolate of (*S*)-3-methyl-2-pentanone was allowed to react with several aldehydes; in the case of propanal, the two products were formed in 15% diastereomeric excess (Scheme 14).<sup>22</sup> In 1979, we prepared and investigated the reactions of a chiral version of reagent **1**.<sup>23</sup> As shown in Scheme 15, ketone **8** forms a *Z* enolate (we call it the lithium 'superenolate') which shows modest to excellent diastereofacial selectivity in its reactions with aldehydes. Masamune and co-workers introduced a similar reagent, **9**, which was used as the *Z* boron enolate to obtain even higher diastereofacial selectivity (Scheme 16).<sup>24</sup>

It is noteworthy that the *Z* lithium enolate of **8** and the *Z* boron enolate of **9** have opposite diastereofacial preferences. A rationale for this fascinating difference is presented in Scheme 17.<sup>25</sup> It was suggested that the lithium cation can simultaneously coordinate three oxygens in the transition state. This orients the stereogenic center in such a way that the two enolate faces are strongly differentiated. As a result, the aldol reaction occurs on the *re* face of the *S* enantiomer, leading to the *syn* isomer shown in Scheme 17. On the other hand, boron has two alkyl ligands and can coordinate only two oxygens in the aldol transition state. Since one of these must be the enolate oxygen, it follows that the silyloxy group must be released in order for boron to coordinate and activate the aldehyde carbonyl for addition. As shown in the Scheme, it was suggested that the dipolar repulsion of the

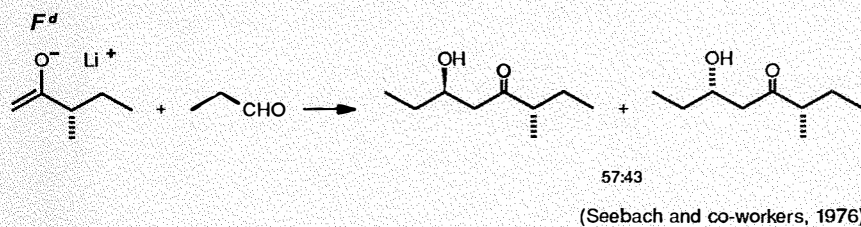
two adjacent C-O bonds in the boron enolate provides an orientation that reverses its facial preference, relative to that of the lithium enolate.

The fact that either *syn* aldol can be prepared from a *Z* enolate by a simple choice of cation led us to formulate the hypothesis illustrated in Scheme 18. In principle, one could convert a given chiral ketone  $R^*COEt$  into each of its four possible diastereomeric aldol products by regulating the stereochemistry of enolate formation and by selecting whether it reacts on its *si* or *re* face. In order to consummate this plan, it is necessary to have reagent **8** in scalemic form.<sup>26</sup> A convenient synthesis is summarized in Scheme 19. Diazotization of *tert*-butylglycine gives  $\alpha$ -hydroxy acid **10**.<sup>27</sup> Reaction of this material with excess ethyllithium provides a hydroxy ketone, which is silylated with *N*-(trimethylsilyl)imidazole to obtain (-)-**8** in 50% overall yield from *tert*-butylglycine. An analogous reagent was obtained by silylation with *tert*-butyldimethylsilyl chloride.

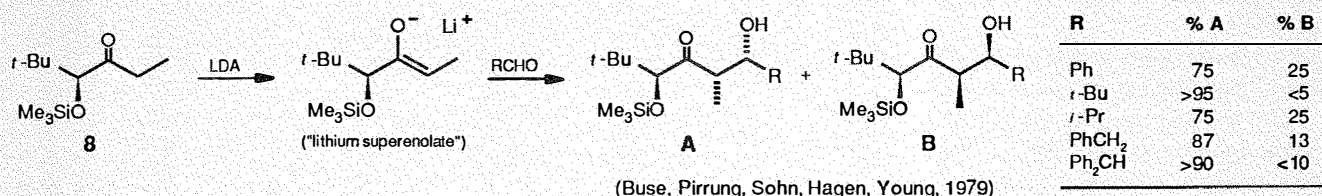
Scheme 20 summarizes experiments with (-)-**8** that were carried out under optimized conditions. The lithium enolate of (-)-**8** is prepared by treatment of the ketone with LDA in THF at -78°C for 2.5 h. To this solution is added 1.0 equiv. of tetramethylethylenediamine (TMEDA). After 2 min. the aldehyde is added, and

Scheme 14

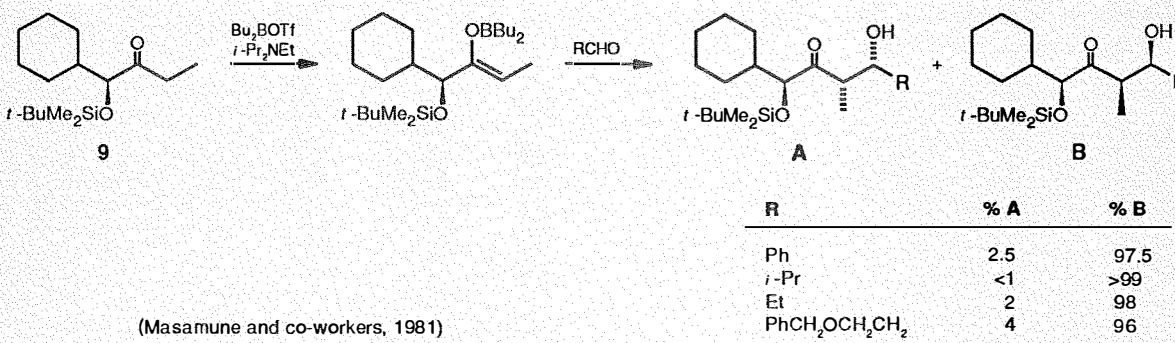
Facial Diastereoselectivity (One Reactant Chiral)



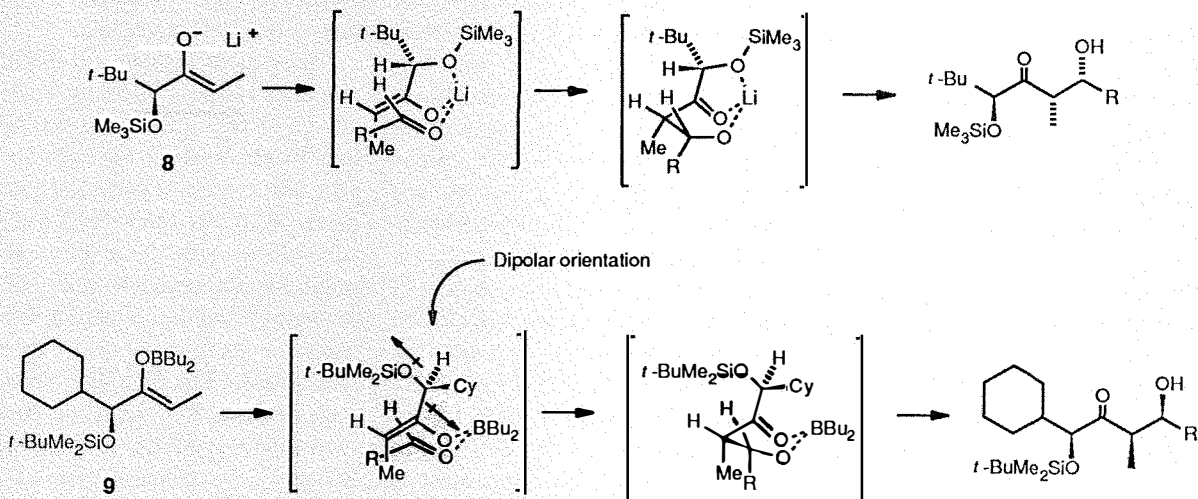
Scheme 15



Scheme 16



Scheme 17

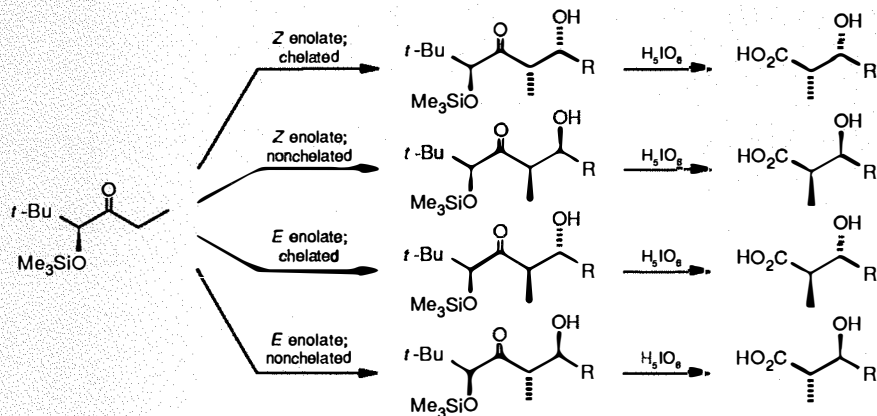


after an additional 8 min. the reaction is quenched. This optimized procedure gives aldols in 75-80% yield. With isobutyraldehyde, pivalaldehyde and benzaldehyde, the stereoselectivity is >95:5.<sup>28</sup> With 3-benzyloxypropanal, the stereoselectivity is 95:5. The relative configuration of the major aldol from benzaldehyde was ascertained by single-crystal X-ray analysis of the keto diol obtained by hydrolysis of its racemic counterpart.<sup>29</sup> Scheme 21 shows the comparable reactions of the *Z* boron enolate of (-)-**8**, prepared in the conventional manner.<sup>30</sup> In each case studied, the stereoselectivity is >95:5, and in each case, the *syn* aldol that is not the major product from the lithium enolate is obtained.

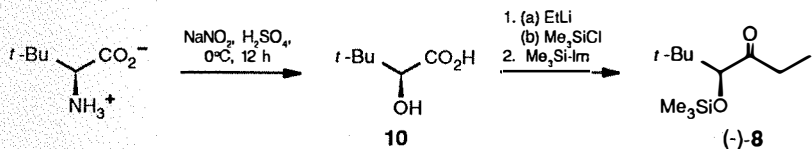
The *E* magnesium enolate of (-)-**8**, obtained by adding the ketone to a solution of *N*-bromomagnesium-2,2,6,6-tetramethylpiperidine (MTMP) in THF at -5°C, reacts with trimethylsilyl chloride to give the *E* silyl enol ether (Scheme 22).<sup>31</sup> A possible rationale for the unique ability of this base to produce the *E* enolate is suggested in Scheme 23. The importance of the α-alkoxy group is shown

Scheme 18

**Hypothesis:** In principle, all four diastereomeric aldols could be obtained from the same chiral, scalemic reagent if one could control the double-bond geometry and diastereofacial preference of the enolate.

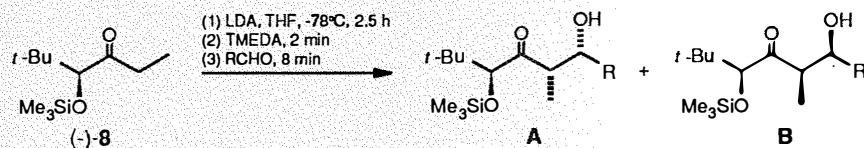


Scheme 19



(Van Draanen, Arseniyadis, 1990)

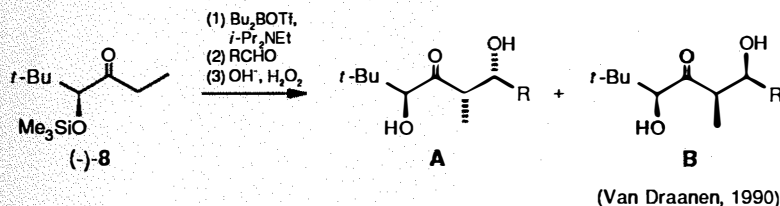
Scheme 20



(Van Draanen, 1990)

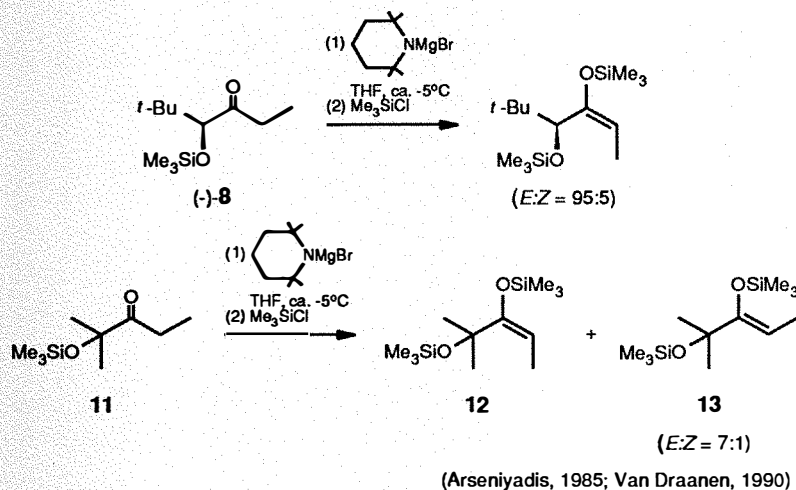
R	Yield, %	A:B
Ph	80	>95:5
<i>i</i> -Pr	80	>95:5
<i>t</i> -Bu	75	>95:5
PhCH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub>	80	95:5

## Scheme 21

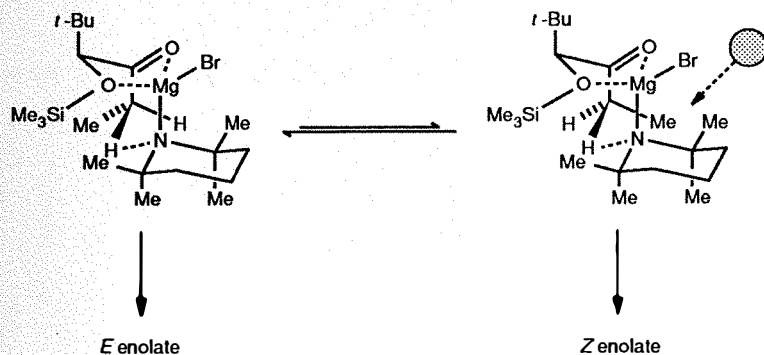


R	Yield, %	A:B
Ph	80	<5:95
<i>i</i> -Pr	85	<5:95
<i>t</i> -Bu	85	<5:95
$\text{PhCH}_2\text{OCH}_2\text{CH}_2$	88	<5:95

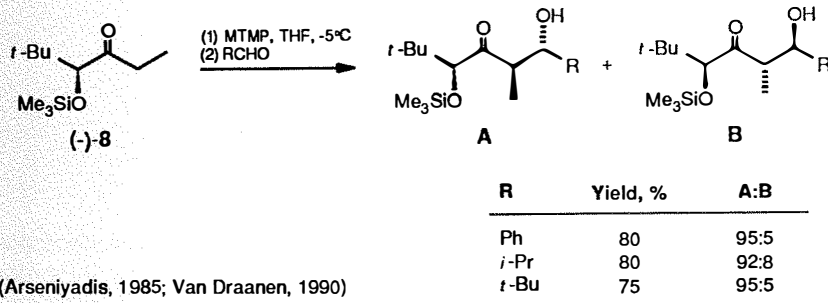
## Scheme 22



## Scheme 23



## Scheme 24



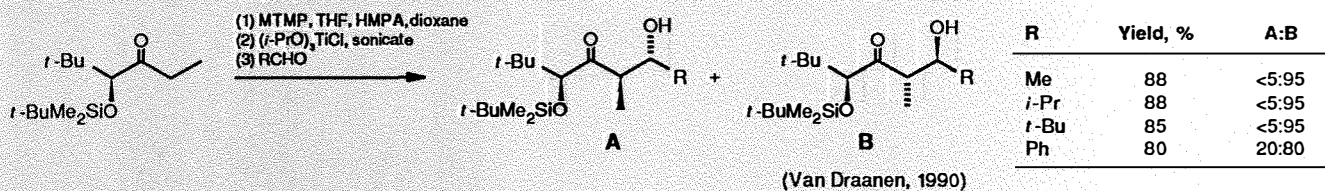
by the fact that MTMP also deprotonates ketone **11**<sup>32</sup> to give a 7:1 mixture of *E* and *Z* enolates, which can be converted into silyl enol ethers **12** and **13** (Scheme 22). For comparison, LDA reacts with ketone **11** to give only the *Z* enolate.

Reaction of the *E* magnesium enolate of (-)-**8** with various aldehydes provides *anti* aldols in ratios of 92:8 to 95:5 and yields of 75-85% (Scheme 24). The relative stereostructure of the major aldol from benzaldehyde was ascertained by single-crystal X-ray analysis of the *keto* diol obtained by hydrolysis of its racemic counterpart.

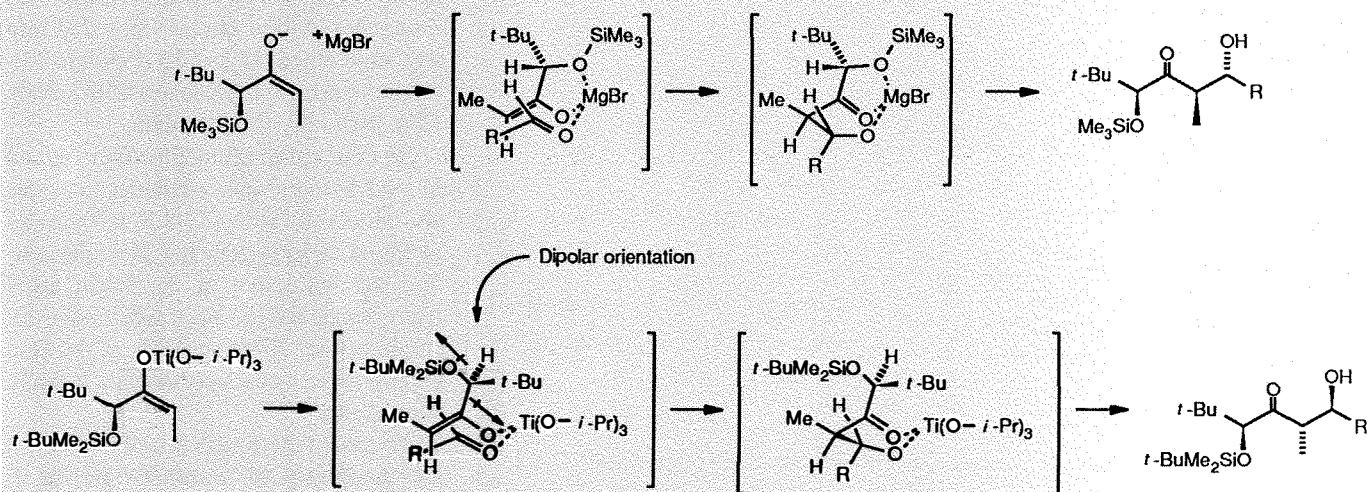
To obtain the fourth possible aldol, it was necessary to transmetallate the *E* magnesium enolate with a metal that does not undergo the three-point coordination depicted in Scheme 17. The ideal species would be the *E* boron enolate; however, numerous attempts to exchange magnesium for boron failed and attempts to prepare the *E* boron enolate directly from ketone (-)-**8** by the method of Brown and co-workers<sup>33</sup> were also unsuccessful. Eventually we found conditions that permit the replacement of magnesium by titanium. Thus, a solution of the magnesium enolate of the *tert*-butyldimethylsilyl analog of (-)-**8** and tri(isopropoxy)titanium chloride in a mixture of HMPA, dioxane, and THF is sonicated at 25-45°C for 4 h. The use of (*i*-PrO)<sub>3</sub>TiCl for enolate exchange was adapted from the work of Siegel and Thornton, who performed a similar exchange with a lithium enolate.<sup>34</sup> Each of the additives (HMPA, dioxane) and the sonication period was shown to be necessary by appropriate control experiments. By this protocol, benzaldehyde gave the two *anti* aldols in a ratio of 1:4. However, acetaldehyde, isobutyraldehyde, and pivalaldehyde gave the two *anti* aldols in ratios of <5:95 and 85-88% yield (Scheme 25). In each case, the major aldol was the same as the minor



Scheme 25



Scheme 26



aldol obtained from the magnesium enolate reaction.

The mechanistic rationale for the magnesium and titanium enolate reactions is shown in Scheme 26. These postulated transition states are identical to those for lithium and boron, respectively, except that an *E* enolate is involved rather than a *Z* enolate. As a result, the magnesium and titanium aldols have the same stereochemistry as the lithium and boron aldols, except at the methyl-bearing center.

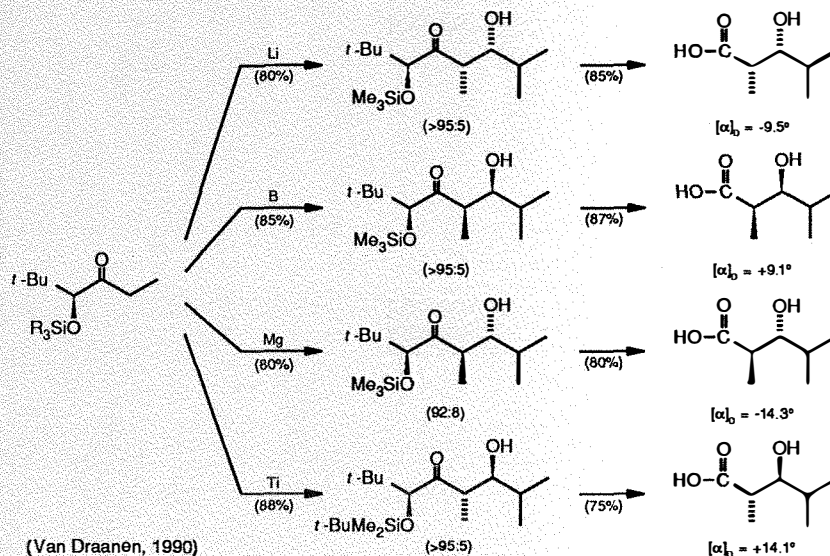
The aldols produced from (-)-**8** and its *tert*-butyldimethylsilyl analog in the foregoing manner can be cleaved with periodic acid to obtain scalemic  $\alpha$ -methyl- $\beta$ -hydroxy carboxylic acids. The products obtained from isobutyraldehyde are depicted in Scheme 27, thus demonstrating the ability to synthesize all four of the possible stereoisomers of a given  $\alpha$ -alkyl- $\beta$ -hydroxy carboxylic acid from a single enantiomer of reagent (-)-**8**.

Scheme 28 summarizes the Evans asymmetric aldol reaction, one of the most useful synthetic methods to emerge from the aldol renaissance period.<sup>35</sup> Chiral imides such as **14** have very high dia-

Scheme 27

## Summary:

## Preparation of the four stereoisomeric 3-hydroxy-2,4-dimethylpentanoic acids



stereofacial preferences in their reactions with aldehydes. Hydrolysis of the resulting *syn* aldol provides the  $\alpha$ -alkyl- $\beta$ -hydroxy carboxylic acid. As with the boron

enolate of **8**, enolate **15** is burdened with two alkyl ligands and can only coordinate two oxygens in the aldol transition state. The high diastereofacial preference seen

in the Evans aldol reactions is consistent with the transition state conformation depicted in the insert in Scheme 28. As with the boron enolate of **8**, the organization might be due to dipolar repulsion, as indicated.

In connection with a total synthesis project, we had occasion to use the Evans reaction with a series of  $\beta$ -(arythio)acroleins. To our surprise, we obtained mainly the *anti* aldols, as shown in Scheme 29.<sup>36</sup> The cause of the unexpected be-

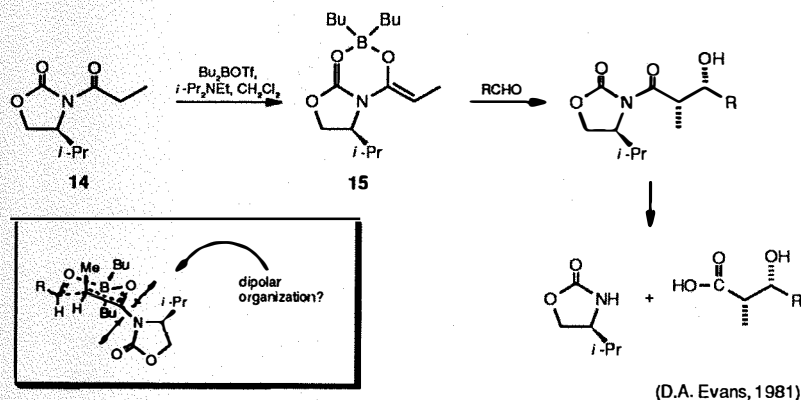
havior was soon traced to an error in measurement; because of a miscalibration, we had inadvertently used two equivalents of dibutylboron triflate in formation of the boron enolate. When we used only one equivalent, we obtained the expected Evans *syn* aldol (Scheme 30).

But what role does the extra dibutylboron triflate play? A mechanistic interpretation is suggested in Scheme 31. It is clearly seen by <sup>11</sup>B NMR spec-

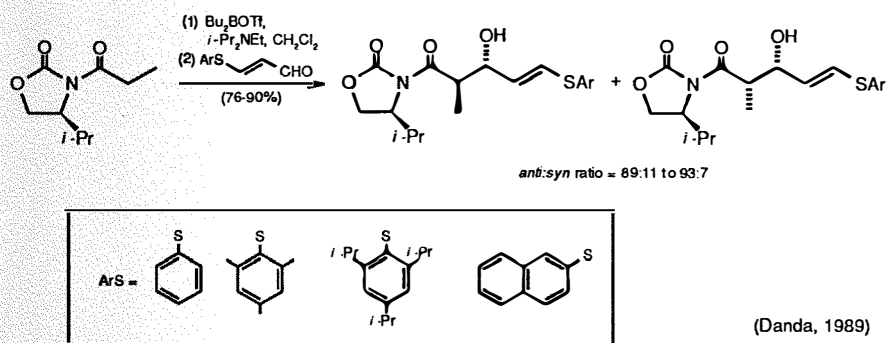
troscopy that **16**, the boron enolate of **15**, exists in the chelated form shown in Scheme 31. However, a boron enolate is not a very reactive species. Before aldol addition can occur, it is necessary that the aldehyde carbonyl be activated by coordination with a Lewis acid. In the absence of an external Lewis acid, this activation must be provided by the boron of enolate **16**, which must give up the oxazolidone carbonyl. The ensuing aldol reaction takes place through the closed transition state as previously discussed; the reaction occurs on the enolate *re* face, leading to the *syn* aldol **17** having the *S* configuration at the methyl-bearing stereocenter. However, if there is excess dibutylboron triflate, activation of the carbonyl can be provided by this Lewis acid, and reaction can occur through an open transition state. Since the enolate reacts in this case in its intramolecularly chelated form, the aldol reaction occurs on the *si* face, giving aldol **18** with the *R* configuration at the methyl-bearing stereocenter. The Lewis acid mediated aldol reaction of **16** gives predominantly *anti* simple stereoselection as in the Lewis acid mediated reactions of silyl enol ethers like **5** (see Scheme 4).

Our initial attempts to broaden the scope of the *anti*-selective aldol reactions of the Evans propionimides met with only partial success. As shown in Scheme 32, we were able to achieve *anti* stereoselection to the extent of 75-80% with aromatic aldehydes but simple alkyl or alkenyl carboxaldehydes gave the normal *syn* aldols, even in the presence of a second equivalent of dibutylboron triflate. However, the situation is different if one precomplexes the aldehyde with an external Lewis acid (Scheme 33). Exploratory experiments with methacrolein and several Lewis acids

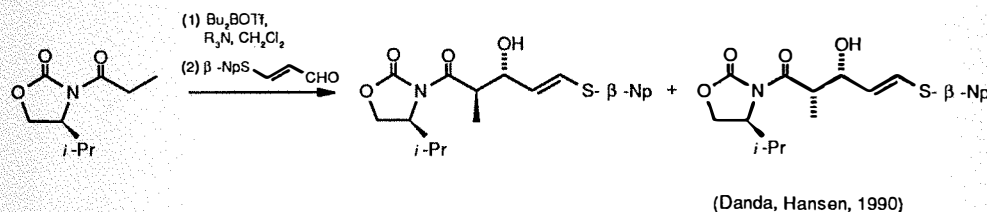
Scheme 28  
The Evans Asymmetric Aldol Reaction



Scheme 29



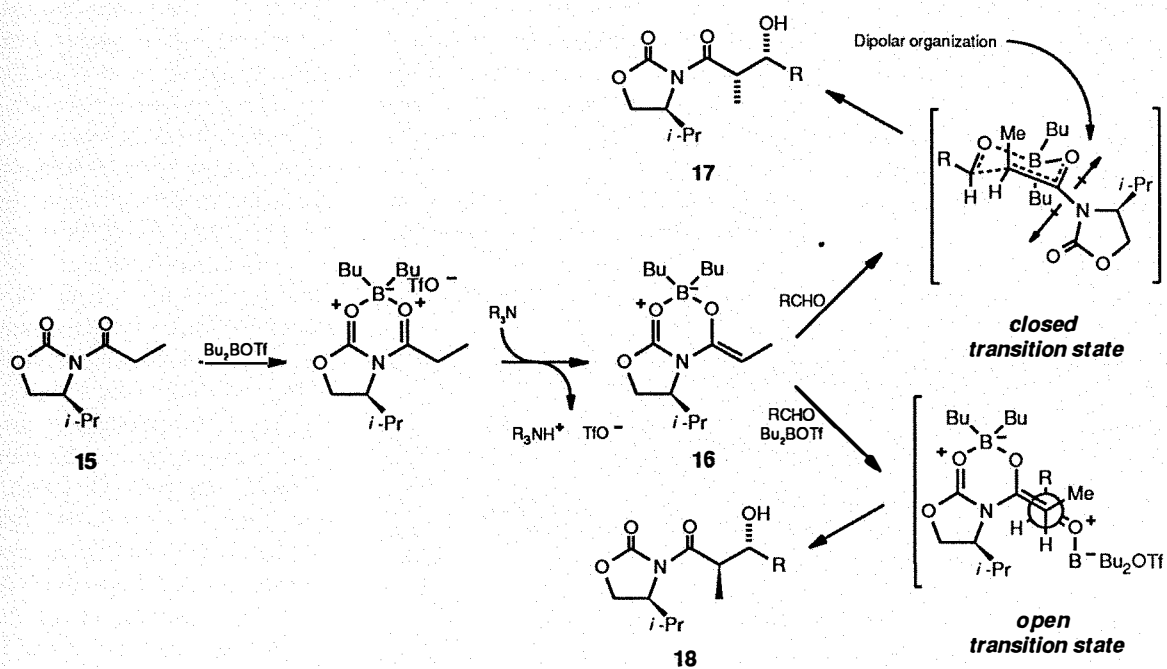
Scheme 30



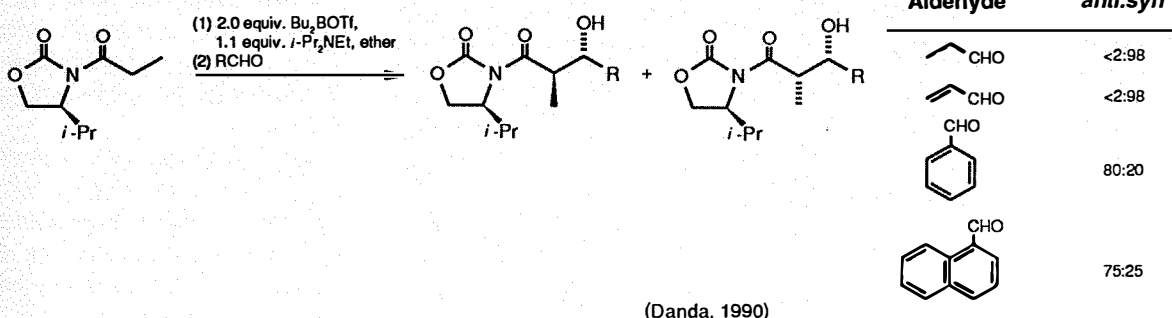
Conditions *anti:syn*

2.0 equiv. Bu <sub>2</sub> BOTf, 2.2 equiv. <i>i</i> -Pr <sub>2</sub> NEt	95:5
1.5 equiv. Bu <sub>2</sub> BOTf, 2.0 equiv. <i>i</i> -Pr <sub>2</sub> NEt	77:23
1.1 equiv. Bu <sub>2</sub> BOTf, 1.3 equiv. <i>i</i> -Pr <sub>2</sub> NEt	<2:98

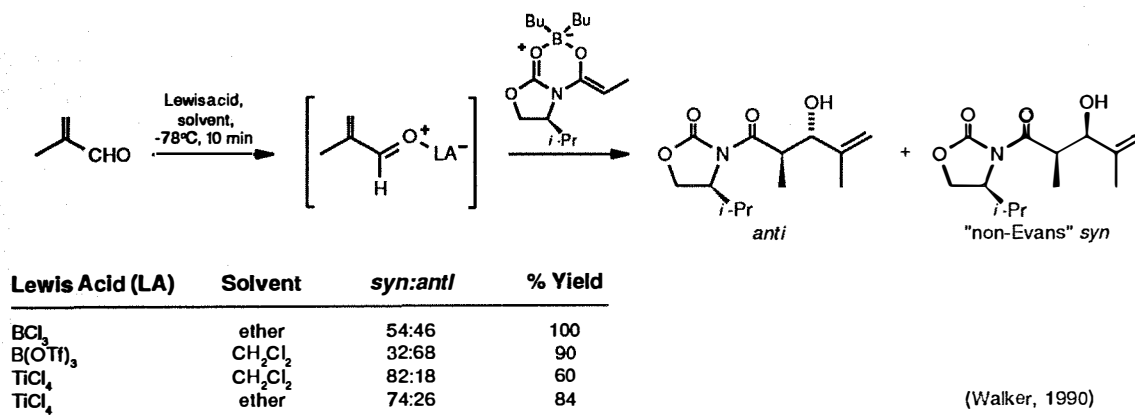
Scheme 31



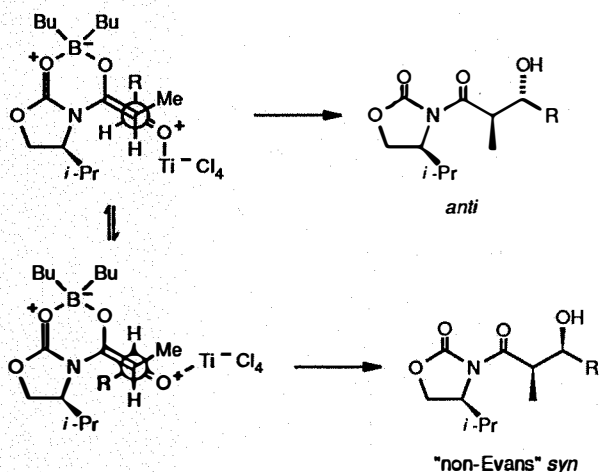
Scheme 32



Scheme 33



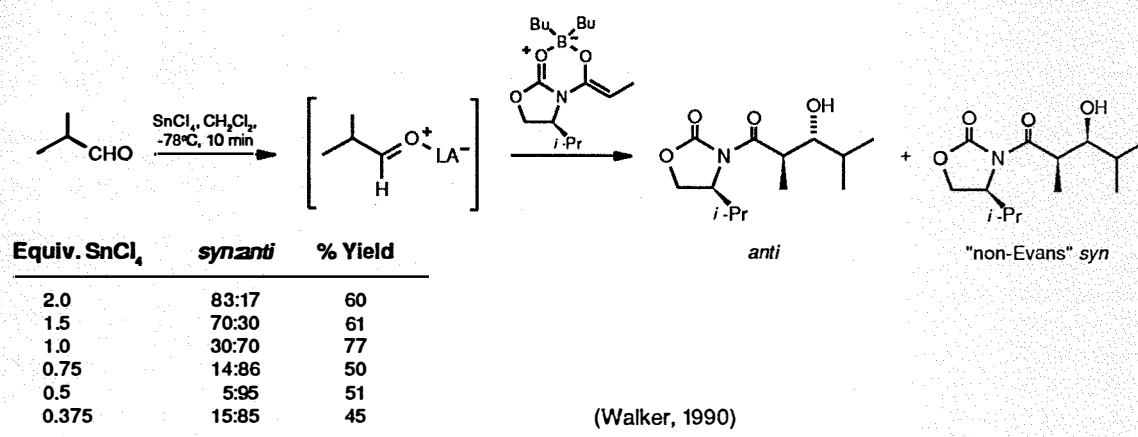
Scheme 34



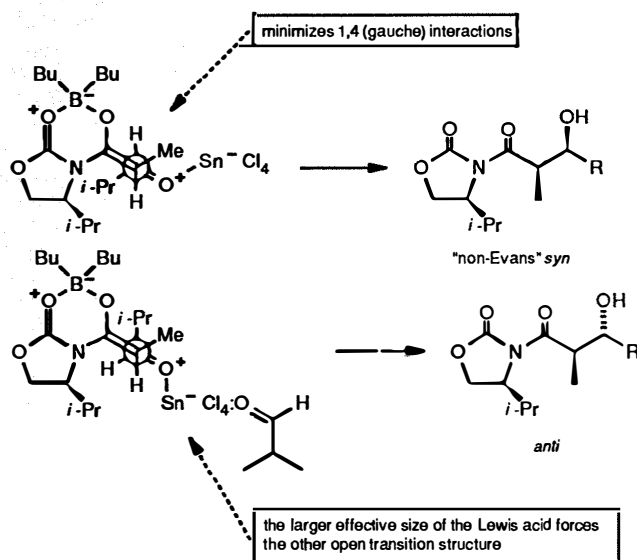
gave mixtures of *syn* and *anti* aldols in all cases. It is significant that, under these conditions, *neither* product is the normal Evans *syn* aldol. Thus, as shown in Scheme 34, both products result from open transition states! The different *anti/syn* ratios must result from nonbonded interactions in the two possible transition states. More importantly, since the *anti/syn* ratios are different for different Lewis acids, it is theoretically possible to optimize the reaction conditions for a given aldehyde so as to obtain either stereoisomer.

At the present time, we are engaged in optimizing this felicitous discovery. We have discovered that there is an as-

Scheme 35



Scheme 36



tonishing effect of Lewis acid stoichiometry. A representative set of data is shown in Scheme 35 for isobutyraldehyde; this aldehyde gives a *syn/anti* ratio of 6:1 with 2.0 equivalents of  $\text{SnCl}_4$  but an *anti/syn* ratio of 20:1 with only 0.5 equivalents of the same Lewis acid! The data are presented graphically in Figure 1. We do not yet know the origins of this marked effect of Lewis acid stoichiometry. One possibility is the existence of 1:1 and 2:1 aldehyde/Lewis acid complexes (Scheme 36). Whatever the explanation, the results shown in Scheme 35 illustrate the enormous potential of Lewis acid catalysis in extending the scope of the Evans imides for stereoselective synthesis. From isobutyraldehyde, for example, one can now prepare three of the four possible stereoisomers of 3-hydroxy-2,4-dimethylpentanoic acid by adjusting the amount of  $\text{SnCl}_4$  that is

used in the aldol reaction of the boron enolate; 0.0 equivalents gives normal Evans *syn* aldol, 0.5 equivalents gives the *anti* aldol, and 2.0 equivalents gives the non-Evans *syn* product. Although our studies are far from complete, we have seen similar behavior with a number of other aldehydes, such as propanal, pivalaldehyde, 3-methylbutanal and benzaldehyde. The effects differ quantitatively, and it is clear that there will probably not be a simple generic protocol that will work for all aldehydes, but it is likely that conditions can be found whereby any one of three different aldols can be obtained from an Evans imide.

### Acknowledgments

I owe a great debt to a large number of co-workers who carried out the experimental work and provided many of the ideas that made this account possible. Their names appear in the references and on the various Schemes. Most of the work discussed has been published. However, part of the recent work dealing with the preparation of multiple aldol stereoisomers from the chiral reagents **8** and **15** has not. For this research, I want to single out two excellent Berkeley graduate students, Nanine Van Draanen and Michael Walker, for special thanks.

Since its inception in 1977, our acyclic stereoselection research has been supported by a research grant from the United States Public Health Service (AI15027). I also wish to thank the USPHS and the National Science Foundation for postdoctoral and predoctoral fellowship support for several co-workers and Glaxo for providing valuable assistance in connection with our 'four aldol' study of reagent (-)-**8**.

### References

- 1) Cornforth, J.W. In *Perspectives in Organic Chemistry*; Todd, A., Ed.; Wiley Interscience: New York, 1956.
- 2) For reviews of aldolization stereochemistry, see: a) Heathcock, C.H. *Science* **1981**, *214*, 395. b) Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* **1982**, *13*, 1. c) Heathcock, C.H. In *Comprehensive Carbanion Chemistry, Part B*; Buncl, E.; Durst, T., Ed.; Elsevier: Amsterdam, 1984; Chapter 4. d) Heathcock, C.H. In *Asymmetric Synthesis, Vol 3*; Morrison, J.D., Ed.; Academic Press: New York, 1984; Chapter 2. e) Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem., Intl.*

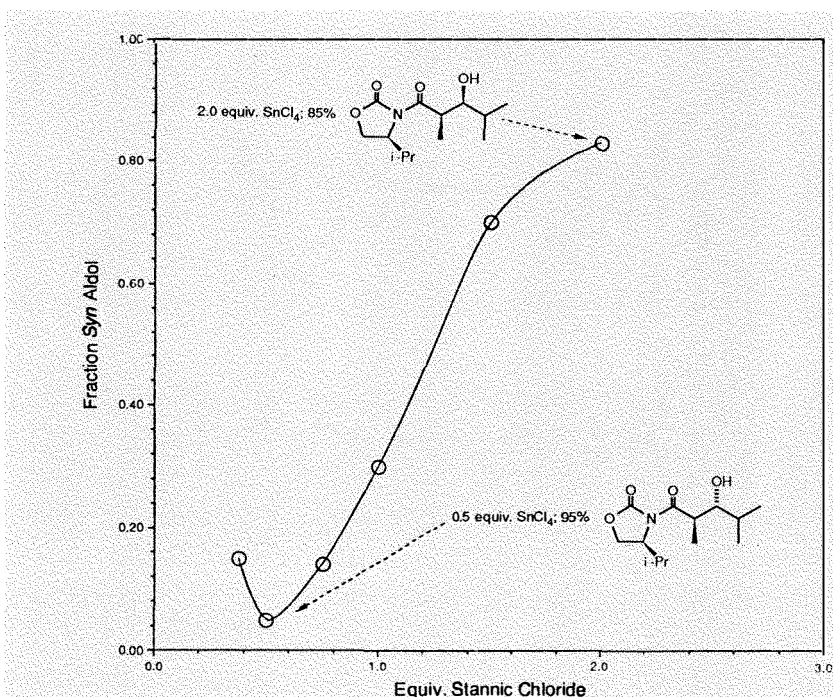


Fig. 1 - Fraction *syn* as a function of equivalents of Lewis acid.

- Ed. Engl. **1985**, *24*, 1. f) Braun, M. *ibid.* **1987**, *26*, 24. g) Heathcock, C.H. In *Comprehensive Organic Synthesis, Volume II*; Heathcock, C.H., Ed.; Pergamon Press: Oxford, 1991; Chapter 1.6.
- 3) The *syn/anti* nomenclature was first suggested by Masamune, S.; Ali, S.A.; Snitman, D.L.; Garvey, D.S. *Angew. Chem., Intl. Ed. Engl.* **1980**, *19*, 557. For a general discussion of stereostructural notations that have been used for aldols, see ref. 2d, p 112-115.
- 4) a) Kleschick, W.A.; Buse, C.T.; Heathcock, C.H. *J. Am. Chem. Soc.* **1977**, *99*, 247. b) Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.C.; Sohn, J.E.; Lampe, J.J. *Org. Chem.* **1980**, *45*, 1066.
- 5) Buse, C.T.; Heathcock, C.H. *J. Am. Chem. Soc.* **1977**, *99*, 2337.
- 6) Mori, I.; Ishihara, K.; Heathcock, C.H. *J. Org. Chem.* **1990**, *55*, 1114.
- 7) Bal, B.; Buse, C.T.; Smith, K.; Heathcock, C.H. *Org. Synth. Coll. Vol.* **1990**, *7*, 185.
- 8) a) Pirrung M.C.; Heathcock, C.H. *J. Org. Chem.* **1980**, *45*, 1727. b) Heathcock, C.H.; Pirrung, M.C.; Montgomery S.H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087.
- 9) Montgomery, S.H.; Pirrung, M.C.; Heathcock, C.H. *Org. Synth. Coll. Vol.* **1990**, *7*, 190.
- 10) a) Heathcock, C.H.; Hagen, J.P.; Jarvi, E.T.; Pirrung, M.C.; Young, S.D. *J. Am. Chem. Soc.* **1981**, *103*, 4972. b) Heathcock, C.H.; Pirrung, M.C.; Young, S.D.; Hagen, J.P.; Jarvi, E.T.; Badertscher, U.; Märki, H.-P.; Montgomery, S. *ibid.* **1984**, *106*, 8161.
- 11) Heathcock, C.H.; Hug, K.T.; Flippin, L.A. *Tetrahedron Lett.* **1984**, *25*, 5793.
- 12) Heathcock, C.H.; Davidsen, S.K.; Hug, K.T.; Flippin, L.A. *J. Org. Chem.* **1986**, *51*, 3027.
- 13) See reference 6.
- 14) a) Heathcock, C.H.; Flippin, L.A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. b) Lodge, E.P.; Heathcock, C.H. *ibid.* **1987**, *109*, 3353.
- 15) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J.F., Jr. *ibid.* **1982**, *104*, 360.
- 16) Heathcock, C.H.; Flippin, L.A. *ibid.* **1983**, *105*, 1667.
- 17) Reetz, M.T.; Hüllman, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymann, P. *ibid.* **1986**, *108*, 2405.
- 18) Chèrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
- 19) Mori, I.; Ishihara, K.; Nozaki, K.; Flippin, L.; Yamamoto, H.; Bartlett, P.A.; Heathcock, C.H. *J. Org. Chem.*, in press.
- 20) Mori, I.; Bartlett, P.A.; Heathcock, C.H. *J. Am. Chem. Soc.* **1987**, *109*, 7199.
- 21) *Idem.* *J. Org. Chem.* **1990**, *55*, 5966.
- 22) Seebach, D.; Ehrig, V.; Teschner, M. *Liebigs Ann. Chem.* **1976**, 1357.
- 23) a) Heathcock, C.H.; Pirrung, M.C.; Buse, C.T.; Hagen, J.P.; Young, S.D.; Sohn, J.E. *J. Am. Chem. Soc.* **1979**, *101*, 7077. b) Heathcock, C.H.; Pirrung, M.C.; Lampe, J.; Buse, C.T.; Young, S.D. *J. Org. Chem.* **1981**, *46*, 2290.
- 24) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.
- 25) Heathcock, C.H. *ACS Symposium Series, No. 185, Asymmetric Reactions and Processes in Chemistry*; Eliel, E.L.; Otsuka, S., Eds.; American Chemical Society: 1982.
- 26) Scalemic and racemic are the macroscopic analogs of chiral and achiral, terms that can only be used to refer to single objects such as molecules.
- 27) Arndt, F.; Noller, C.R.; Bergsteisson, I. *Org. Synth. Coll. Vol.* **1943**, *2*, 165.
- 28) Van Draanen, N.A.; Arseniyadis, S.; Crimmins, M.T.; Heathcock, C.H. *J. Org. Chem.*, in press.
- 29) Heathcock, C.H.; Arseniyadis, S. *Tetrahedron Lett.* **1985**, *26*, 6009. *Idem ibid.* **1986**, *27*, 777 (Erratum).

- 30) a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. b) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *ibid.* **1977**, 153. c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. d) Hiram, M.; Masamune, S. *Tetrahedron Lett.* **1979**, 2225. e) Van Horn, D.E.; Masamune, S. *ibid.* **1979**, 2229. f) Evans, D.A.; Vogel, E.; Nelson, J.V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.
- 31) See references 28 and 29.
- 32) See reference 7.
- 33) Brown, H.C.; Dhar, R.K.; Bakshi, R.K.; Pandiarajan, P.K.; Singaram, B.J.J. *Am. Chem. Soc.* **1989**, *111*, 5493.
- 34) Siegel, C.; Thornton, E.R. *ibid.* **1989**, *111*, 5722.
- 35) Evans, D.A.; Bartroli, J.; Shih, T.L. *ibid.* **1981**, *103*, 2127.
- 36) Danda, H.; Hansen, M.; Heathcock, C.H. *J. Org. Chem.* **1990**, *55*, 173.

### About the Author

Clayton H. Heathcock was born in San Antonio, Texas, on July 21, 1936. He spent his early years there and received the B.S degree in chemistry from Abilene Christian College in 1958. From 1958 until 1960 he was Supervisor of Chemical Tests for the Champion Paper & Fibre company in Pasadena, Texas. He returned to school at the University of Colorado in 1960 and received the Ph.D. in organic chemistry in 1963. His graduate work, under the direction of Alfred Hassner, dealt with synthetic modifications of steroids. After a year of postdoctoral work with Gilbert Stork at Columbia University, Heathcock joined the Chemistry Department at the University of California, Berkeley. He has remained a member of that department through his entire career and served as its Vice-Chairman in 1971-76 and Chairman in 1986-89. In 1982-83, he was Miller Research Professor at the University of California and has been appointed to this post again for 1991-92. From 1968 to 1978, he was a Consultant to the Research Laboratories of Merck Sharp & Dohme in Rahway, New Jersey, and since 1986 has been a member of the Scientific Advisory Board of Abbott Laboratories. He is past Editor of *Organic Syntheses* and current Editor-in-Chief of the *Journal of Organic Chemistry*. He has chaired the Organic Chemistry Division of the American Chemical Society, the Medicinal Chemistry Study Section of the NIH, and the Gordon Conference on Stereochemistry.

Professor Heathcock has directed research in several areas of organic synthesis, including acyclic stereoselection and natural product synthesis. He is the author of more than 170 research publications and a number of review articles and books, including *Introduction to Organic Chemistry*, a sophomore text that he coauthored with his Berkeley colleague Andrew Streitwieser. He is the Editor of Volume II of *Comprehensive Organic Synthesis*, an eight-volume encyclopedia of the field, due for publication in June, 1991. He has held a number of lectureships, including the Liebig (University of Colorado), the Reilly (Notre Dame), the Bergmann (Yale University), and the Bachmann (University of Michigan). He was the 1987 Manchester (England) Lecturer and the 1990 E. Merck North German Lecturer. In addition to being the 1990 recipient of the ACS Award for Creative Work in Organic Synthesis, he received the Ernest Guenther Award in 1986 and is a 1990 Arthur C. Cope Scholar.

Professor Heathcock has several extracurricular interests, including genealogy (he has traced his lineage back as far as the sixteenth century) and breeding and showing Rhodesian ridgeback dogs (two of his dogs have achieved American Kennel Club conformation championships).



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