

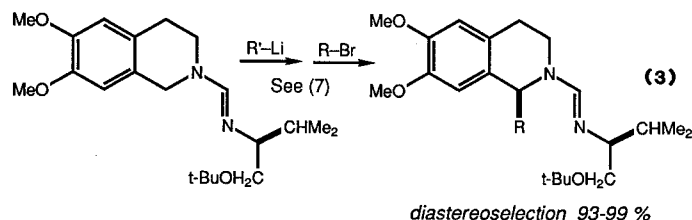
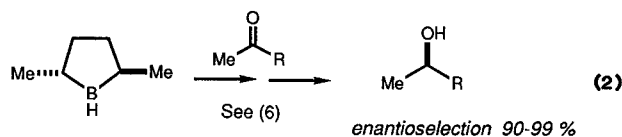
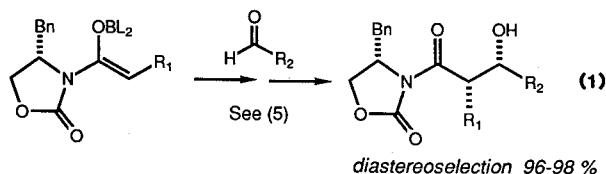
Stereoselective Organic Reactions: Catalysts for Carbonyl Addition Processes

DAVID A. EVANS

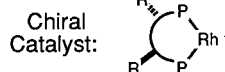
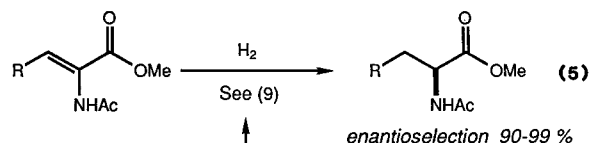
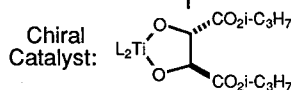
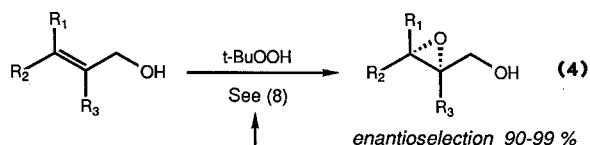
Important advances are being made in the development of stereoselective organic reactions. Some of the emerging research directions that hold forth great promise in this area deal with the development of chiral catalysts for these processes. This review attempts to unify one aspect of this field, the development of catalysts and catalyst models for the enantioselective addition of hydride and carbon nucleophiles to carbonyl substrates. Mechanistic constructs for the stereodifferentiating transition states are provided.

OVER THE LAST 8 YEARS THERE HAS BEEN A VIRTUAL explosion in the discovery of organic reactions that deliver levels of stereocontrol once thought to be impossible to achieve via nonenzymatic means (1-4). These new tools have dramatically redefined the way absolute stereochemical issues in organic synthesis are being addressed both in academic and industrial environments. A multitude of chiral reagents and an increasing number of catalysts now exist that are capable of exercising nearly perfect control over those bond constructions where new stereochemical relations are established. Several examples of reactions falling into each category are illustrated below (Eqs. 1 through 5; abbreviations: Bn, benzyl; L, ligand; R_i, some alkyl or silicon group; Me, methyl; t-Bu, *tert*-butyl; and Ac, acetyl) (5-9).

Stoichiometric asymmetric induction



Catalytic asymmetric induction

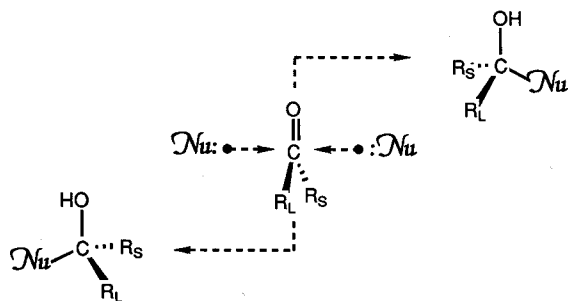


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In these reactions, defined stereochemical relations can be dictated by either stoichiometric or catalytic asymmetric induction through proper selection of the absolute stereochemical relations in either the "chiral auxiliary" (Eqs. 1 to 3) or the chiral catalyst (Eqs. 4 and 5). Such reactions, whether designed by keen insight or discovered by serendipity, have provided a new dimension to the art and science of molecule building. With this background, one might ask what steps are currently being taken to "invent" the next generation of stereoselective organic reactions. In addressing this topic, an agenda of important, but as yet unattained, objectives in reaction design would be desirable. In this article the progress currently being made in reaction design is assessed for one such process, enantioselective carbonyl addition.

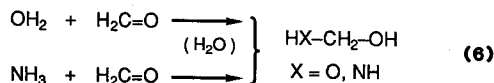
Enantioselective Carbonyl Addition Reactions

It would be a major accomplishment to be able to dictate the direction of attack of any given nucleophile (Nu) to a predefined carbonyl enantioface exclusively through the agency of a chiral catalyst.

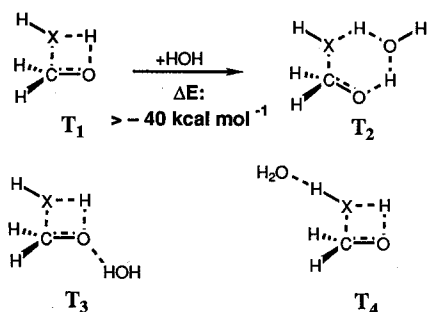


A prerequisite to the development of a rational solution to this problem is a set of reasonable mechanistic postulates for the carbonyl addition process. Unfortunately, the general level of understanding in this area of mechanism is still rather primitive when compared to the wealth of knowledge that exists for numerous other families of reactions.

Recently, a series of theoretical papers has evaluated the addition of both water and ammonia to formaldehyde (Eq. 6) (10). Ab initio calculations convincingly demonstrate the catalytic role that water could play in both processes.

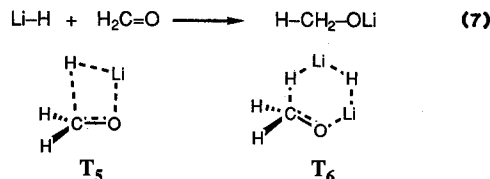


In the addition of both of these nucleophiles to formaldehyde, the four-centered transition structure T_1 was calculated to be >40 kcal mol⁻¹ less stable (ΔE , activation energy) than the six-centered transition structure T_2 , in which the ancillary water molecule serves



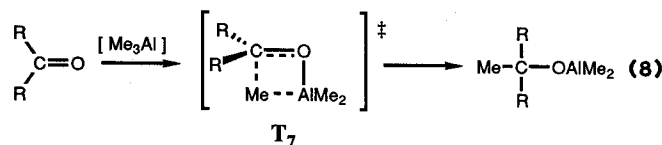
as a bifunctional catalyst by providing both a hydrogen-bond donor and acceptor to stabilize the transition state in the addition process. On the other hand, for the hydration reaction ($X = \text{O}$), transition structures T_3 and T_4 were only moderately stabilized relative to the T_1 reference. This theoretical study thus provides reasonable support for the preferential intervention of six- rather than four-centered transition states in the carbonyl addition process.

In one other recent theoretical study, the reaction of lithium hydride with formaldehyde (Eq. 7) was analyzed at the restricted self-consistent field (SCF) level by using the 3-21G basis set (11). Unfortunately, although the transition structure T_5 was evaluated, the relative stabilities of those transition structures comprised of both one and two Li-H molecules, for example, T_5 and T_6 , were not compared.

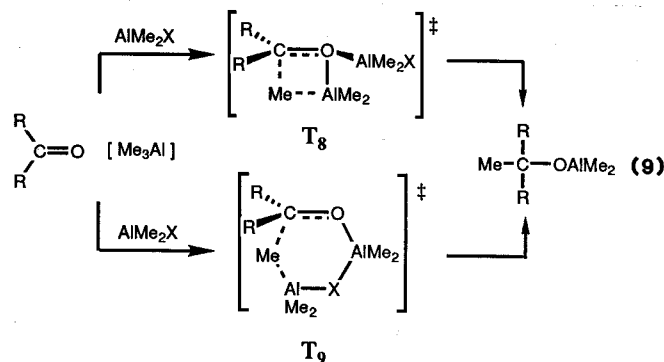


What sort of mechanistic information is available on the addition of organometallic reagents to carbonyl substrates? Again, little of a definitive nature has been documented in this area (12). The addition of trimethylaluminum to ketones is probably one of the most carefully studied reactions to date (13-15). The available evidence strongly suggests that there are two distinct mechanistic options (Eqs. 8 and 9), the choice of which depends on reactant stoichiometry. For example, at a 1:1 stoichiometry in benzene, trimethylaluminum undergoes addition via an apparent four-center transition state T_7 , whereas at higher ratios of organometallic reagent to ketone, a more facile reaction ensues that is second order in aluminum reagent. This process presumably proceeds through either the catalyzed four-center transition state T_8 , as originally suggested by Mole and co-workers (16), or the alternate bimetallic six-centered transition state T_9 ($X = \text{Me}$), which has been favored by a number of other investigators (17). A comparison of these proposed transition states with the analogous structures calculated for formaldehyde hydration and amination (T_2 and T_3) reveals a strong structural homology for the two sets of catalyzed processes and provides added circumstantial evidence to support the contention that T_9 is the more stable of the two catalyzed transition structures.

The uncatalyzed process

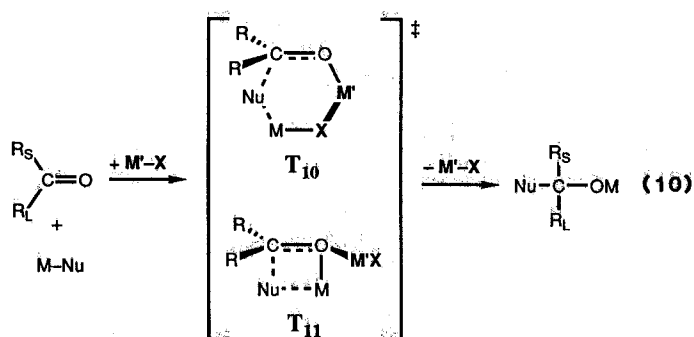


The catalyzed variant



Catalysis by Lewis acids such as ZnX_2 and MgX_2 has also been reported for the carbonyl addition reactions of dialkylzinc reagents; however, these studies have been fragmentary in nature (18). Nonetheless, transition states analogous to either T_8 or T_9 might be a reasonable model upon which to design a chiral catalyst for this reaction (vide infra). Finally, it has been documented that the intervention of a catalyzed process in the chiral borane reduction illustrated in Eq. 2 is essential for high levels of asymmetric induction (6, 19). In this instance, both ab initio and MM2 calculations support a catalyzed four-center transition state analogous to T_8 .

Based upon the evidence presented in the preceding discussion, it appears reasonable that chiral catalysts $M'-X$ for carbonyl addition reactions might be designed on the basis of either of the general transition state geometries T_{10} or T_{11} illustrated below (Eq. 10). In both transition structures the catalyst constituent M' must participate in carbonyl polarization, whereas the associated ligand X might be assigned to carry the stereochemical information to be relayed during the course of the reaction. In the six-membered transition structure T_{10} , this ligand must also function as a Lewis base to facilitate delivery of the metal nucleophile. On the other hand, no such requirement need be demanded of X in the alternative transition structure T_{11} .

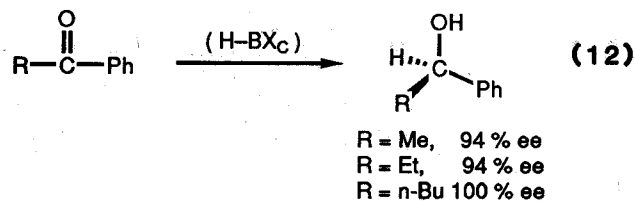
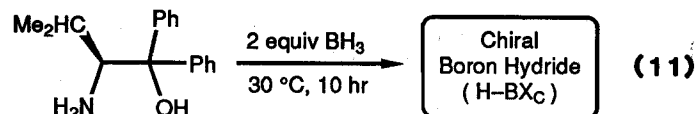


In the ensuing discussion, recent advances in the development of chiral catalysts for carbonyl addition will be presented and evaluated in terms of these mechanistic constructs.

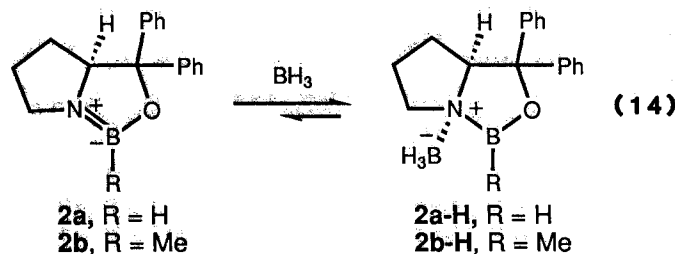
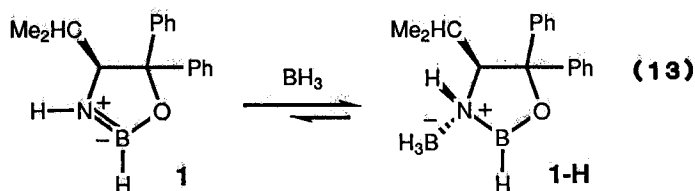
Enantioselective Ketone Reduction

Over the last decade a large body of information has accumulated on the synthesis of a diverse array of chiral metal hydride reagents that have been developed for the enantioselective reduction of ketones (20). In almost every instance, the reported chiral hydride has not been well characterized structurally either in the solid state or in solution. The lack of rigor in this area has been pointedly criticized by J. D. Morrison in a recent review on chiral aluminum hydride reagents (21).

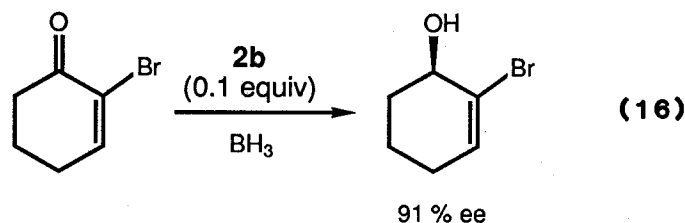
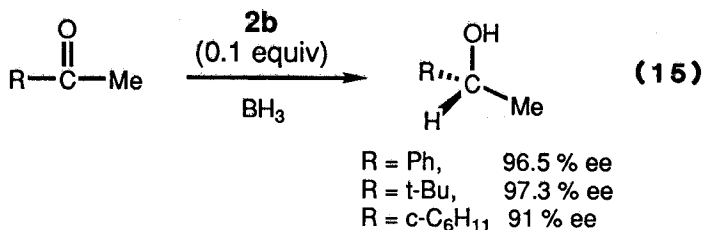
One of the most interesting "recipes" for the production of a highly effective chiral boron hydride reagent has been reported in a series of papers by Itsuno and co-workers (22). His boron hydride preparation and several representative reductions are summarized below (abbreviations: Ph, phenyl; Et, ethyl; n-Bu, *n*-butyl; and ee, enantiomeric excess). Even more striking was the observation that, if the amino alcohol-borane complex were isolated, it could function as a chiral catalyst in the enantioselective reduction of acetophenone *O*-benzyl oxime (95% ee) in the presence of borane in tetrahydrofuran (THF) (23). Coincident publications by Corey and co-workers have not only revealed the structure of this catalyst **1**, but have also reported improved catalyst variants **2a** and **2b**, as well as provided a mechanistic rationale for



the overall process (24). These catalysts, which may be isolated as crystalline solids, as well as the associated borane adducts, are illustrated below.



Several representative enantioselective reductions that use the chiral catalyst **2b** (10 mole percent) and borane in THF at temperatures ranging from ambient to -10°C provide evidence as to the effectiveness of this chiral reducing system (Eqs. 15 and 16). Corey proposed that these catalysts effect reduction through a six-centered transition state analogous to T_{10} ($M' = B$, $X = N$) uniting both reducing agent and carbonyl substrate in a termolecular complex. The presumed geometry of the acetophenone complex that leads to



the observed sense of asymmetric induction in this reaction is illustrated in Fig. 1 (25).

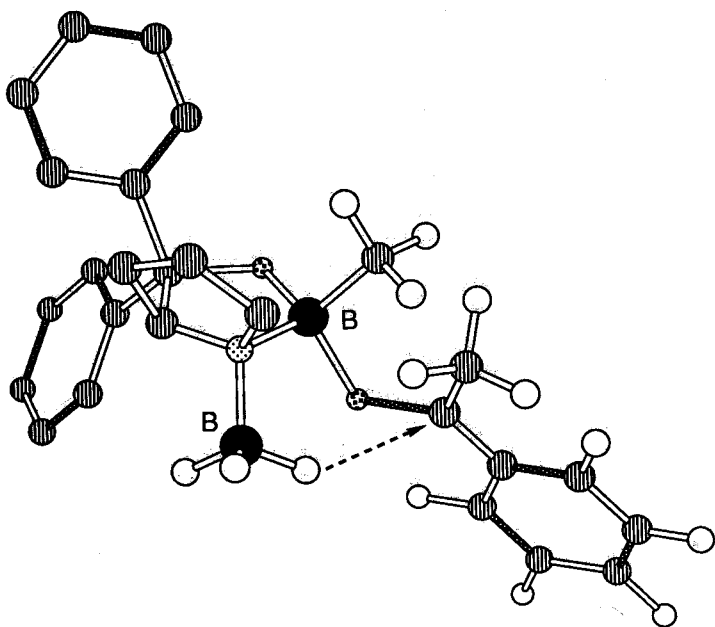
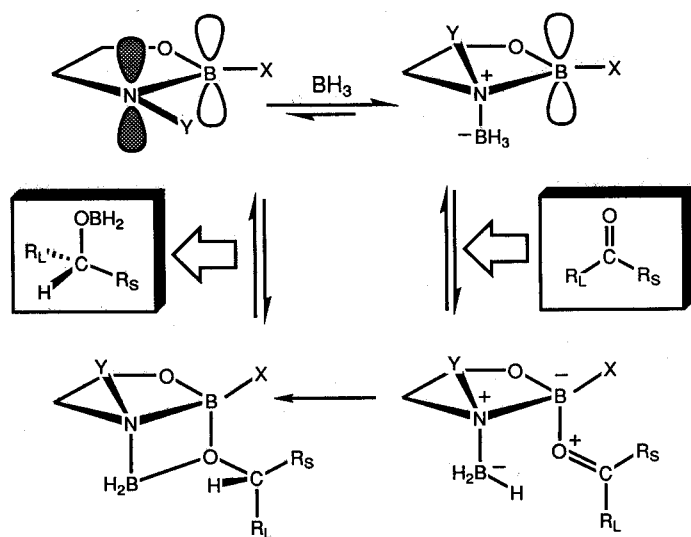


Fig. 1. A three-dimensional representation of acetophenone reduction with catalyst **2b**.

The individual steps that are proposed to comprise the catalytic cycle are illustrated below. Hopefully the full potential of the catalyst design attributes illustrated by this reaction will be revealed.

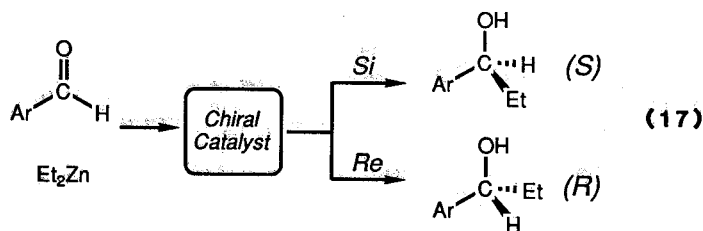


Scheme 1.

Enantioselective Aldehyde Addition

The nucleophilic addition of organometallic reagents to aldehydes and ketones constitutes one of the most reliable methods for the construction of carbon-carbon bonds. As a consequence, considerable effort has been directed toward the development of chiral addends that might exert a stereochemical bias on this process (26). In general, these reactions are characterized by the use of stoichiometric amounts of a chiral multidentate ligand and the execution of the reaction at very low temperatures. In individual cases the

expressed enantioselectivity can be quite high (>90% ee); however, a disappointing lack of generality detracts from the usefulness of these reactions. In 1984, the first report appeared of a catalyzed organozinc addition to benzaldehyde (27). This reaction has now been investigated by a number of research groups with a range of chiral catalysts, several of which have been shown to exhibit high levels of enantioselectivity (Eq. 17; Ar, aryl) (28–32).



A survey of the more selective catalysts reported to date is shown in Fig. 2. The sense of asymmetric induction and level of observed enantioselectivity in the benzaldehyde-diethylzinc reaction (Eq. 17) is provided for comparison.

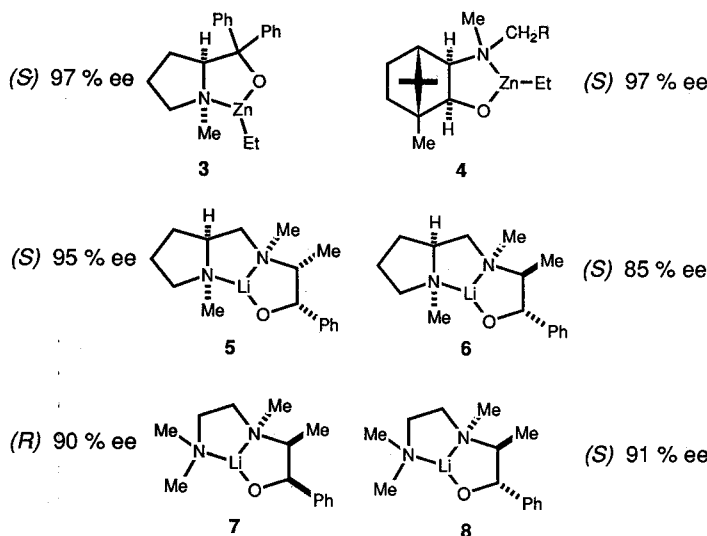


Fig. 2. Catalyst enantioselectivity for benzaldehyde addition (Eq. 17).

Zinc complexes **3** (Soai) (30) and **4** (Noyori-Frechet) (31, 32) afford the same sense and degree of asymmetric induction. Corey and Hannon have shown that the lithium chelates **5** through **8** also perform admirably as catalysts (28), and have provided a self-consistent mechanistic rationale for the sense of asymmetric induction conferred by these complexes. Itsuno and Frechet have conducted several important controls with their polymer-bound variant of catalyst **4** ($R = \text{Ar-polymer}$) (31). From these experiments it was concluded that the catalyst itself is not an active alkyl transfer reagent and that the product of the reaction was a soluble zinc alkoxide that could be separated from the catalyst. Furthermore, they demonstrated that the recovered catalyst may be recycled without regeneration. Thus it was concluded that the chiral alkoxide produced by the reaction is not bound covalently to the polymer-immobilized zinc catalyst and that ethylation occurs from the diethylzinc in solution.

In conclusion, it is the consensus view that this reaction may well proceed through a six-centered bimetallic transition state such as T_{10} as illustrated in general terms in the preceding discussion (Eq. 10). A three-dimensional representation of the termolecular complex for the benzaldehyde ethylation that rationalizes the observed sense of

asymmetric induction is provided below (Fig. 3), as proposed by both Corey *et al.* (28) and Frechet *et al.* (31). Analogous structures have also been provided for the other catalysts illustrated in Fig. 2 (28).

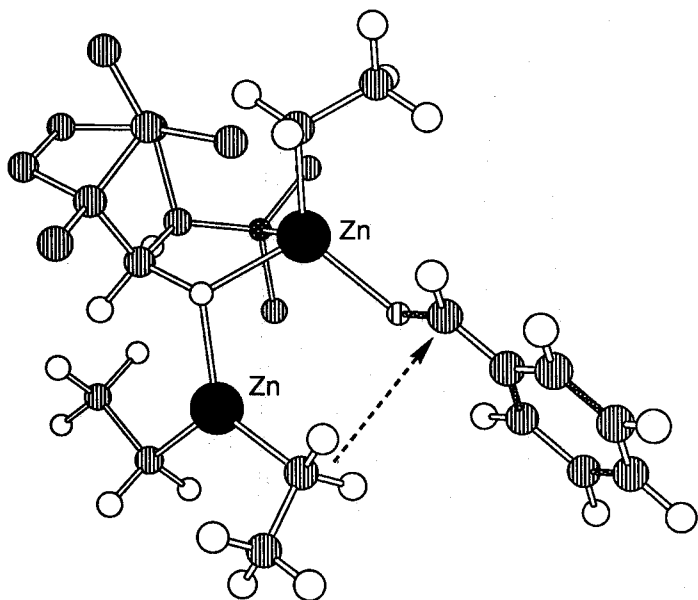
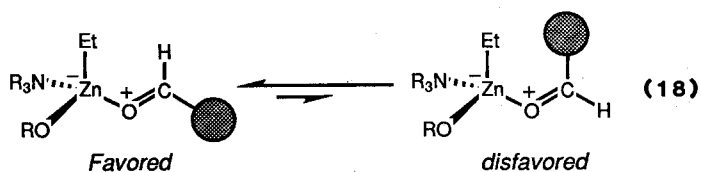


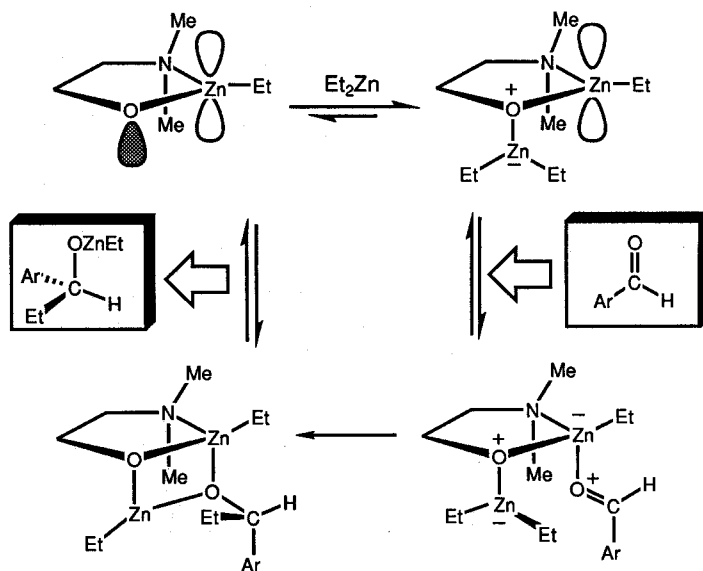
Fig. 3. A three-dimensional representation of benzaldehyde ethylation with the Noyori-Frechet catalyst.

Although a detailed analysis of all the design features exhibited by these catalysts falls outside the scope of this review, several points deserve comment. Each of the catalysts presents a well-defined facial bias in the vicinity of the metal center so that both reactants may be ligated to the same face of the catalyst through Lewis acid-base interactions. Additional nonbonding interactions between the coordinated aldehyde and ethyl ligand appear to preferentially orient one of the two carbonyl enantiofaces relative to the coordinated organozinc reagent, as illustrated below for the Lewis acid-carbonyl complex (Eq. 18) (33). This conformational issue is handled by other steric control elements in the tridentate lithium catalysts 5 through 8.



A reasonable set of individual events in the catalytic cycle for these reactions is illustrated below (scheme 2). It is instructive to compare the intermediates in this cycle with the analogous intermediates in the catalyzed reduction presented in the preceding discussion (scheme 1).

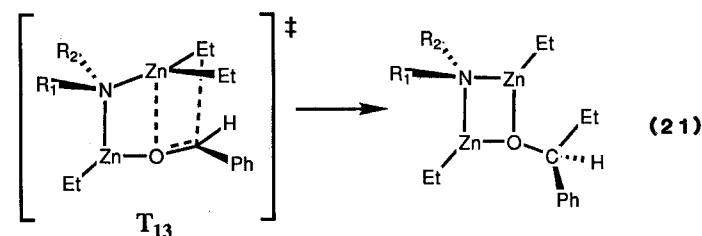
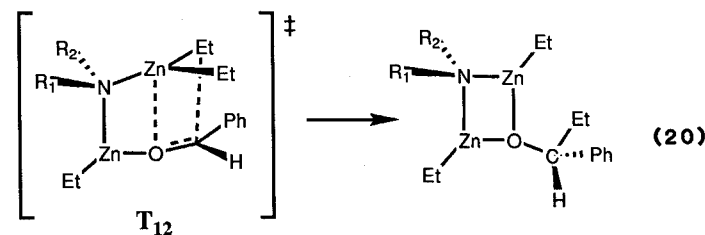
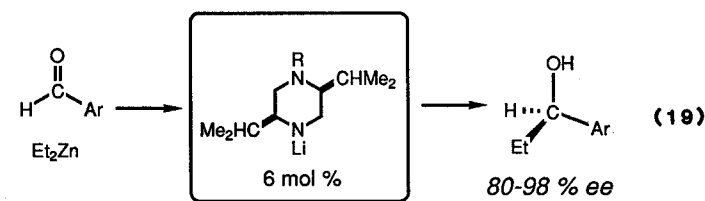
The transition state geometry. Both of the catalyzed addition reactions illustrated in schemes 1 and 2 might be expressed to proceed through either chair- or boatlike transition states. A reasonable case might be made for a boatlike geometry in the alkylzinc addition process. Since it is well known that zinc alkoxides readily form aggregates (dimeric-tetrameric) through bridging metal-oxygen coordination (34), the development of this coordination in conjunction with ethyl transfer, as illustrated above, enforces a boatlike, or "open book-like," geometry and considerably restricts the flexibility of the transition state. This type of transition state, or a



Scheme 2.

modest variant thereof, appears to have been first suggested by Ashby and co-workers as one of the possible transition states for the addition of trialkylaluminum reagents to ketones (13, 14). An illustration of this possible transition state geometry for a zinc amide catalyst will be presented below.

What about catalysts that are structurally distinct from those presented in the preceding discussion? So far there is little data to present, with the exception of one report that recently appeared. Soai and co-workers have disclosed that the dilithiated piperazine illustrated below, at 6 mole percent, was highly effective in mediating the addition of diethylzinc to several aromatic aldehydes (Eq. 19) (35). No rationale was extended for either the mechanism of this reaction or the observed asymmetric induction. Although there is insufficient information to begin to analyze this reaction in detail, the diastereomeric boatlike transition states suggested above are



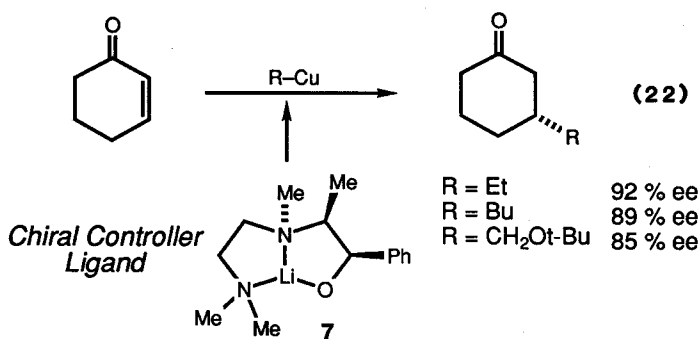
provided to stimulate further introspection on the stereochemical control elements that may be responsible for the high levels of asymmetric induction (Eqs. 20 and 21).

On a more somber note, these reactions still appear to be limited in scope. Aromatic aldehydes are superior to their aliphatic counterparts, yet the reasons for this predisposition are not yet known. In addition, dialkylzinc reagents must be used for optimal results. It is well documented that chloroalkylzinc reagents react with substantially lower enantioselectivity. One might speculate that these reagents could provide a competing achiral catalyst, $L\text{-Zn}$ -halogen, which might also facilitate carbonyl addition.

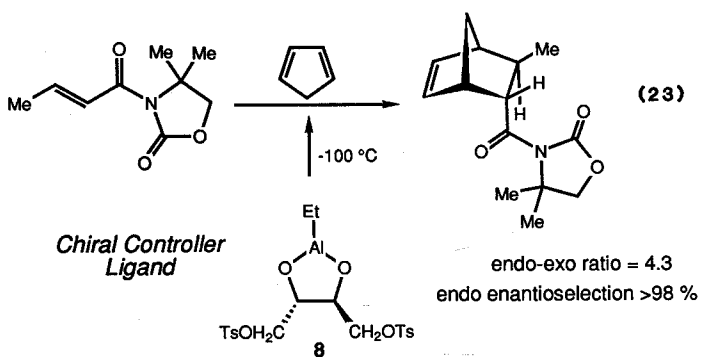
The Organizational Role of Chiral Metal Centers

The catalyzed reactions highlighted in the two previous sections appear to share a number of common attributes, both in the presumed transition structures and in the mode of catalysis. These cases will certainly form the basis of future investigations in catalyst design for other types of carbonyl addition reactions. Clearly, other mechanistic constructs for catalyst design will emerge. The underlying theme in a multitude of recent studies involves the use of a Lewis acidic metal center, clothed in a chiral environment, in either catalytic or stoichiometric stereodifferentiating reactions. Some of the exciting accomplishments in this area deserve special recognition.

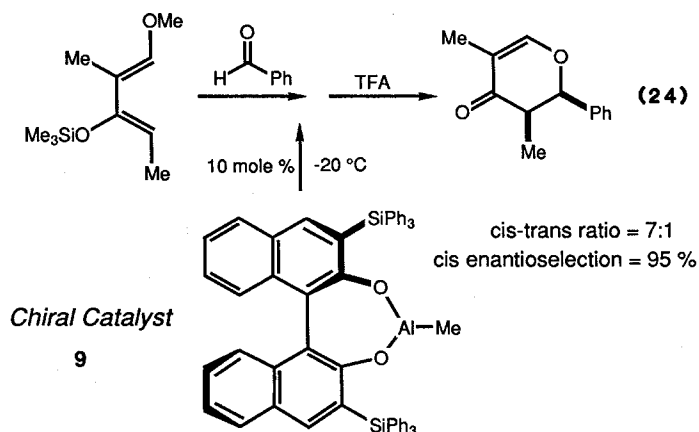
There has been a long-standing interest in the development of chiral ligand-modified organocuprate reagents that might exhibit high levels of asymmetric induction in conjugate addition reactions (36). Recent results from the Corey laboratory reveal that the tridentate chelate 7, which has found use as a catalyst in the previously discussed diethylzinc reactions, also effects stoichiometric asymmetric induction in conjugate addition reactions of organocuprate reagents (Eq. 22) (37).



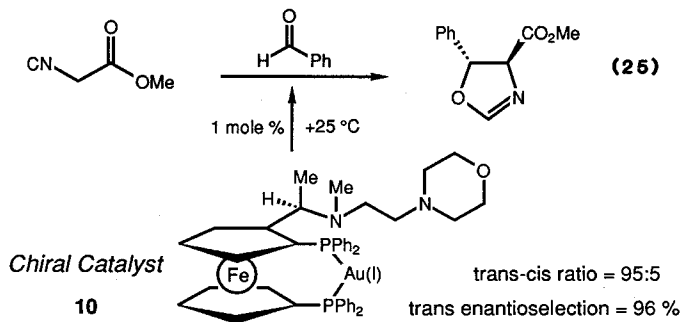
In an allied activity, there has been great interest and some encouraging progress in the development of families of chiral Lewis acids that might control the absolute stereochemical course of those reactions subject to this form of catalysis (38, 39). One such example is illustrated below (Eq. 23; Ts, tosyl) (38). Chapuis and Jurczak have investigated a range of C_2 symmetric ligand-Lewis acid conjugates in catalyzed Diels-Alder cycloaddition reactions. As in the preceding case, the chiral controller ligand 8, although it must be used in stoichiometric quantities, provides excellent levels of enantioselectivity. One can only speculate at this point as to the structure of the solution complex responsible for the asymmetric induction. This report has recently been followed by the disclosure of a chiral Lewis acid-promoted hetero Diels-Alder reaction that proceeds with high levels of asymmetric induction (Eq. 24; TFA, trifluoro-acetic acid). It is most significant that this reaction exploits



the chiral catalyst 9 in catalytic quantities (40).



On a final note, a spectacular advance has recently been made in the design of a chiral catalyst for an aldol reaction between isocyanoacetate and a variety of aldehydes (41). Ito, Sawamura, and Hayashi have found that the chiral gold(I)-ferrocenyl complex 10, at 1 mole percent, effects a highly selective aldol addition with excellent stereocontrol at both newly generated stereocenters (Eq. 25). This reaction provides an elegant entry into the enantioselective synthesis of β -hydroxy α -amino acids.



The upcoming years will witness many more advances of the type discussed in this review. One disquieting aspect accompanying these advances is that one is continually on "thin ice" from a mechanistic standpoint in both designing and attempting to rationalize the events that occur during the course of such reactions. It is hoped that the rigorous documentation of the mechanistic details of such reactions will accompany future developments in this field.

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