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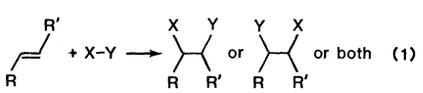
Selectivity: A Key to Synthetic Efficiency

Barry M. Trost

Summary. The efficient synthesis of organic compounds requires the development of processes with enhanced selectivity. Selectivity is categorized according to chemical reactivity (chemoselectivity), orientation (regioselectivity), and spatial arrangement (diastereoselectivity and enantioselectivity). Recent developments in reduction-oxidation methods and C–C bond forming reactions illustrate some solutions to problems of selectivity. The design of selectivity-inducing groups and the increased role of main group and transition metals in enhancing selectivity are especially noted.

The demand for ready access to complex organic molecules has increased markedly. Increased sophistication of the bulk chemical industry has created the need for more elaborate inexpensive raw materials. The isolation and identification of complex organic molecules that play important roles in living systems, but whose availability from natural sources is precluded because of very low concentrations, has brought about a demand for compounds such as insect hormones and pheromones, prostaglandins and other members of the arachidonic acid cascade, vitamin D metabolites, and various antitumor compounds. Varying the structure of complex natural products of known biological activity in order to probe the mechanism of their function and to improve their therapeutic properties requires their partial or total synthesis; β-lactam antibiotics represent one of many recent examples of such products. The synthetic chemist has enthusiastically embraced this challenge with an outpouring of new tools—namely, reactions and reagents.

In searching for such tools, selectivity becomes the prime motivator. Three general classes of selectivity can be recognized. Complex organic molecules normally have more than one reactive site or functional group. The ability to discriminate among the reactive sites is referred to as chemoselectivity. For example, preferential reaction at a ketone over an olefin, or vice versa, represents a problem of chemoselectivity. At a given reactive site, there may be several orientations by which a reagent may approach the reactive site; this defines the problem of regioselectivity. The addition of X–Y to an unsymmetrical olefin (Eq. 1) exemplifies such a problem. Ste-



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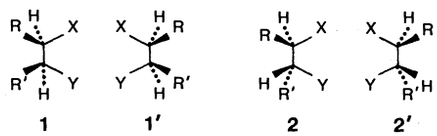
reochemical control comprises two types of selectivity. First, the control of relative stereochemistry between two or more centers is referred to as diastereoselectivity. For example, each regioisomeric product of Eq. 1 can differ in the relative configuration at each carbon leading to the two isomers **1** and **2** (and **1′** and **2′**). In each of these two relative stereoisomers there are two further ste-



reoisomers that differ from each other as mirror images, **1** and **1′**, **2** and **2′**. Enantioselectivity refers to discrimination between such mirror-image isomers or enantiomers.

Reactions and reagents that possess such discriminating ability are required for the solution of the types of problems being encountered today. Enzymes represent the pinnacle of "reagents" characterized by extraordinary selectivity. Fermentation methods and immobilized enzyme techniques enhanced by genetic engineering constitute one important approach to the production of selective reagents. In this article, we focus on chemical approaches that potentially possess greater flexibility, and we have summarized a few selected approaches in each major category of selectivity to illustrate some of the successes.

Chemoselectivity

The degree of difficulty of chemoselectivity depends on the similarity of two or more functional groups. Thus, discrimination is simpler if the functional groups belong to two different classes, such as a C=O and a C=C, than if they are members of the same class, such as two different C=O groups in the same molecule. In most reactions, there is differential reactivity among the functional groups present in a molecule, at least to some extent. The reduction of a ketone in the presence of an olefin, or vice versa, represents an early problem that has been largely resolved by the use of the metal hydrides for the former and catalytic hydrogenation for the latter (*1*). Fine tuning of both of these reactions continues. For example, addition of various metal salts to borohydride profoundly changes the selectivity of this reducing

Dr. Trost is Vilas and Helfaer Professor of Chemistry, McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin, Madison 53706.

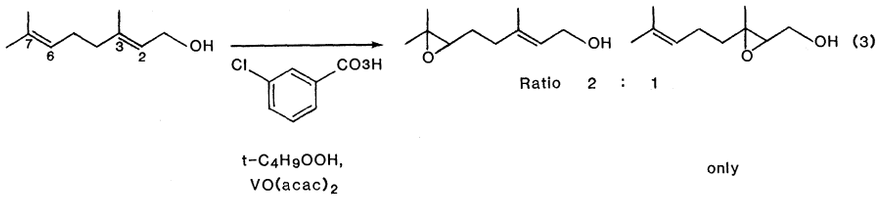
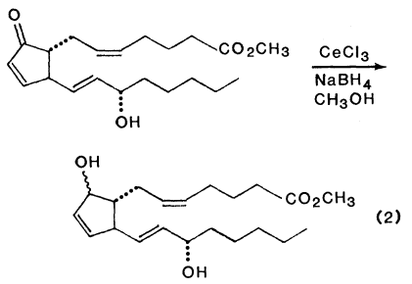


Fig. 1. Chemoselective epoxidation.

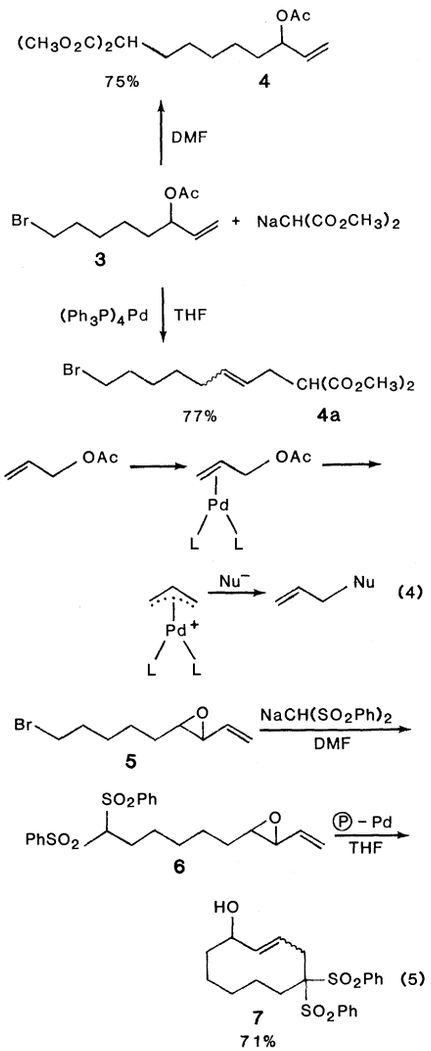
agent (*2*). Reductions of cyclopentenones with sodium borohydride normally lead to appreciable saturation of the double bond in addition to reduction of the carbonyl group. Addition of ceric chloride leads to carbonyl group reduction without appreciable double bond reduction (see Eq. 2) (*3*). Metal salts have



marked effects on many reactions. While the underlying reasons for the effects are frequently unknown, as in the above example, the practical consequences lead to a great deal of an Edisonian type of effort with the understanding yet to evolve.

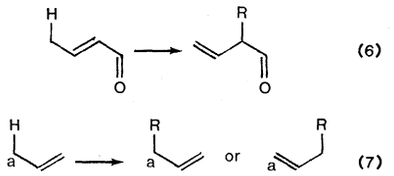
Catalysis has the broadest impact on enhancing selectivity and developing selectivities not previously possible. Applications of metal catalysts in the adjustment of oxidation levels and the formation of C–C bonds illustrate the broadened uses for chemoselectivity in such processes. Epoxidations of olefins with peracids normally involves reaction of the most electron-rich double bond; for geraniol, the 6,7-olefin reacts perferentially with moderate selectivity (Eq. 3). However, coordination of vanadium with an allylic hydroxyl group reorders the relative reactivity of the two olefins present in geraniol in the metal-catalyzed epoxidation with *tert*-butylhydroperoxide (Fig. 1) (*4*, *5*).

Reordering reactivity of two functional groups can be achieved in alkylation reactions. Allylic acetates normally do not serve as substrates for nucleophilic attack. Reaction of the bromoacetate **3** with dimethyl sodiomalonate in dimethylformamide (DMF) as solvent leads, via bromide displacement, only to **4**. However, addition of a palladium(0) catalyst in tetrahydrofuran (THF) specifically activates an allylic acetate as a result of prior coordination with the olefin (Eq. 4) and leads to exclusive displacement of the allylic acetate to give **4a**—a total reordering of the reactivities of a halide and an allylic acetate (*6*, *7*). Such a differential reactivity leads to a novel approach to macrocyclization (Eq. 5) (*8*).

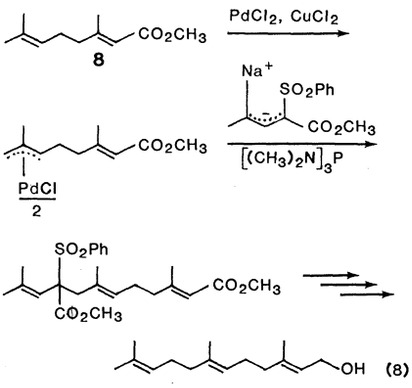


The bromide of **5** selectively reacts with nucleophiles to give **6** in the presence of the vinyl epoxide. A polymerically bound palladium catalyst then specifically activates the vinyl epoxide, with simultaneous unmasking of the nucleophilic and electrophilic centers, resulting in cyclization to **7**. The combined effect of having relatively few isolated reactive sites on the polymerically bound catalyst and even fewer occupied ensures an intramolecular reaction, even though an unfavorable ring size ensues (such as a ten-membered ring), and high bulk concentrations of substrate (0.1*M* to 0.5*M*) are used.

Whereas activation of a hydrogen alpha to a carbonyl group or one that is vinylogously alpha to a carbonyl group (separated from the carbonyl group by the intervention of a double bond) permits its replacement by a C–C bond with



allyl inversion (Eq. 6), the corresponding reaction with an isolated double bond with or without allyl inversion was not normally possible (Eq. 7). Palladium salts that react selectively with less polarized double bonds reorder this reactivity sequence (*7*) so that methyl geraniate **8** can be prenylated at the isolated double bond to give the higher terpene farnesol (Eq. 8) (*9*).

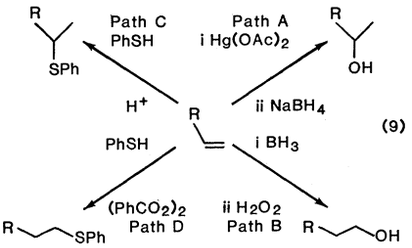


These examples illustrate how metals are revolutionizing the approach to the solution of problems that require putting together a carbon framework and adjusting its oxidation level. New synthetic challenges continue to reveal newly required selectivities. Considering that lack of chemoselectivity frequently accounts for as many as 40 percent of the steps of a complex synthesis, much remains to be done for enhanced synthetic efficiency.

Regioselectivity

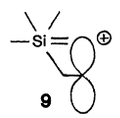
Classic problems of regioselectivity, such as the addition of the elements of H–X across an unsymmetrical olefin, continue to arise in synthesis. Some of these problems have been resolved. For example, the equivalent of a hydration of an olefin can be controlled to give the

more substituted product (path A in Eq. 9) (*10*) or the less substituted product (path B in Eq. 9) (*11*) by use of different reagents. Varying the mechanism of a reaction can alter its regiochemical path, as in the acid catalyzed (path C in Eq. 9) or free radical (path D in Eq. 9) addition of thiophenol to an olefin (*12*).



(9)

A different concept is involved in the use of a substituent that strongly directs the regiochemistry of a reaction and that can be removed during the course of the reaction or subsequently. Such directing groups can be referred to as regiochemical control elements. Silicon substituents serve such a function in electrophilic substitution on unsaturated systems. The known ability for silicon to stabilize an electron deficiency on a carbon beta to itself as in **9** provides the impetus for



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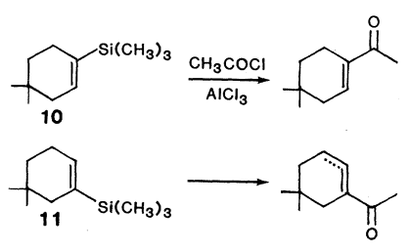
such control. For example, in a vinyl silane such as **10** and **11**, electrophilic substitution involves attack of the electrophile at the carbon bearing silicon exclusively (*13*). Without silicon, a mixture of both types of products would have resulted. With allylsilanes, electrophilic attack occurs exclusively with allyl inversion, as in the synthesis of artemisia ketone **12** (Eq. 10) (*14, 15*). Normally, such a trisubstituted olefin would



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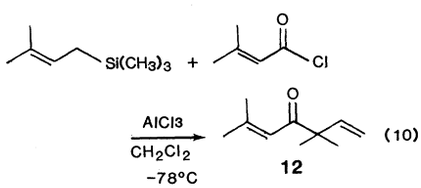

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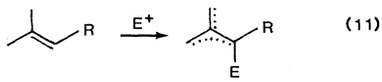

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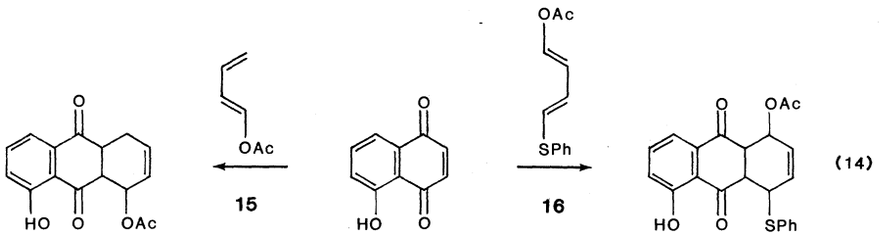

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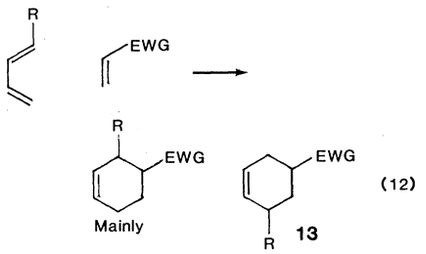
Fig. 2. Regiochemical control element in cycloadditions.

have combined with the electrophile (E^+) at the less substituted carbon (Eq. 11). Thus, the silicon redirects the bias for attack in a system that intrinsically prefers the opposite orientation.

Among the more potent synthetic reactions are cycloadditions; yet orientational control remained rather limited. In the Diels-Alder reaction (Eqs. 12 and 13), a 1-substituted diene reacts with a dienophile (EWG, electron withdrawing group) to give mainly "ortho" substitution (Eq. 12), whereas a 2-substituted diene gives mainly "para" substitution (Eq. 13) (*16*). "Meta"-like products **13** and **14** are either absent or, at best, minor products. Sulfur substitution in the diene reorients the two reacting partners as demonstrated in the cycloaddition of 1-acetoxybutadiene **15** and its sulfur analog **16** (Fig. 2) (*17, 18*). Whereas 2-acetoxybuta-1,3-diene reacts according to Eq. 13, the sulfur analog **17** produces the meta type of product **18** (Eq. 15) (*19, 20*). While desulfurization methodology permits replacement of a C–S bond with a C–H bond, the sulfur substituent provides synthetic versatility, as demonstrated by its elimination to **19**. The transformation illustrated in Eq. 15 (*21*) serves as a regiocontrolled cyclohexenone annulation that complements the regiochemistry available through the use of dienes reacting via the normally observed directive effects shown in Eqs. 12 and 13 (*22*).



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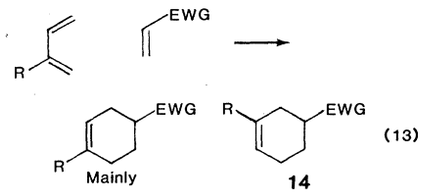

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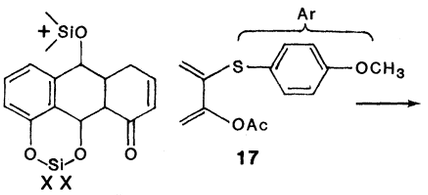

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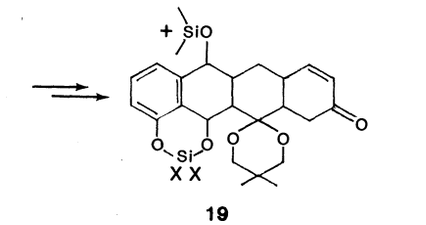

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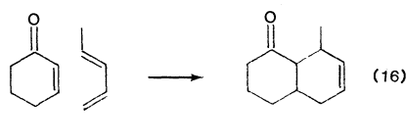
The regiochemical control element can be inserted into the dienophile instead of the diene. One of the more interesting of such groups is nitro (*23*). The regiochemical complement **21** to the normal Diels-Alder adduct **20** (Eq. 16) is available by



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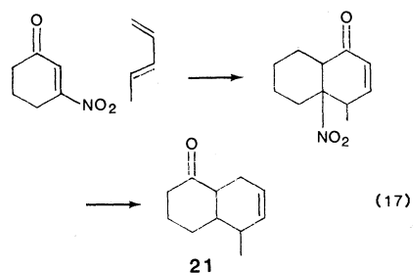

(17)

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the cycloaddition of 3-nitrocyclohex-2-en-1-one with pentadiene (Eq. 17) (*24*). The nitro group in the initial adduct can undergo β elimination to create an enone or, as illustrated in Eq. 17, be reductively cleaved with tri-*n*-butyltin hydride.

The inability to control the orientation between two reacting partners represents a major limitation in the application of many reactions to synthetic targets. The realization that rational approaches to manipulate such reactions may exist

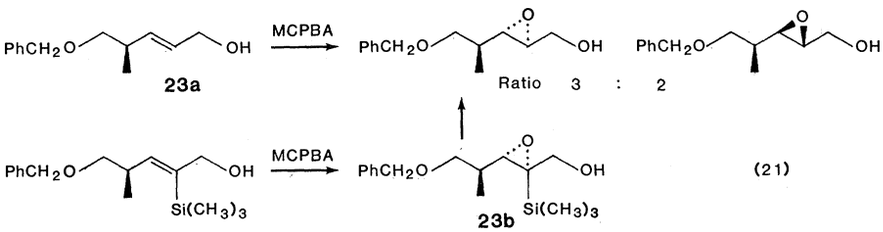
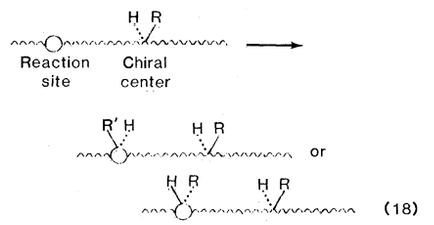


Fig. 3. Diastereochemical control element in epoxidation.

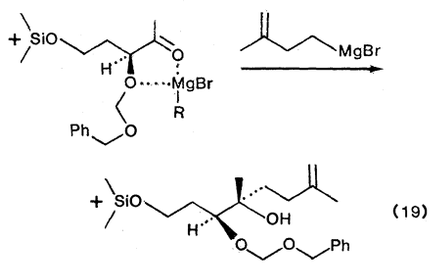
can greatly simplify synthetic design. The concept of a regiochemical control element provides a powerful tool in achieving this goal. The characteristics of such a group will differ according to the type of reaction.

Diastereoselectivity

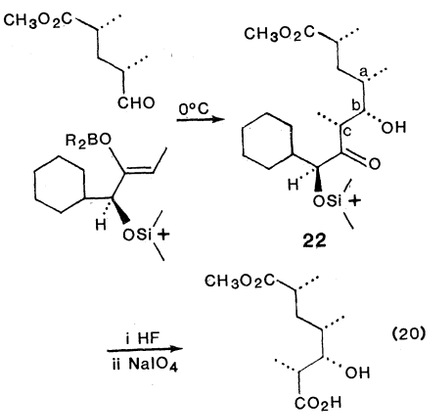
The control of stereochemistry at a reaction site by an existing center of chirality differs in complexity as a function of the separation of the two centers (see Eq. 18). In conformationally rigid



molecules, knowledge of the conformations usually permits rational solutions to such stereochemical problems. Conformationally nonrigid molecules, in contrast, present great challenges. If the two centers are on adjacent carbons, such selectivity appears approachable. In nucleophilic addition to a carbonyl group, metal chelation can provide temporary conformational rigidity and there-



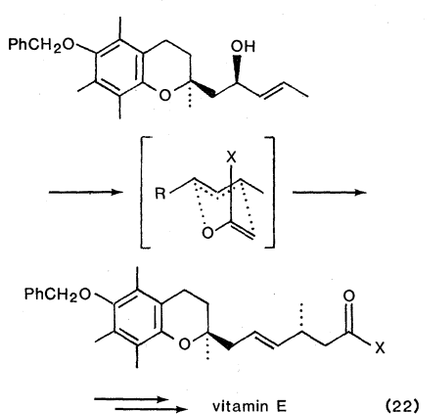
by enhance the steric differentiation between the two faces of the carbonyl group, with resultant high diastereoselectivity (Eq. 19) (*25*). The common occurrence of a 1,3-diol functionality in natural products has focused attention on the stereochemistry of the aldol condensation (the addition of an enolate onto a carbonyl group) (*26–28*). By clever design of the attacking enolate, two new contiguous chiral centers were created (b and c in **22**) with very high stereocontrol (referred to as double stereodifferentiation), which have served as a critical part of an elegant synthesis in the erythronolide series of macrolide antibiotics (Eq. 20) (*29*).



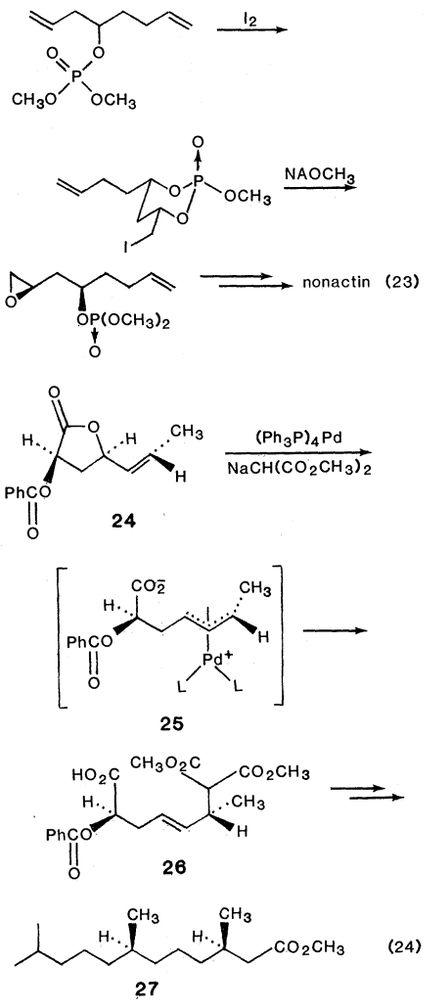
Epoxidations of allylic, and in certain cases, homoallylic alcohols has led to high diastereoselectivity (*5, 30*). Its failure in cases such as **23a** led to the introduction of a trimethylsilyl group as a diastereochemical control element that could be dismissed by treatment of the product **23b** with fluoride ion (Fig. 3) (*31*).

The greatest challenges derive from reaction sites that are noncontiguous with the existing chiral center in conformationally nonrigid systems. In one approach, invoking reactions that pass through conformationally well-behaved transition states (Eq. 22) (*32*) or intermediates (Eq. 23) (*33*) resolves the problem.

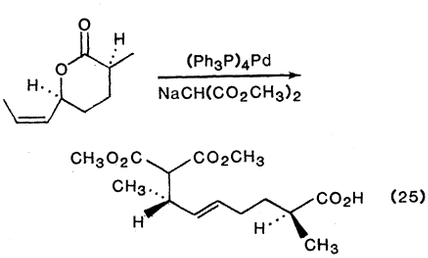
A different strategy utilizes transition



metal templates to superimpose conformational rigidity into acyclic chains. A catalyst comprised of palladium(0) and its attendant phosphine ligands induces ionization of **24** specifically from the conformation depicted (Eq. 24) (*34*). The



transitory intermediate **25** combines with a nucleophile faster than stereorandomization occurs, with the overall effect of faithful translation of the stereochemistry of **24** into product **26**, a key intermediate for the stereocontrolled synthesis of the side chain of vitamins E and K, in which the two chiral centers are in a 1,5 relation (*35*). Switching from a five-membered to a six-membered ring lactone extends this separation to six carbons (Eq. 25) (*36*).

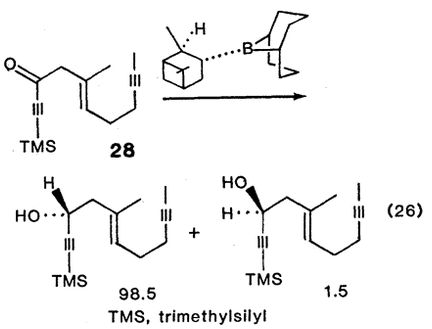


Imposition of conformational rigidity on conformationally mobile systems

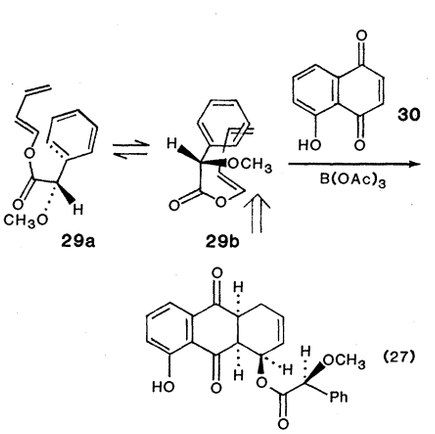
constitutes the most successful approach to diastereoselectivity. Main group metals whose Lewis acidity permits creation of metallocycles and transition metals that, combined with ligands, form an "active site" capable of exercising steric and electronic control over a reaction pathway have achieved remarkable success. While working hypotheses of the type presented allow applications to outpace our understanding of underlying principles, the evolution of the latter will have a dramatic effect on extending these concepts.

Enantioselectivity

To induce asymmetry in an achiral molecule such as **28** requires the presence of a chiral environment. Of the two approaches that can be discerned, the

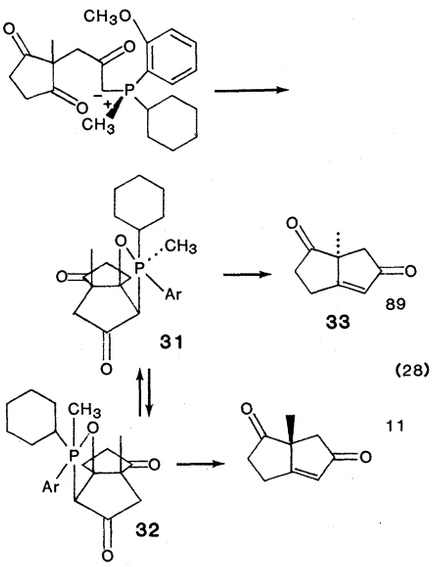


more successful one is to convert enantioselectivity into diastereoselectivity, the chiral inducing agent becoming covalently bonded to the substrate in such a fashion that it can be subsequently cleaved. The Diels-Alder reaction is an excellent framework with which to explore such possibilities since many chiral centers are created from two normally achiral starting materials (*37–39*). Interaction of a phenyl ring with the π-system of a dienophile or a diene (a so-called π-stacking interaction) can induce cycloaddition to occur preferentially to one of the two enantiotopic (or, in reality, diastereotopic) faces of these reacting partners. For example, preferential reaction of juglone (**30**) as a dienophile with diene **29** would be predicted to occur preferentially from the bottom face of **29b**. Indeed, a single product emerges whose absolute configuration conforms to this prediction (Eq. 27) (*37*). Use of such weak secondary interactions has had remarkable success in related thermal processes (*39, 40*).



In these processes, the reaction is normally thought of as proceeding through intermediates in which nonbonded steric interactions are minimized, as in the example in Eq. 27. Nevertheless, caution must be exercised. In the Wittig reaction (Eq. 28), the less stable intermediate **31** apparently eliminates faster than **32** [see the Curtin-Hammett principle (*41*)], since the *S* isomer **33** predominates (*42*). This compound is a basic building block for polycondensed cyclopentanoid natural products (*43*).

The alternative approach envisions a transfer of chirality in which the chiral inducing agent does not become covalently bonded to the achiral substrate. The carbonyl reduction depicted in Eq. 26 proceeds with a remarkable enantiomeric excess (ee) of 97 percent (98.5 − 1.5) (*44, 45*). Transition metal templates offer some of the most promising approaches (Fig. 4) (*46–49*). The subtlety of the effects responsible for the asymmetric induction make it difficult to design chiral inducing agents. As already



mentioned, simply focusing on the most stable intermediate as the product-determining intermediate can be risky. In the asymmetric synthesis of the amino acid phenylalanine (Eq. 32), the most stable complex is not the product-determining intermediate (*50*).

To a large extent, progress in the development of an asymmetric process has

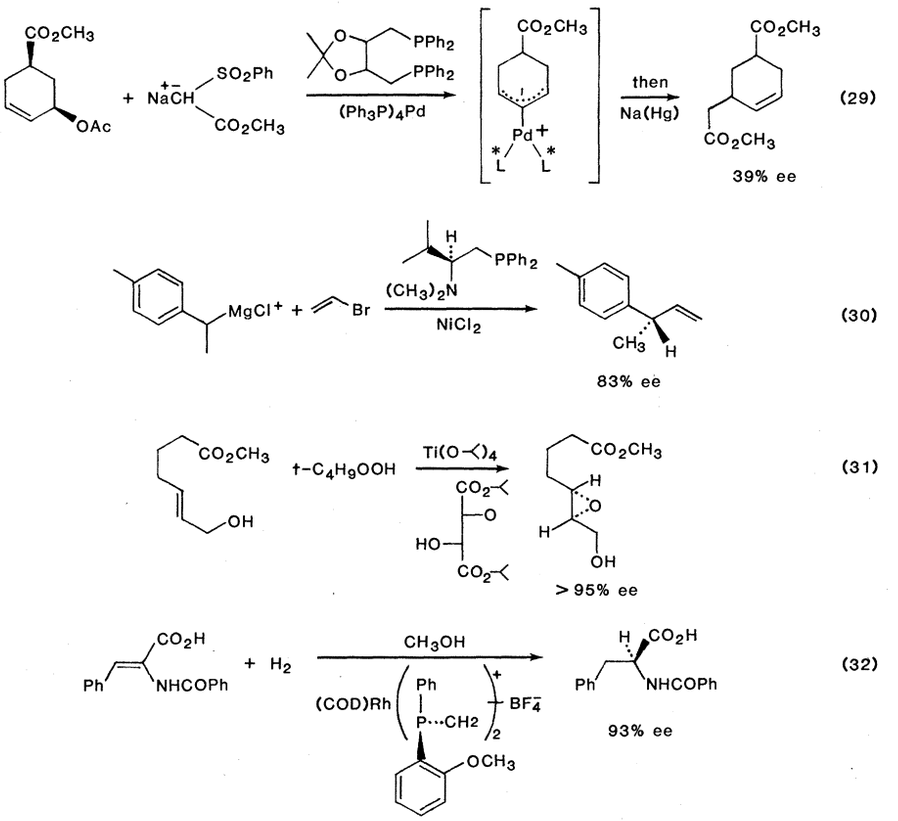


Fig. 4. Selected examples of enantioselective reactions.

been empirical. Retrospective analysis helps to provide more rational direction for the future. It is clear that examination of nonbonded interactions alone will not suffice to generate fruitful paths. Kinetic considerations coupled with steric factors ultimately determine the degree of selectivity. The fact that the balance varies among different types of reactions means that broad generalizations will be unlikely.

Conclusions

It has been stated that the practice of organic synthesis is an exercise in perturbation theory. Nothing so highlights such a feeling as the problems of selectivity. Achieving the type of selectivity that has a profound effect on the outcome of a reaction normally means that the competing pathway will differ by less than 3 kilocalories per mole—a very small energy difference. It is no wonder that the understanding of the underlying factors required for the field to progress remains limited. Selectivity inserts the art into organic synthesis; its challenge provides the excitement.

References and Notes

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