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Long-Range Electron Transfer in Proteins

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

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About Our Cover:

Fig. 1

Readers of our *Acta* know how much our chemist collector loves the works of one Rembrandt student, Gerbrand van den Eeckhout, who was also Rembrandt's good friend. This is our fourth cover depicting an Eeckhout.

There is a preparatory drawing (Fig. 1) for this painting (oil on canvas, 21½x 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

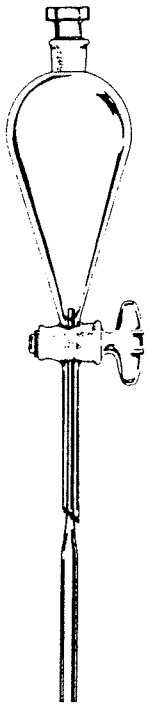
A collection of nineteen papers, seventeen in English and two in German, by Rachel Wischnitzer (1885-1989) ranging from synagogue architecture to the iconography of works by Rembrandt, together with this remarkable woman's life story, written by Prof. Bezalel Narkiss, the director of the Center for Jewish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

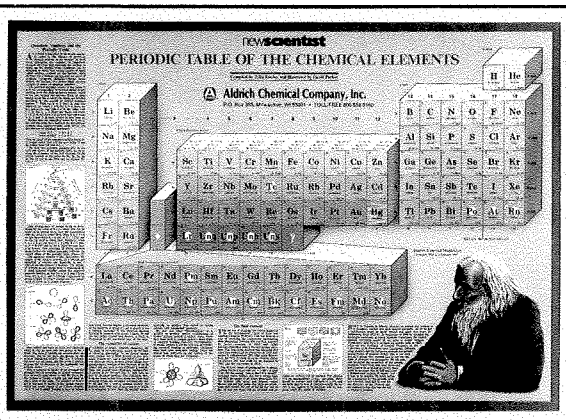
If you relish detective work and puzzles about Old Master paintings, you will find much to enjoy in this fully illustrated catalog, and you will learn something about our chemist collector's interest in art and connoisseurship as well.

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

Professor Alfred Hassner of Bar-Ilan University kindly suggested that we offer a polymeric quaternary ammonium azide reagent.[1] Alkyl, benzyl, and alpha-keto azides[2] 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

Harry B. Gray
Beckman Institute
California Institute of Technology
Pasadena, California 91125

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 Å) at biologically significant rates.[1-4] 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 ammines are attached to surface histidines of structurally characterized redox proteins.[5-7] Surface modification of a protein is expected to be nonperturbative,[8] 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.

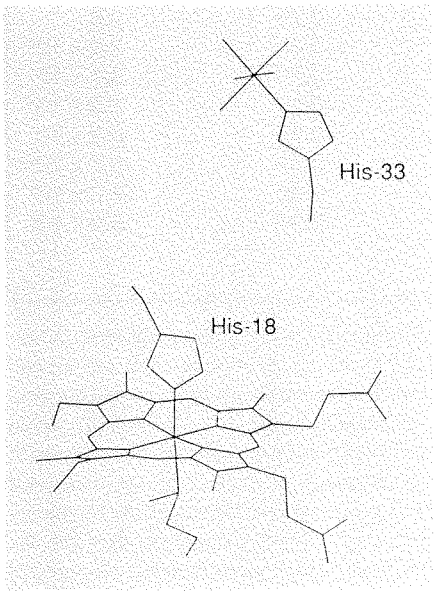

Fig. 1. Redox centers in a_5Ru(His33)cyt c. Edge-edge distances: His33 to His18, 11.7 Å; His33 to the heme, 13.2 Å.

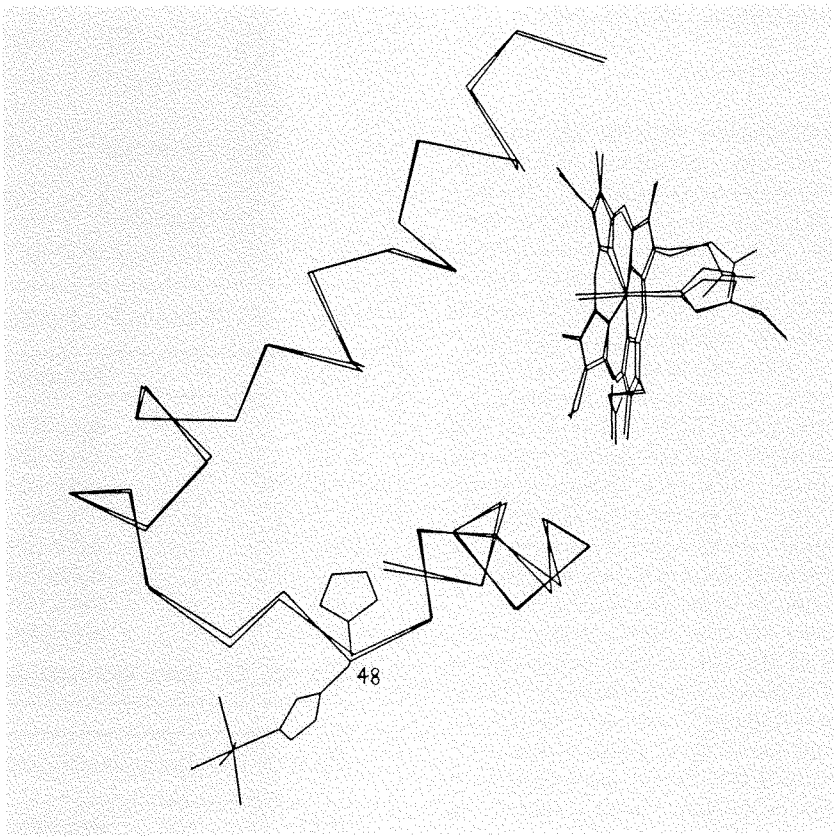

Fig. 2. Comparison of the structures of the His48 and heme regions of native and a_5Ru(His48)-modified myoglobin.

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.[6,7,9-13] Importantly, the a_5Ru(histidine)-modified proteins are relatively robust in both the Ru(II) and Ru(III) oxidation states.[14,15] Modified proteins that have been studied extensively include a_5Ru(His33)cytochrome *c* (Fig. 1)[6,9,15] and a_5Ru(His48)myoglobin (Fig. 2).[11,13]

Kinetics Methods

Flash photolysis and pulse radiolysis techniques have been employed to study electron transfer in ruthenated proteins.[3,11] 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 suface 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.[10] 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 $-\Delta G°$ in the ~1 eV range) has been investigated in zinc-porphyrin (ZnP) derivatives of ruthenated cytochrome *c* and myoglobin.[16,17] 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^b_{ET}) 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 $3x10^1$ to $3.3x10^6$ s^{-1} (Table 1). The rates show a strong dependence on driving force ($-\Delta G°$), as predicted by Marcus.[18] Replacement of the heme in Ru(His48)Mb by several metalloporphyrins (MP: M = H_2, 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 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.

$$Ru(bpy)_3^{2+} \xrightarrow{h\nu} Ru(bpy)_3^{2+*} \quad \text{(eq.1)}$$

$$Ru^{3+}(protein)Fe^{3+} + Ru(bpy)_3^{2+*} \longrightarrow Ru^{2+}(protein)Fe^{3+} + Ru(bpy)_3^{3+} \quad \text{(eq. 2)}$$

$$Ru(bpy)_3^{3+} \xrightarrow{EDTA} Ru(bpy)_3^{2+} \quad \text{(eq. 3)}$$

$$Ru^{2+}(protein)Fe^{3+} \xrightarrow{k_{ET}} Ru^{3+}(protein)Fe^{2+} \quad \text{(eq. 4)}$$

$$ZnP(protein)Ru^{3+} \xrightarrow{h\nu} {}^3ZnP^*(protein)Ru^{3+} \quad \text{(eq. 5)}$$

$$^3ZnP^*(protein)Ru^{3+} \xrightarrow{k^*_{ET}} ZnP^+(protein)Ru^{2+} \quad \text{(eq. 6)}$$

$$ZnP^+(protein)Ru^{2+} \xrightarrow{k^b_{ET}} ZnP(protein)Ru^{3+} \quad \text{(eq. 7)}$$

Table 1. ET Rates in Ru(His33)cyt *c* Derivatives[a]

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

[a] From ref. 17: isn = isonicotinamide; py = pyridine.

Table 2. ET Rates in Ru(His48)Mb Derivatives[b]

Donor	Acceptor	$-\Delta G°$ (eV)	k_{ET} (s^{-1})
FeP	a_5Ru^{3+}	0.02	0.04
FeP	a_4(py)Ru^{3+}	0.28	2.5
$H_2P^•$	a_5Ru^{3+}	0.53	7.6×10^2
$PdP^•$	a_5Ru^{3+}	0.70	9.1×10^3
$PtP^•$	a_5Ru^{3+}	0.73	1.2×10^4
$CdP^•$	a_5Ru^{3+}	0.85	6.3×10^4
$MgP^•$	a_5Ru^{3+}	0.87	5.7×10^4
$ZnP^•$	a_5Ru^{3+}	0.88	7.0×10^4
$PdP^•$	a_4(py)Ru^{3+}	0.96	9.0×10^4

[b] From refs. 11 and 16.

Reorganization Energies and Electronic Couplings

In semiclassical electron-transfer theory, three parameters govern the reaction rates: the electronic coupling between the donor and acceptor (κ_E); the free-energy change for the reaction ($\Delta G°$); and a parameter (λ) related to the extent of inner-shell and solvent nuclear reorganization accompanying the electron-transfer reaction.[18] Additionally, when intrinsic electron-transfer barriers are small, the dynamics of nuclear motion can limit electron-transfer rates through the frequency factor, υ_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-

$$k_{ET} = \nu_N \kappa_E \exp\left[\frac{-(\Delta G + \lambda)^2}{4\lambda RT}\right] \quad \text{(eq. 8)} \qquad \kappa_E = \kappa_E^{\circ}\exp[-\beta(d-d_0)] \quad \text{(eq. 9)}$$

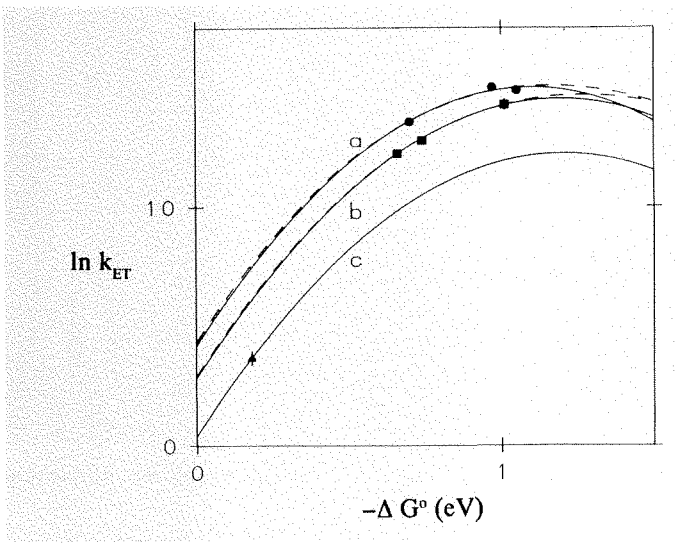

Fig. 3. Ln $k_{ET}/\Delta G^{o}$ plots for Ru(His33)cyt c derivatives.

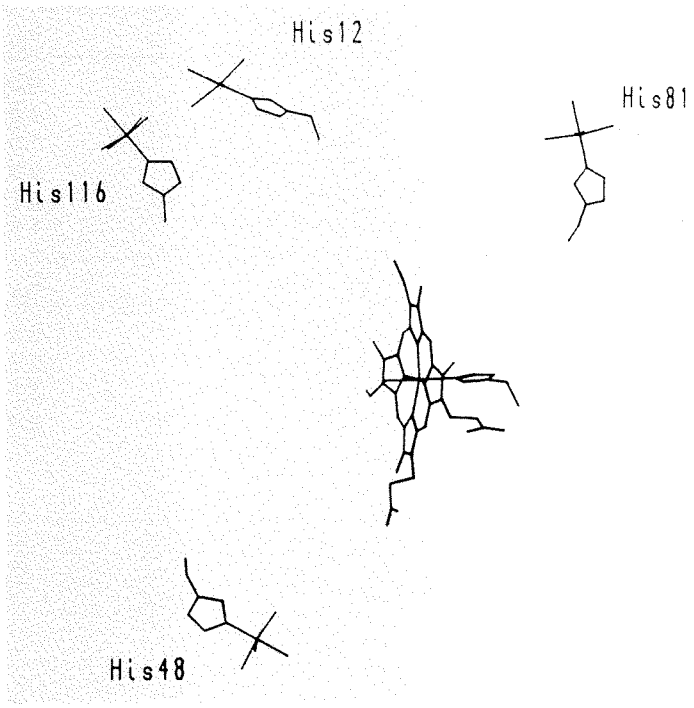

Fig. 4. Relative positions of four surface histidines and the heme in ruthenated myoglobin.

Table 3. ET Distances and Rates for a_5Ru(HisX)Mb(ZnP) Derivatives

X	Distance (Å)[c]	k_{ET} (s^{-1})[d]
48	11.8 - 16.6 (12.7)	7.2×10^4
81	18.8 - 19.3 (19.3)	1.5×10^2
116	19.8 - 20.4 (20.1)	3.0×10^1
12	21.5 - 22.3 (22.0)	1.4×10^2

[c] Edge-edge distances (d) from ref. 11; estimated d(eq) values in parentheses.
[d] $^3ZnP^{*} \rightarrow Ru^{3+}$ rates from refs. 16 and 21.

range electron transfer the electronic factor (κ_E) will decrease exponentially with the donor-acceptor edge-edge distance, d (eq. 9).[18] The closest contact distance, d_0, is normally taken to be 3 Å (van der Waals contact of the edges of the donor and acceptor). The value of β 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_5Ru(His48)Mb(MP) derivatives gives $\lambda \sim 1.4$ eV.[1] The maximum electron-transfer rate, $\upsilon_N\kappa_E \sim 3.5 \times 10^5 s^{-1}$, is proportional to the square of the matrix element, H_{AB}, that describes the electronic coupling between a_5Ru(His48) and the metalloporphyrin. In the nonadiabatic limit ($H_{AB} << k_BT$), the proportionality constant is $(\pi/\hbar 2\lambda RT)^{1/2}$,[18] which gives an H_{AB} of roughly $0.05 cm^{-1}$ for the a_5Ru(His48)Mb(MP) system.

In an analysis of Ru(His33)cyt *c*, plots of ln k_{ET} *vs.* -ΔG° for (a) $^3ZnP^{*} \rightarrow Ru^{3+}$, (b) $Ru^{2+} \rightarrow ZnP^{+}$, and (c) $Ru^{2+} \rightarrow Fe^{3+}$ reactions were fit separately to eq. 8 (Fig. 3).[17] The values of λ range from 1.15 to 1.25 eV, which are slightly smaller than the λ for myoglobin. H_{AB} values are ~0.03 (FeP) and $\sim 0.12 cm^{-1}$ (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).[16,19-21] 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 β values in the 0.8-1.0 $Å^{-1}$ range. It is of interest that the rates of related electron-transfer reactions in a_5Ru(His33)cytochrome *c*[17] and Zn,Fe-hybrid hemoglobin[22] fall near the lines in Fig. 5. It also has been found that the $Ru(bpy)_3^{2+*} \rightarrow Fe^{3+}$ and $Fe^{2+} \rightarrow Ru(bpy)_3^{3+}$ electron-transfer rates in $Ru(bpy)_3$(lysine) derivatives of horse heart cytochrome *c* scale roughly with edge-edge distance.[23]

One notable observation is that $^3ZnP^{*} \rightarrow a_5Ru(His12)^{3+}$ 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.[16,19,20] One possibility is that β is approximately 0.1 $Å^{-1}$ less for a_5Ru(His12)Mb than for the other myoglobin derivatives.[16] However,

the rate of electron transfer from $a_5Ru(His62)^{2+}$ to 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.[24]

Several unusually slow electron-transfer rates at short edge-edge separation distances have been reported for ruthenium-modified proteins.[14,25-28] The most striking examples have come from experiments involving plastocyanins modified with a_5Ru^{3+} at His59.[27,28] The electron-transfer rates in these proteins (k_{ET}<0.3s^{-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).[29] 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 $a_4LRu(His39)$ derivatives (L = NH_3, pyridine, isonicotinamide) of Zn-substituted *Candida krusei* cytochrome *c*[30] and $a_4LRu(His62)$ derivatives (L = NH_3, pyridine) of Zn-substituted *Saccharomyces cerevisiae* cytochrome *c*.[31] Electron-transfer rates are set out in Table 4. The rates of both excited-state electron transfer ($^3ZnP^* \rightarrow Ru^{3+}$) and thermal recombination ($Ru^{2+} \rightarrow ZnP^+$) 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 λ is nearly the same for the electron-transfer reactions in the three proteins (~1.2 eV), the H_{AB} value for Ru(His39)cyt *c* (0.21 cm^{-1}) is almost twice as large as that for Ru(His33)cyt *c* (0.12 cm^{-1}) and over twenty times larger than H_{AB} for Ru(His62)cyt *c* (0.01 cm^{-1}). Since virtually the same donor and acceptor electronic states are found in the three proteins, the differences in H_{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

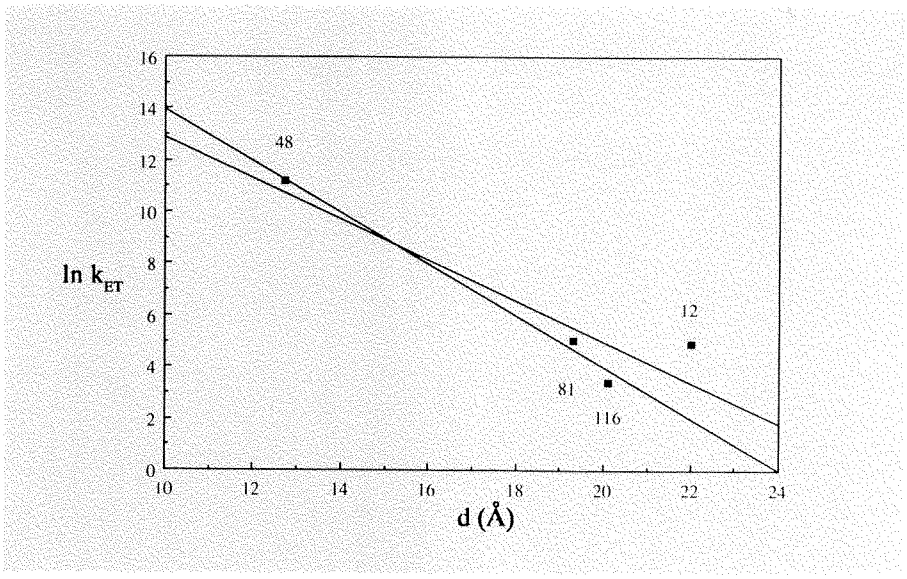

Fig. 5. Ln k_{ET} vs. distance for $^3ZnP^* \rightarrow a_5Ru^{3+}$ ET reactions in ruthenated myoglobin. All four points give β=0.79 Å^{-1}; exclusion of His12 gives β=1.0 Å^{-1}.

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

Ru(His39)cyt *c*[e]	-ΔG° (eV)	k_{ET} (s^{-1})
$a_4(isn)Ru^{2+} \rightarrow ZnP^+$	0.66	6.5 x 10^5
$^3ZnP^* \rightarrow a_5Ru^{3+}$	0.70	1.5 x 10^6
$a_4(py)Ru^{2+} \rightarrow ZnP^+$	0.74	1.5 x 10^6
$^3ZnP^* \rightarrow a_4(py)Ru^{3+}$	0.97	8.9 x 10^6
$a_5Ru^{2+} \rightarrow ZnP^+$	1.01	5.7 x 10^6
$^3ZnP^* \rightarrow a_4(isn)Ru^{3+}$	1.05	1.0 x 10^7
Ru(His62)cyt *c*[f]	**-ΔG° (eV)**	**k_{ET} (s^{-1})**
$^3ZnP^* \rightarrow a_5Ru^{3+}$	0.70	6.5 x 10^3
$a_4(py)Ru^{2+} \rightarrow ZnP^+$	0.74	2.6 x 10^3
$^3ZnP^* \rightarrow a_4(py)Ru^{3+}$	0.97	2.7 x 10^4
$a_5Ru^{2+} \rightarrow ZnP^+$	1.01	2.0 x 10^4

[e] From ref. 30.
[f] From ref. 31.

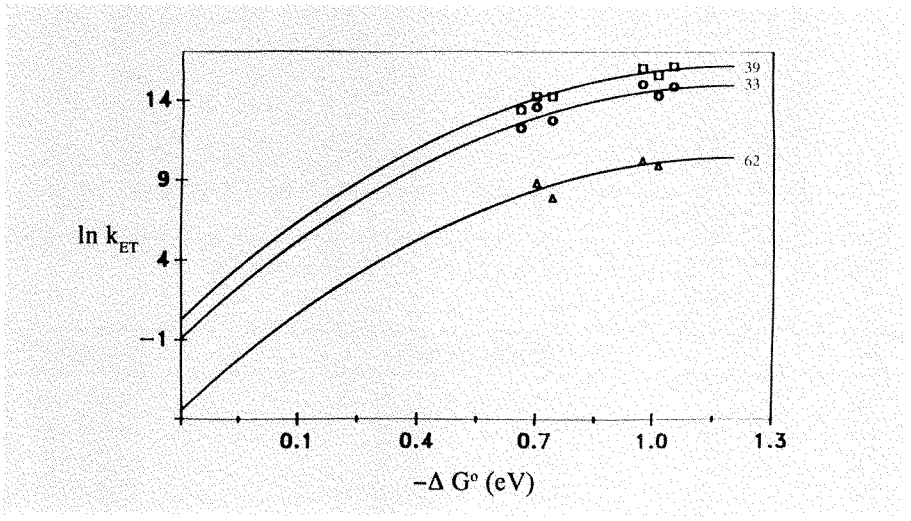

Fig. 6. Plots of ln k_{ET} vs. -ΔG° for Ru(HisX)cytochrome c ET reactions: boxes (X=39); circles (X=33); triangles (X=62).

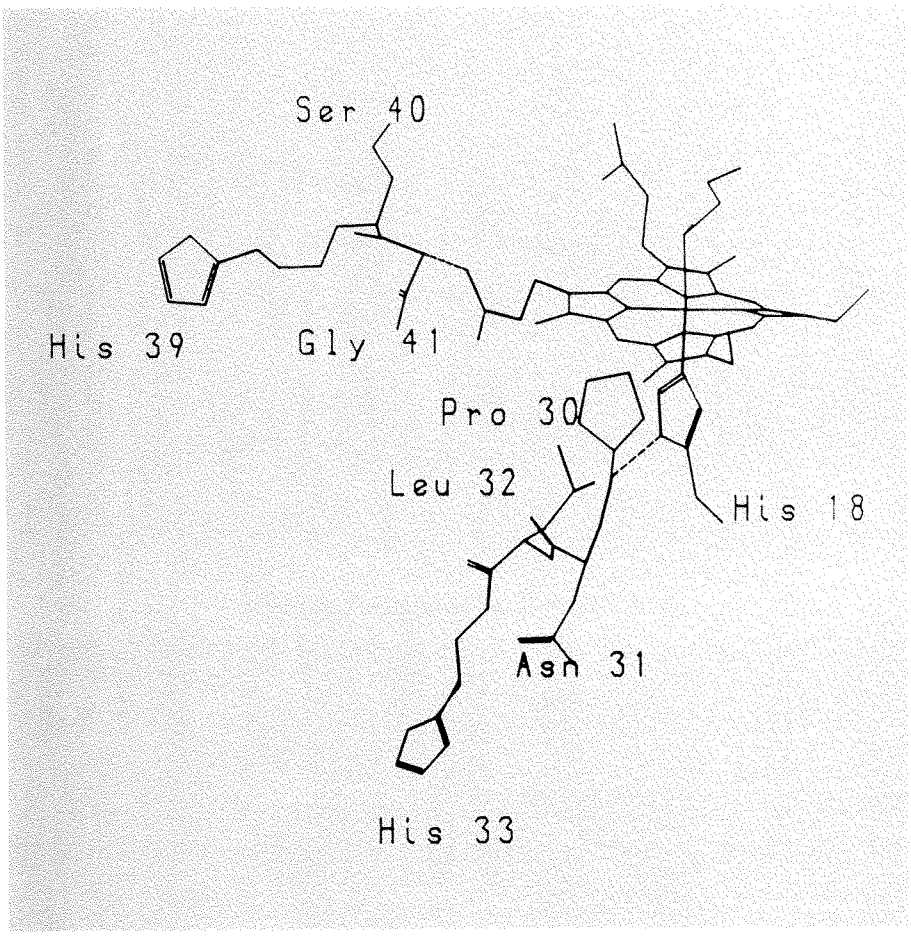

Fig. 7. ET pathways from His33 and His39 (d=13.0 Å) to the heme in cytochrome c.

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

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

$$\varepsilon_S = \sigma_S \bar{\varepsilon}_B exp\,[-\beta_1(R-R_{eq}^{B})] \quad \text{(eq. 12)}$$

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*.[30,31] 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 λ can be greater than that of H_{AB}.[32] Dielectric continuum models of solvent reorganization predict that λ_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.[33] Modeling the Ru-Zn-cyt *c* systems as single spheres suggests, however, that variations in λ_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).[31]

Winkler has examined the maximum variation in λ_0 predicted by the single-sphere continuum model.[31,34] 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 λ_0 for electron transfer between the two metals is calculated by treating the solvent as a dielectric continuum. The magnitude of λ_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 λ (±0.1 eV). The invariance of λ 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.[35-40] Several investigators have begun to examine potential electron-tunneling pathways in proteins.[41-47] Interestingly, the through-peptide routes generally involve so many bonds that they cannot possibly account for the observed rates.[16,17] 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.[41] 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 (ε_B = 0.6). Ionic contacts (H-bonds and salt bridges) and through-space jumps decrease H_{AB} by somewhat larger factors (ε_H is the H-bond coupling; ε_S is the through-space coupling). The decay factors are described in eq. 10-12. The β's specify the distance dependence of the interactions, and the σ's give their orientation dependences. A computer program has been written employing these interactions to search for electron-tunneling pathways through proteins.[46] In its simplest version, the parameters are as follows: $\varepsilon_B = \bar{\varepsilon}_B$, $\sigma_H = 1.0$, $\sigma_S = 1.0$, $\beta_0 = \beta_1 = \beta_2 = 1.7$ Å^{-1}, and 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 carboxyl oxygen 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 α-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.[43-45] All three calculations show that the electron-transfer rate constant decreases with distance roughly as predicted by eq. 9, with β values from theory (~0.8 $Å^{-1}$) 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 [~200 for Ru(His48)Mb] than for any protein studied to date.[46]

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 π-π superexchange model might be stronger in the $Ru^{2+} \rightarrow ZnP^{+}$ direction than for $^{3}ZnP^{*} \rightarrow Ru^{3+}$ 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 σ-hole tunneling as the dominant mechanism for long-range interactions.[48]

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

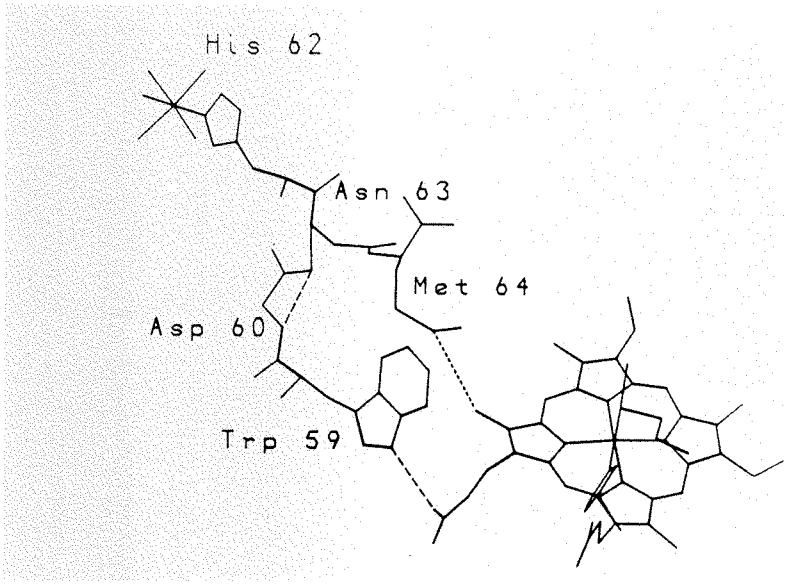

Fig. 8. ET pathways for Ru(His62)cyt c (d=15.6 Å).

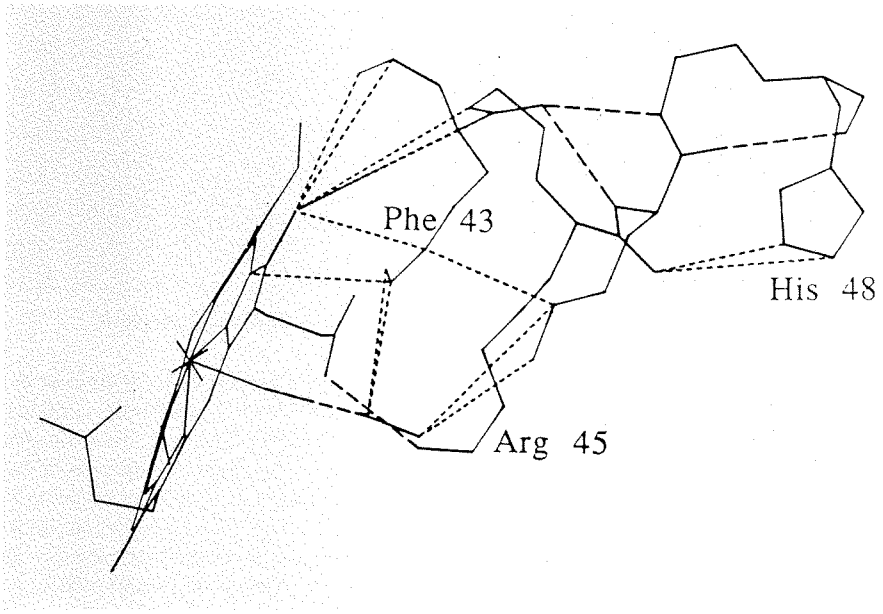

Fig. 9. ET pathways for Ru(His48)Mb.

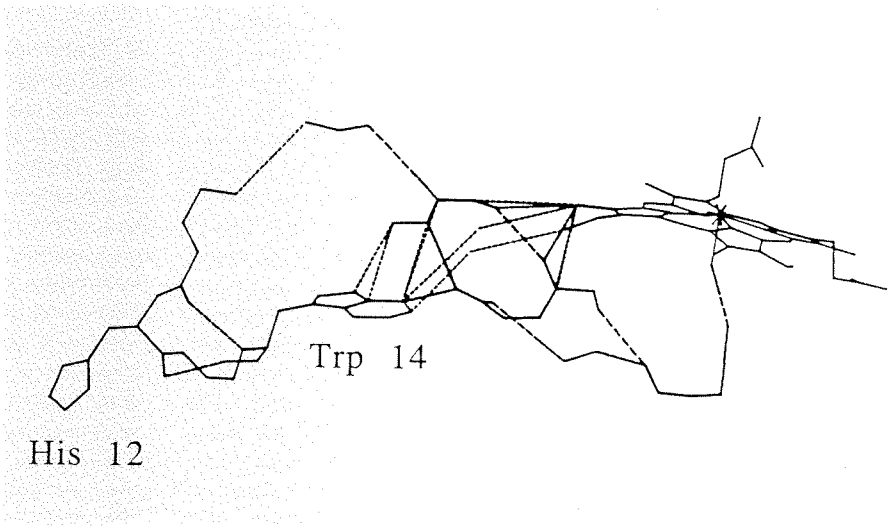

Fig. 10. ET pathways for Ru(His12)Mb.

cal[43,45] and experimental[19,20] evidence for electron-transfer rate enhancement by an intervening aromatic group. In the His12-modified protein, the important pathways involve residues in two α-helices linked through space by Trp14 or Leu76(Fig. 10).[46] In the σ-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.[46] 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.

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About the Author:

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

Clayton H. Heathcock
Department of Chemistry
University of California
Berkeley, CA 94720

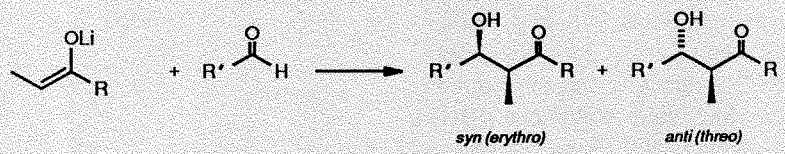
"Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations..."[1]

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 ^{13}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.[2] 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, Caesare Gennari, Manfred Braun and Ian Paterson.

The reaction between a prochiral enolate and an aldehyde can give two diastereomeric β-hydroxy ketones, sometimes referred to as *syn* (*erythro*) and *anti* (*threo*) (Scheme 1).[3] 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.[4] This relationship was capitalized upon by the creation of several reagents that can be used to prepare *syn* or *anti* α-alkyl-β-hydroxy carboxylic acids. The useful α-trimethylsilyloxy ketone **1** (Buse's reagent)[5] and β,γ-unsaturated ketone **2** (Mori's reagent)[6] 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* α-alkyl-β-hydroxy carboxylic acids;[7] those derived from ketone **2** are reduced and the resulting homoallylic alcohols cleaved with lead tetraacetate to acquire α-alkyl-β-hydroxy carboxaldehydes.

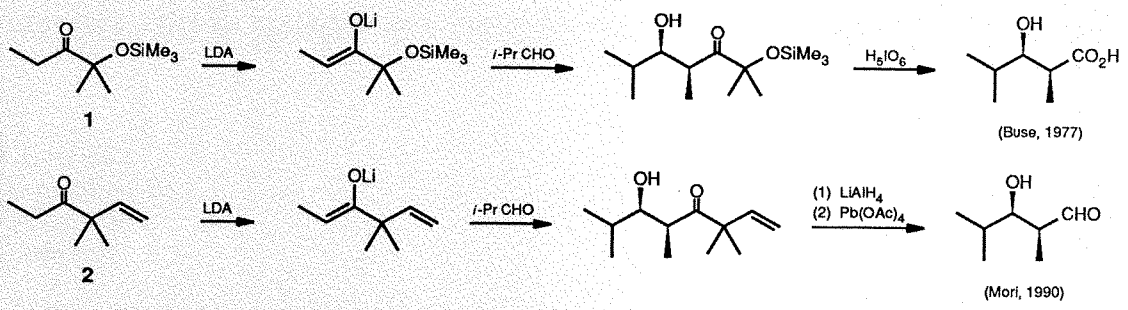
On the other hand, esters tend to give *E* enolates upon deprotonation with LDA

Scheme 1

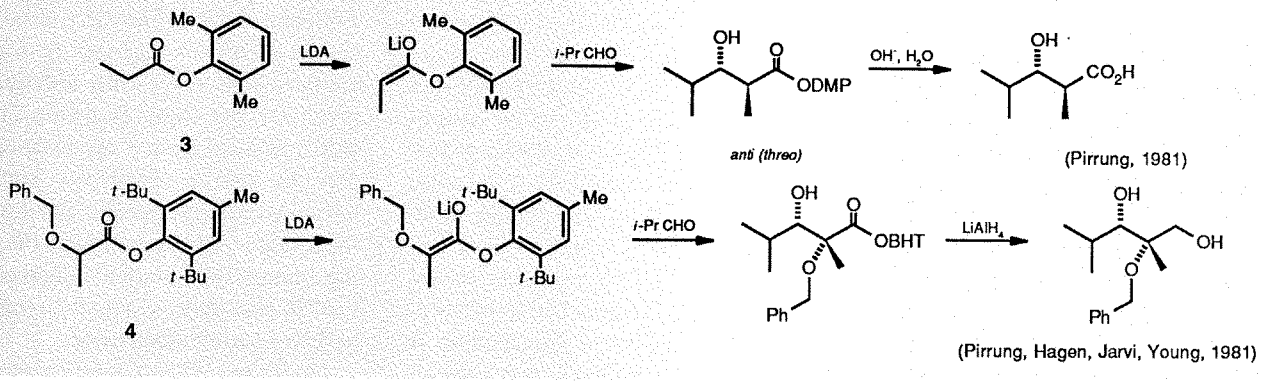


Professor Clayton H. Heathcock (right) receiving the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry from Dr. Alfred Bader.

Scheme 2

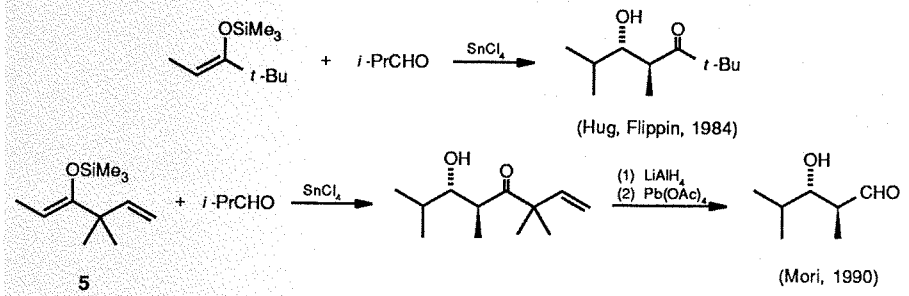


Scheme 3



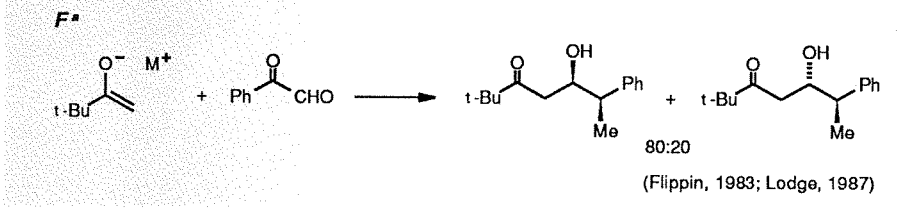
and other lithium amide bases, but the enolates of normal alkyl esters show essentially no simple stereoselection in their aldol reactions. However, the *E* enolates derived from esters of 2,6-dimethylphenol (DMP), 4-methyl-2,6-di-*tert*-butylphenol ('butylated hydroxytoluene', BHT), and 4-methoxy-2,6-di-*tert*-butylphenol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

Scheme 4



Scheme 5

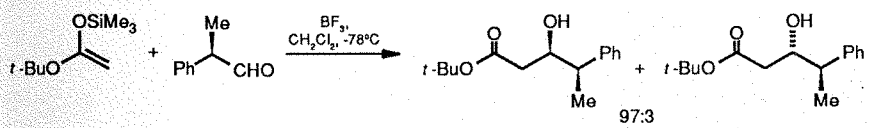
Facial Diastereoselectivity (One Reactant Chiral)



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,[11] those derived from *tert*-alkyl ketones do give *anti* α-alkyl-β-hydroxy ketones with good stereoselectivity (Scheme 4).[12] Compound **5**, prepared from the Mori reagent, **2**, provides a useful complement to the corresponding *syn*-selective lithium enolate.[13]

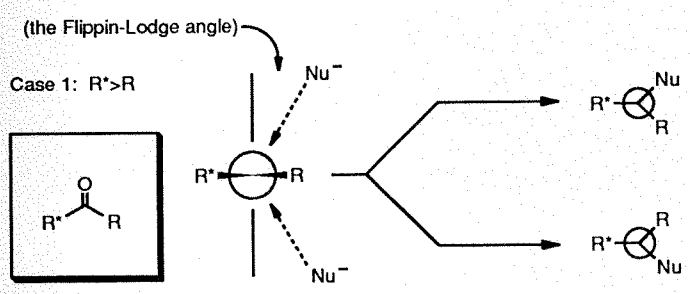
When one of the two reaction partners in an aldol reaction is chiral, there exists the possibility of a fundamentally different kind of stereoselection. In this instance, the two faces of the carbonyl acceptor or enolate donor are diastereotopic, and there exist two

Scheme 6



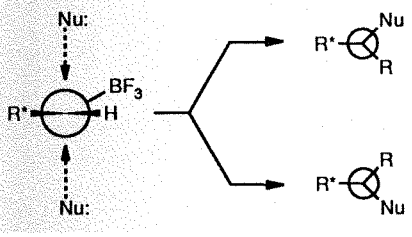
(Flippin, 1983)

Scheme 7



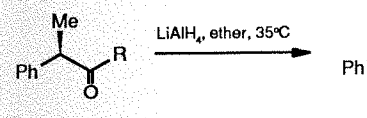
(Flippin, 1983; Lodge, 1987)

Scheme 8

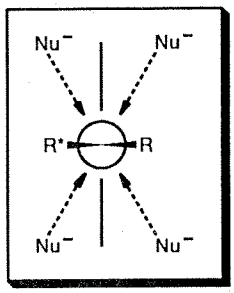


diastereomeric transition states (Scheme 5). For additions of lithium enolates to chiral aldehydes in which the stereogenic center is adjacent to the carbonyl group, the intrinsic diastereofacial preference (F^a) is usually relatively low—on the order of 2:1 to 6:1.[14]

Scheme 9



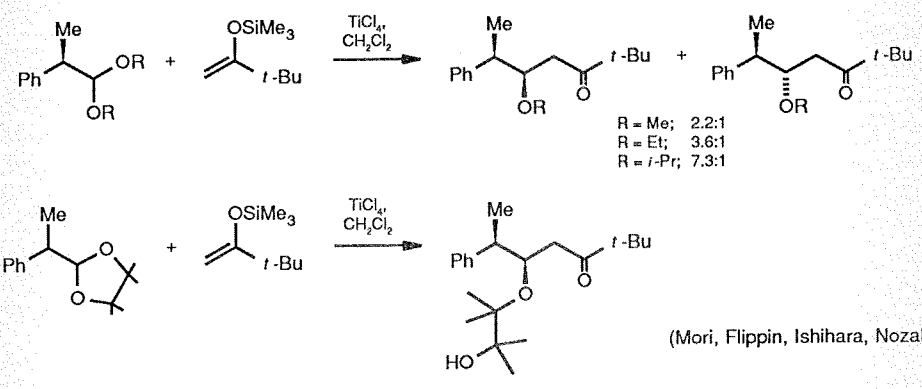
R	Diastereoselectivity
Me	3:1
Et	3:1
i-Pr	5:1
t-Bu	50:1

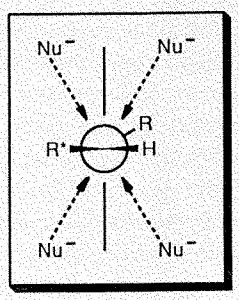


(Cherest, Felkin, Prudent, 1968)

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,[15] we found that the 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).[16] The theory that was advanced to explain the extraordinary diastereofacial preferences of 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.[17] Thus, the bulky 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

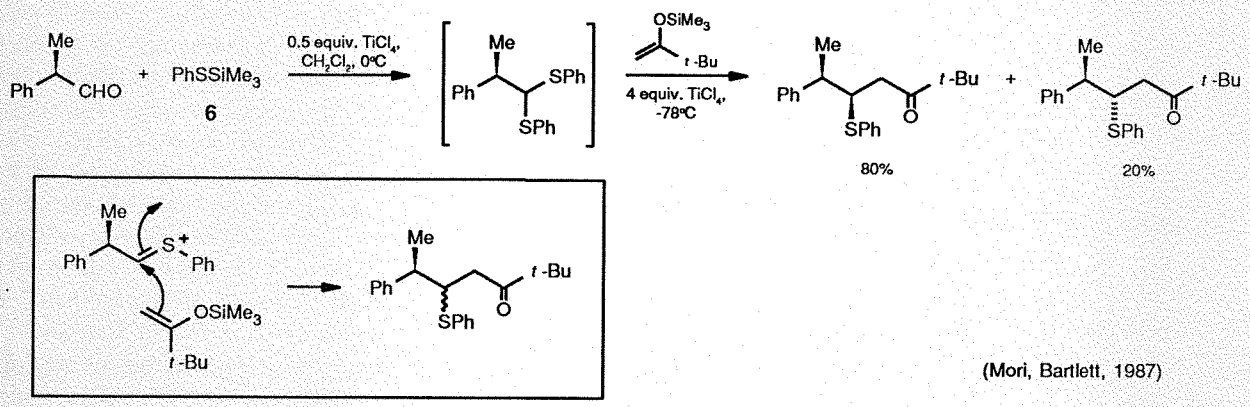
Scheme 10





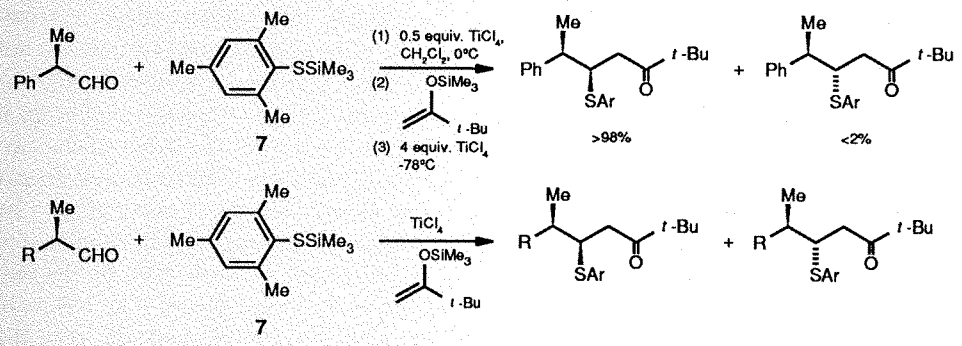
(Mori, Flippin, Ishihara, Nozaki, Yamamoto, Bartlett, 1990)

Scheme 11



(Mori, Bartlett, 1987)

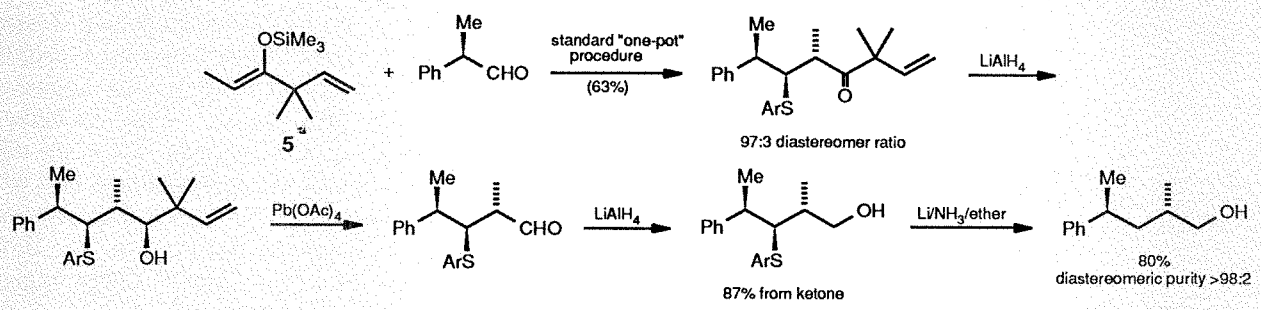
Scheme 12



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

(Mori, Bartlett, 1987)

Scheme 13



(Mori, Bartlett, 1990)

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).[18] 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.[19]

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 β-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 β-mesitylthio ketone is obtained from 2-phenylpropanal (Scheme 12).[20] 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.[21]

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).[22] In 1979, we prepared and investigated the reactions of a chiral version of reagent **1**.[23] 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).[24]

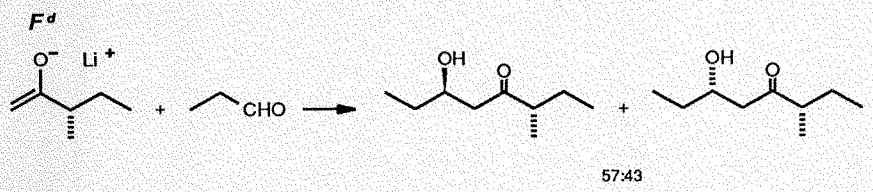
It is noteworthy that the *Z* lithium enolate of **8** and the *Z* boron enolate of **9** have opposite diastereofacial preferences. A rationale for this fascinating difference is presented in Scheme 17.[25] It was suggested that the lithium cation can simultaneously coordinate three oxygens in the transition 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.[26] A convenient synthesis is summarized in Scheme 19. Diazotization of *tert*-butylglycine gives α-hydroxy acid **10**.[27] 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

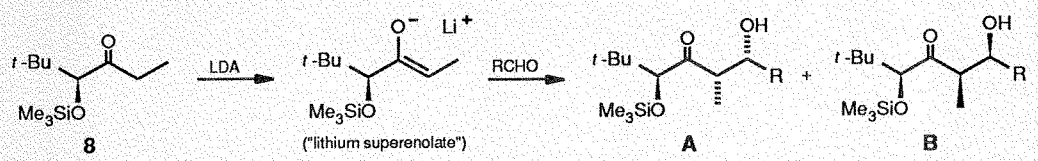
Scheme 14

Facial Diastereoselectivity (One Reactant Chiral)



(Seebach and co-workers, 1976)

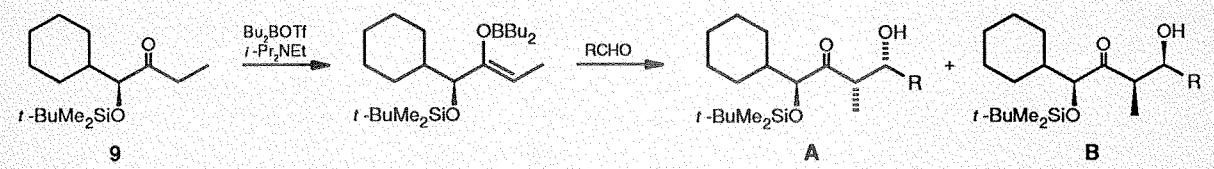
Scheme 15



R	% A	% B
Ph	75	25
t-Bu	>95	<5
i-Pr	75	25
$PhCH_2$	87	13
Ph_2CH	>90	<10

(Buse, Pirrung, Sohn, Hagen, Young, 1979)

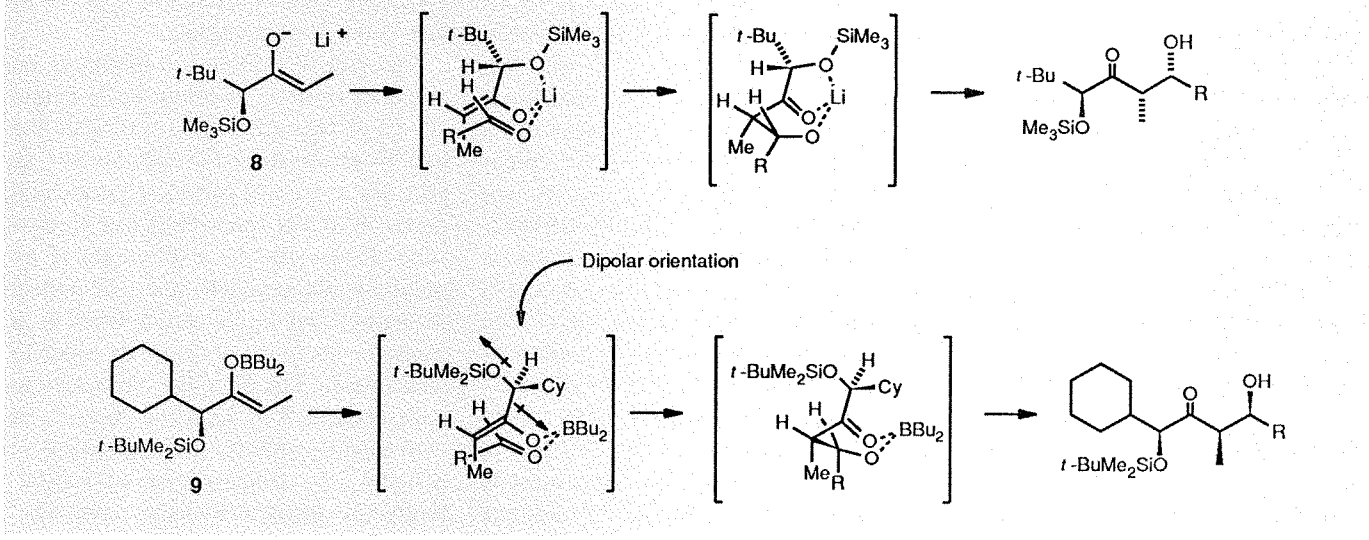
Scheme 16



R	% A	% B
Ph	2.5	97.5
i-Pr	<1	>99
Et	2	98
$PhCH_2OCH_2CH_2$	4	96

(Masamune and co-workers, 1981)

Scheme 17

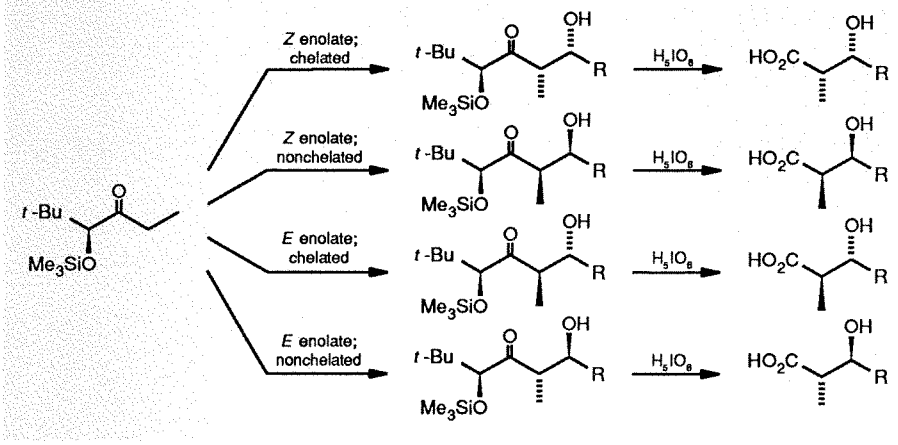


after an additional 8 min. the reaction is quenched. This optimized procedure gives aldols in 75-80% yield. With isobutyraldehyde, pivalaldehyde and benzaldehyde, the stereoselectivity is >95:5.[28] With 3-benzyloxypropanal, the stereoselectivity is 95:5. The relative configuration of the major aldol from benzaldehyde was ascertained by single-crystal X-ray analysis of the keto diol obtained by hydrolysis of its racemic counterpart.[29] Scheme 21 shows the comparable reactions of the *Z* boron enolate of (-)-**8**, prepared in the conventional manner.[30] 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.

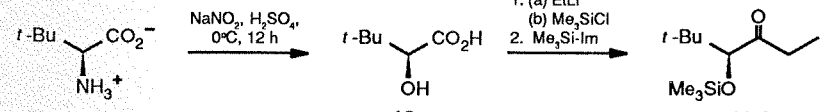
The *E* magnesium enolate of (-)-**8**, obtained by adding the ketone to a solution of *N*-bromomagnesium-2,2,6,6-tetramethylpiperidine (MTMP) in THF at -5°C, reacts with trimethylsilyl chloride to give the *E* silyl enol ether (Scheme 22).[31] A possible rationale for the unique ability of this base 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.***

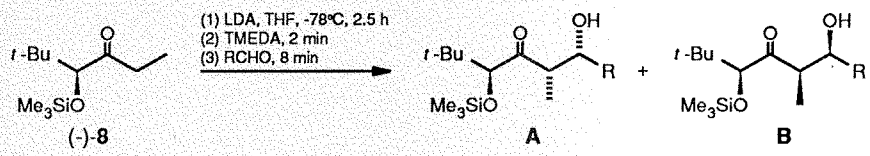


Scheme 19



(Van Draanen, Arseniyadis, 1990)

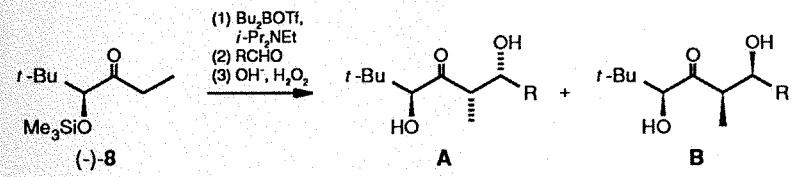
Scheme 20



R	Yield, %	A:B
Ph	80	>95:5
i-Pr	80	>95:5
t-Bu	75	>95:5
$PhCH_2OCH_2CH_2$	80	95:5

(Van Draanen, 1990)

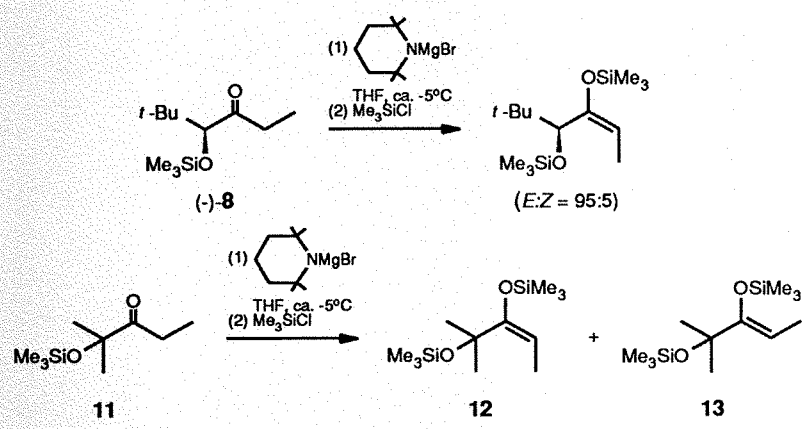
Scheme 21



(Van Draanen, 1990)

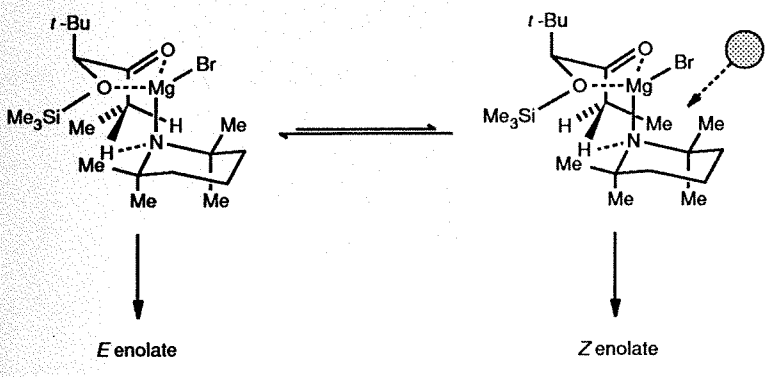
R	Yield, %	A:B
Ph	80	<5:95
i-Pr	85	<5:95
t-Bu	85	<5:95
$PhCH_2OCH_2CH_2$	88	<5:95

Scheme 22

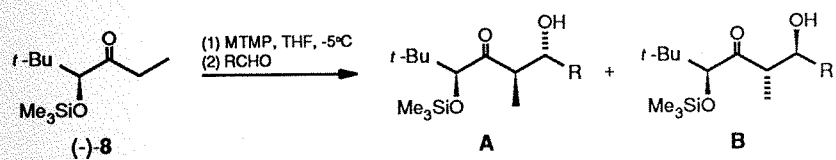


(Arseniyadis, 1985; Van Draanen, 1990)

Scheme 23



Scheme 24



R	Yield, %	A:B
Ph	80	95:5
i-Pr	80	92:8
t-Bu	75	95:5

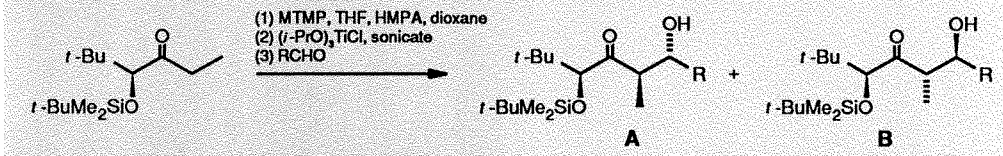
(Arseniyadis, 1985; Van Draanen, 1990)

by the fact that MTMP also deprotonates ketone **11**[32] 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[33] 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 $(i\text{-PrO})_3TiCl$ for enolate exchange was adapted from the work of Siegel and Thornton, who performed a similar exchange with a lithium enolate.[34] 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

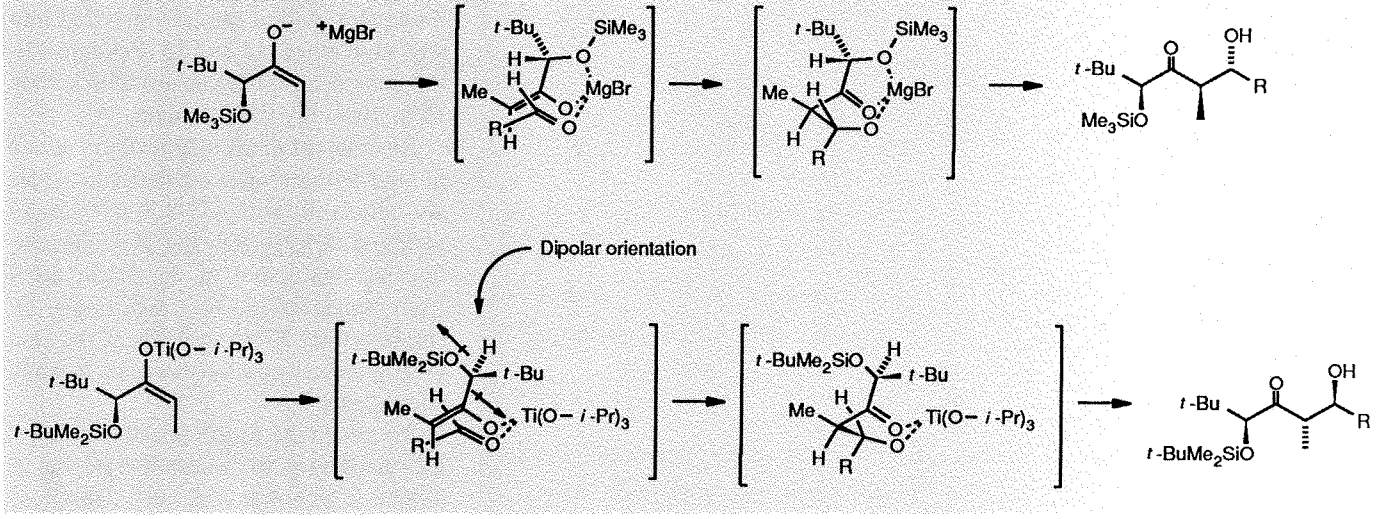
Scheme 25



R	Yield, %	A:B
Me	88	<5:95
i-Pr	88	<5:95
t-Bu	85	<5:95
Ph	80	20:80

(Van Draanen, 1990)

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.

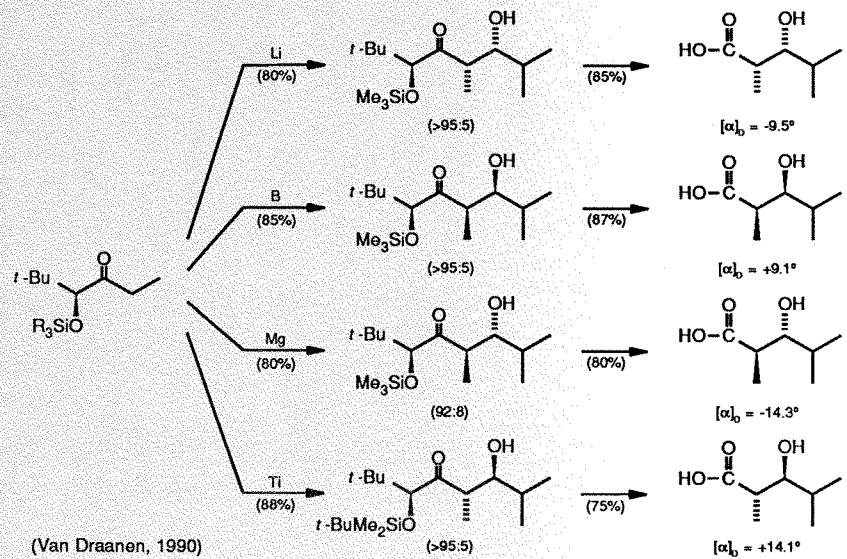
The aldols produced from (-)-**8** and its *tert*-butyldimethylsilyl analog in the foregoing manner can be cleaved with periodic acid to obtain scalemic α-methyl-β-hydroxy carboxylic acids. The products obtained from isobutyraldehyde are depicted in Scheme 27, thus demonstrating the ability to synthesize all four of the possible stereoisomers of a given α-alkyl-β-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.[35] Chiral imides such as **14** have very high diastereofacial preferences in their reactions with aldehydes. Hydrolysis of the resulting *syn* aldol provides the α-alkyl-β-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

Scheme 27

Summary:

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



(Van Draanen, 1990)

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.

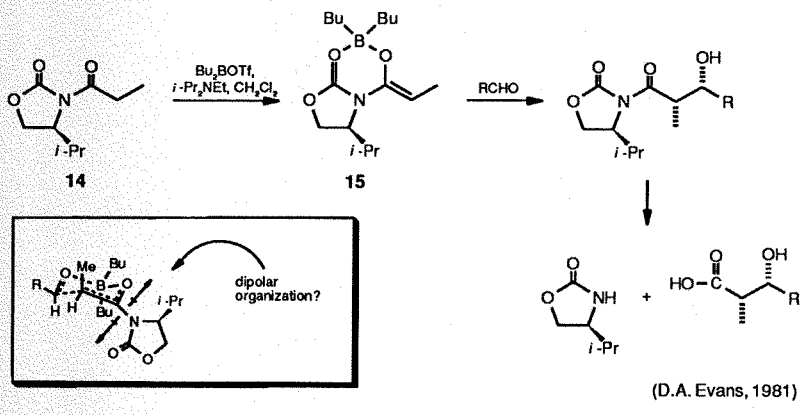
In connection with a total synthesis project, we had occasion to use the Evans reaction with a series of β-(arylthio)-acroleins. To our surprise, we obtained mainly the *anti* aldols, as shown in Scheme 29.[36] The cause of the unexpected behavior was soon traced to an error in measurement; because of 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 ^{11}B NMR spectrometry 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

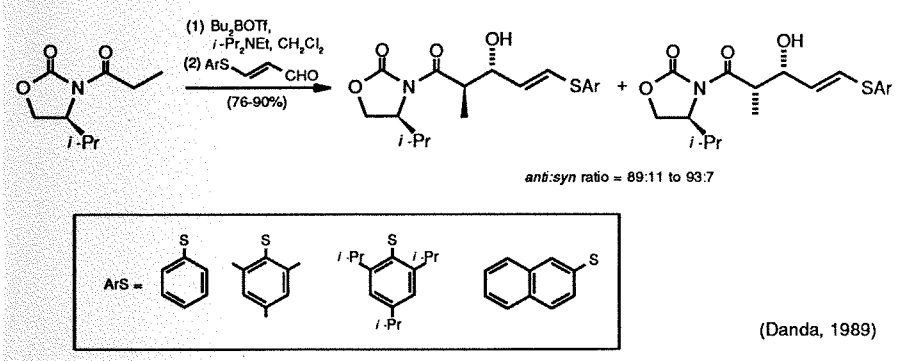
Scheme 28

The Evans Asymmetric Aldol Reaction



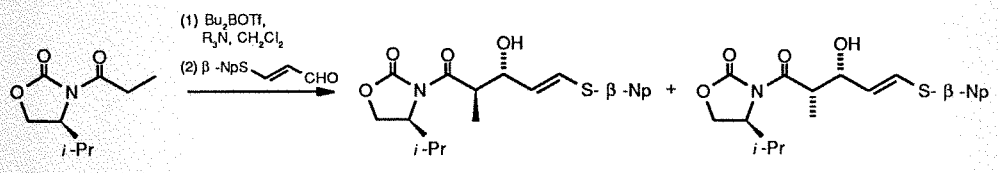
(D.A. Evans, 1981)

Scheme 29



(Danda, 1989)

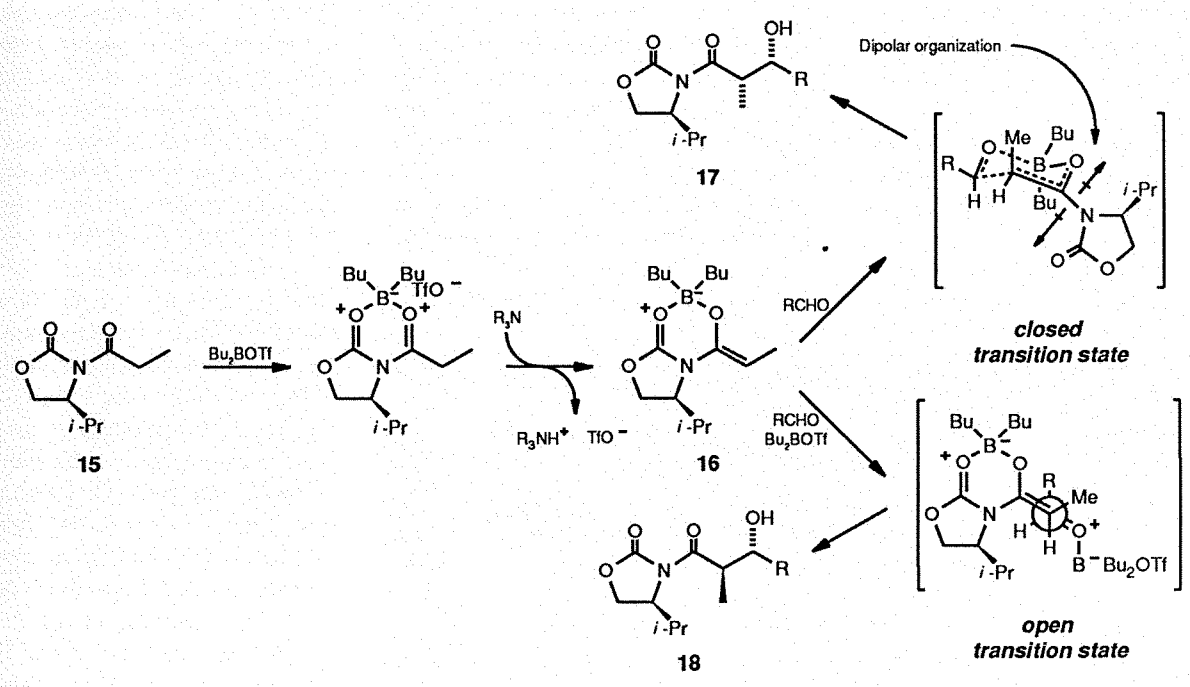
Scheme 30



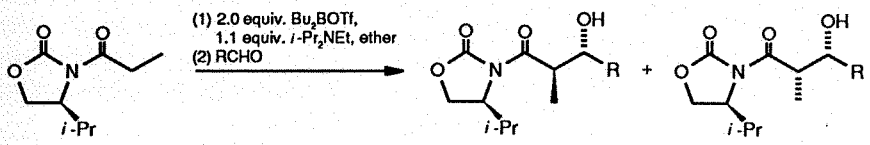
(Danda, Hansen, 1990)

Conditions	*anti:syn*
2.0 equiv. Bu$_2$BOTf, 2.2 equiv. *i*-Pr$_2$NEt	95:5
1.5 equiv. Bu$_2$BOTf, 2.0 equiv. *i*-Pr$_2$NEt	77:23
1.1 equiv. Bu$_2$BOTf, 1.3 equiv. *i*-Pr$_2$NEt	<2:98

Scheme 31



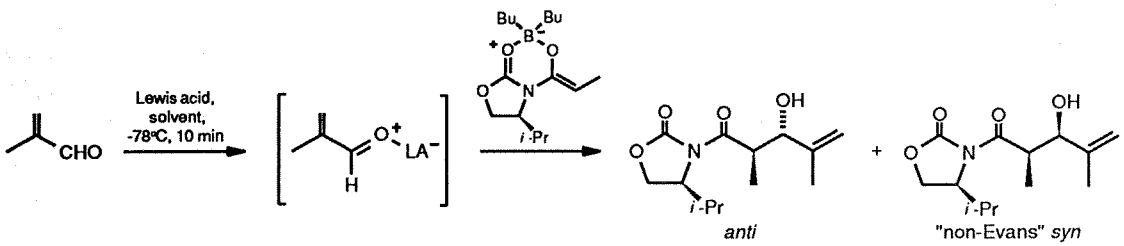
Scheme 32



Aldehyde	*anti:syn*
CHO	<2:98
CHO	<2:98
CHO	80:20
CHO	75:25

(Danda, 1990)

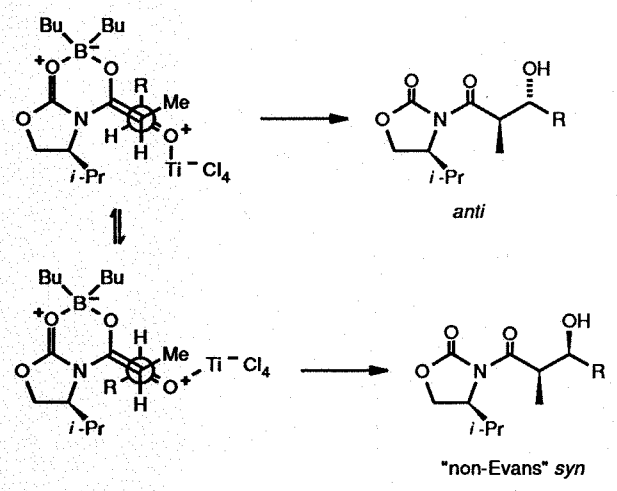
Scheme 33



Lewis Acid (LA)	Solvent	*syn:anti*	% Yield
BCl_3	ether	54:46	100
$B(OTf)_3$	CH_2Cl_2	32:68	90
$TiCl_4$	CH_2Cl_2	82:18	60
$TiCl_4$	ether	74:26	84

(Walker, 1990)

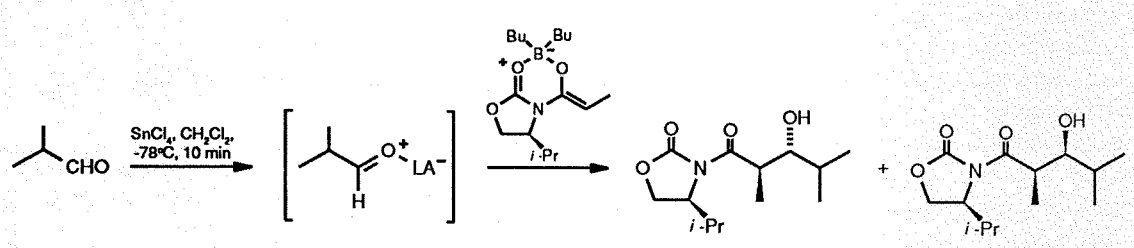
Scheme 34



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-

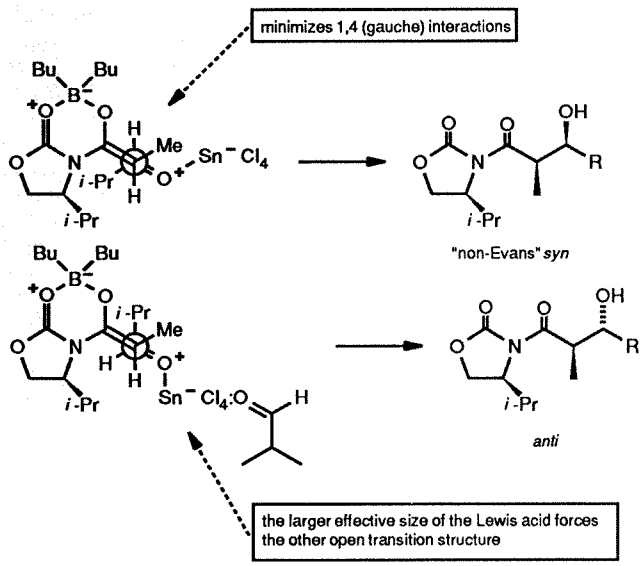
Scheme 35



Equiv. $SnCl_4$	*syn:anti*	% Yield
2.0	83:17	60
1.5	70:30	61
1.0	30:70	77
0.75	14:86	50
0.5	5:95	51
0.375	15:85	45

(Walker, 1990)

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 $SnCl_4$ 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 $SnCl_4$ 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.

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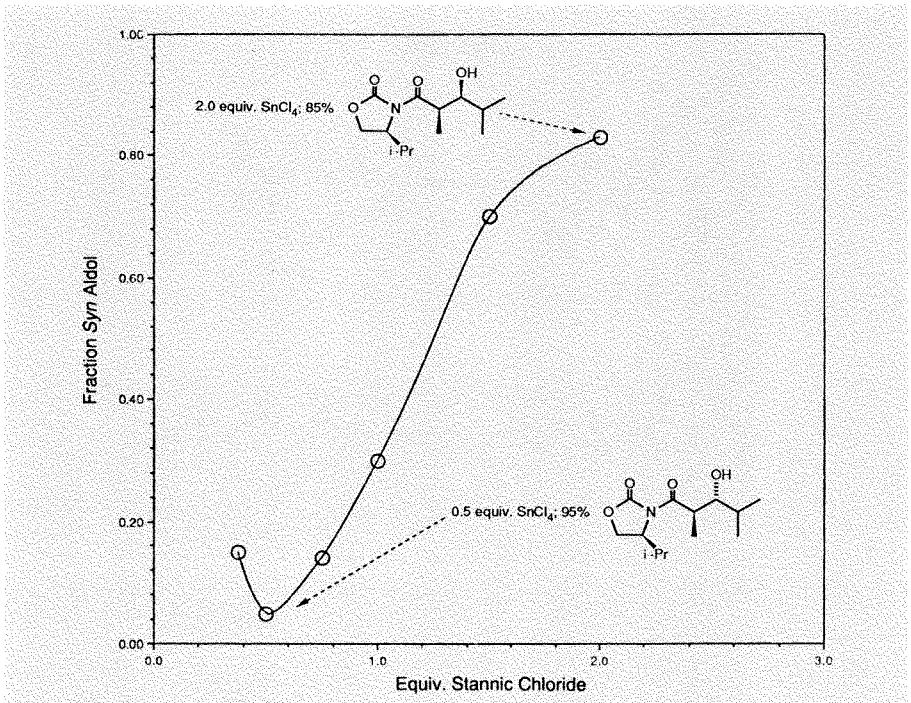

Fig. 1 - Fraction syn as a function of equivalents of Lewis acid.

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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).