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Conservation of helical asymmetry in chiral interactions

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Dedicated to Professor Thomas J. Katz on the occasion of his 69th birthday

Abstract—A theory for chiral molecular recognition and induction is presented that attributes enantioselection to electronic interactions. It assigns helicities to chiral molecules and has a chiral host or catalyst preferentially recognize or induce chirality of the same helicity. This principle of conservation of helical asymmetry agrees well with many experiments, accommodates results that conventional steric reasoning cannot, and promises predictive power. The work suggests that helical electronic effects may generally exert greater control than steric effects in enantioselection.

1. Introduction

The phenomena of molecular chirality and chiral interactions are of fundamental importance in a wide range of fields including chemistry, biology, medicine and materials.[1] Enantioselection, that is, the formation of one enantiomer preferentially over its mirror image in an asymmetric reaction, is usually thought to have a geometrical origin thus to favorably develop through a transition state that has less steric hindrance. It is, therefore, often analyzed by means of steric size-based considerations complemented with, in some cases, such electronic factors as hydrogen-bonding, π–π stacking and electrostatics.[2] However, experimental observations contradicting the prevalent steric theories abound in literature. Described here is an alternative, an electronic theory of chiral interactions,[3] which it will be shown accounts successfully for the enantioselection observed in a large number of chiral induction and recognition experiments. The theory is based on identifying the helicities of chiral molecules, including those that at first do not seem helical. Like theories that account for optical activity as a consequence of electron movement on helical paths,[4,5] it views all chiral molecules as helical.

2. Results and discussion

A simple 5-atom chiral molecule, for example, C*HFBrCl, does not appear to be helical since every pair of covalent bonds seems coplanar. However, helical electronic structures can be visualized and analyzed in these and other molecules by supposing that unbalanced electronic repulsions, measured by group polarizabilities that characterize the sensitivity of a group's electron density to distort in an electric field, deform the bonds into helices. This idea is an outgrowth of earlier attempts, long pursued, to identify helical electronic paths in chiral molecules.[5]

Suppose that in C*$abcd$, a point-chiral molecule in which substituents a, b, c, and d are attached to central chiral atom C*, the polarizabilities of the substituents follow the sequence $a>b>c>d$. The helical structures in this molecule are identified in Scheme 1 by a procedure proposed by Yin.[6] Consider, for example, the pair of covalent bonds a–C*–b. The anisotropic electronic fields of c and d should distort a–C*–b from co-planarity into a micro-helical electronic structure.[3b] If, as in electronic theories of optical activity,[5] the distortion increases with group polarizability, it is reasonable to expect the strength of repulsion, represented by the length of the doubly arrowed lines on the left in Scheme 1, to follow the sequences a–$c>b$–c; and a–$d>b$–d. The result should be to twist the a–C* bond up more than the b–C* bond. The bonds will thus be twisted into a right-handed micro-helix. Similar effects, illustrated in Scheme 1, will twist the a–C*–d, b–C*–c, and c–C*–d bonds into right-handed micro-helices and the a–C*–c and b–C*–d bonds into left-handed

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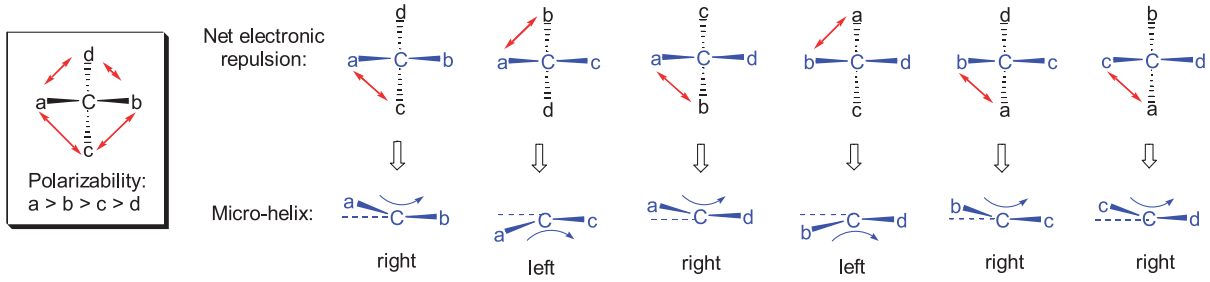
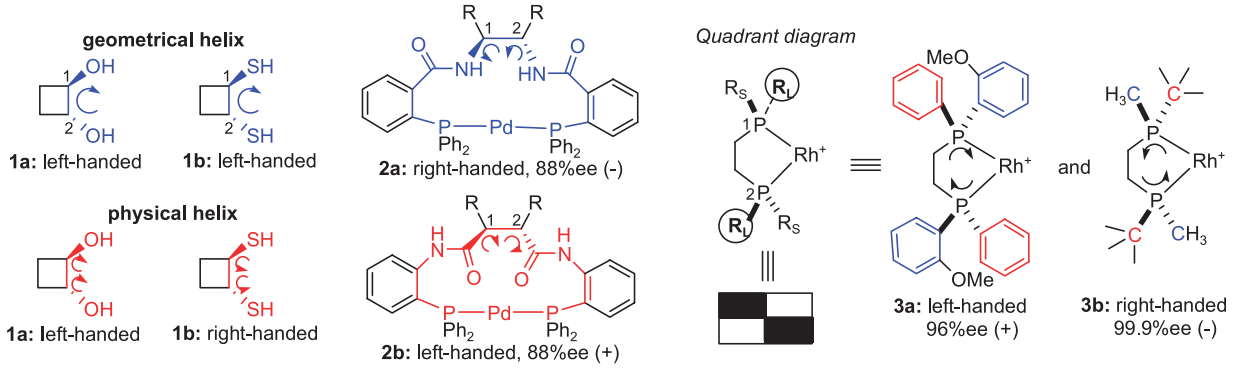


Scheme 1. Helical structures in a typical point-chiral molecule C*abcd* with a group polarizability sequence $a>b>c>d$.

micro-helices. Since there are more right-handed than left-handed structures, the molecule has a net right-handed helicity.[7] A molecule's net electronic helicity, thus its optical activity, would disappear if any two groups are the same.

The polarizabilities of a limited number of common groups can be obtained from measurements of atomic refractive indices ($I>Br>SH>Cl>C{\equiv}N>C_6H_5>C{=}O>CH_3>NH_2>OH>H>D>F$), but not of many other significant groups for which such data are unavailable.[8,9] However, some general ranking principles, which are direct consequences of the polarizability characters and are widely used,[9] make it possible to deduce the sequence of polarizabilities even though precise data are unavailable. These principles include the following: in a group atoms with larger numbers of electron shells > atoms with smaller numbers of electron shells, in a period atoms with lower nuclear charge > atoms with higher nuclear charge, transition metals > organic groups, lone pair electrons > bonding electrons, triple bonds > double bonds > single bonds, aromatic and π-groups > alkyls, strained alkyls > unstrained alkyls, groups with more conjugation > analogous groups with less conjugation, electron-rich groups > electron-poor analogues, and for the central carbon in simple alkyls $CH_3>1^\circ\ CH_2R>2^\circ\ CHR_2>3^\circ\ CR_3$ (because *C*–H > *C*–C).[9] In addition, the electron repulsion responsible for orbital twisting within groups should arise largely from the bonds and atoms that are directly attached to the chiral center. Thus for multi-atom groups, in agreement with Brewster's suggestion, the polarizability ranking should be assigned according to the polarizabilities of the atoms or moieties directly attached to the chiral center (i.e., local polarizability), and not according to the polarizabilities of the whole group.[8a] The above principles serve as general guidelines in group polarizability rankings and will be closely and consistently followed throughout the work. Specifically, polarizability rankings are explicitly shown whenever molecular helicity analyses are needed and also are comprehensively compiled in the Supplementary data of this article.[10]

There is a significant difference between the micro-helical structures described here and those described earlier, notably by Brewster et. al.[5a,11] The former, because of their origins in asymmetric orbital twisting, have electronic properties that the latter, because of their purely geometrical origin, do not. We distinguish the two by calling the former a 'physical helix' and the latter a 'geometrical helix'.[12] Scheme 2 illustrates the difference for two related molecules, **1a** and **1b**. According to Brewster's conformational helix analysis, the HX–C^1*–C^2*–XH fragments define left-handed geometries whether X=O or X=S. However, the group local polarizability sequence around each chiral center is O<C* in **1a** and S>C* in **1b**. Accordingly, when deformed by a CH_2 and an H (the former being more polarizable), the physical helices, which in the HO–C^1*–C^2*–OH moiety are left-handed, in the HS–C^1*–C^2*–SH moiety are right-handed (note that at each chiral center only the local helix that develops along the HX–C^1*–C^2*–XH moiety, that is, –X–C^1*-C^2*– at the C^1* center and –C^1*–C^2*–X– at the C^2* center, but not the total six micro-helices, needs to be considered)! Thus, while as bidentate



Scheme 2. An illustration of the different electronic properties of geometrically similar chiral molecules **1a–b**, and the failure of steric effects and the success of electronic effects to account for the direction of enantioselection in the allylations and hydrogenations catalyzed by Palladium or Rhodium-complexes. Handedness of catalyst ring helices -P-phenyl-amide–C^1*–C^2*-amide-phenyl-P-Pd- in **2a–b** and –P^1*–CH_2–CH_2–P^2*–Rh- in **3a–b**, observed ees and rotation signs of the favored products are shown below each catalyst. The numbers 1 and 2 label the chiral centers. The positions of larger (R_L) and smaller (R_S) substituents in **3a–b** are shown at the left. P-substituents of higher local polarizability are shown in blue and of lower local polarizability in red. R–R = *trans*-9, 10-dihydro-9, 10-ethanoanthracene.

ligands in asymmetric catalysis **1a** and **1b** may resemble each other sterically, electronically they do not. The Supplementary data shows how physical and geometrical helices also can be identified in planar, axial, and other chiralities.[10,13] In small and conformationally flexible point chiral molecules C*abcd*, geometrical helices may be completely absent.

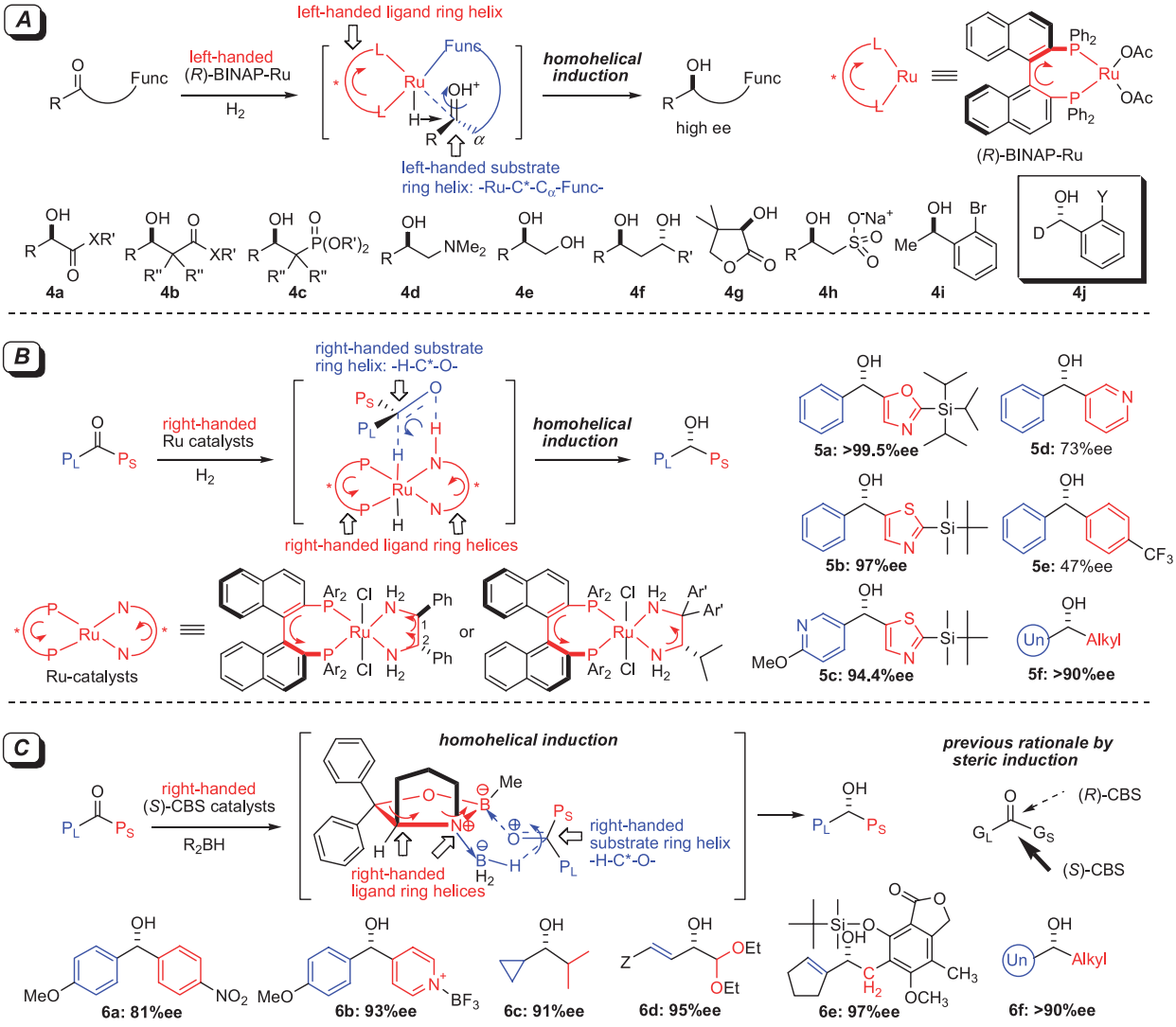
In chemical reactions, geometrical helices relate to asymmetries in the shapes of asymmetric reactants, while physical helices characterize fine electronic tunings, but not steric size. Steric effects in asymmetric interactions have been analyzed frequently. The question considered here is whether electronic effects also play a role. Since, there are only two chiralities, right- and left-handed helicity, the diastereomeric interactions between two chiral molecules are either homohelical (when the interacting helices have the same handedness) or heterohelical (when they do not). The interesting question is whether one is energetically more favorable and, if so, which. In a separate paper,[14a] we have shown, by employing the classical electron-on-a-helix theoretical model of Tinoco and Woody,[14b] that a homohelical electronic interaction is always lower in energy than its diastereomeric heterohelical electronic interaction and their energetic difference, which in an asymmetric reaction corresponds to the difference between the free energy changes that determines the magnitude of enantioselectivity, is sufficient to bring about high enantiomeric excess (ee). Indeed, the remarkable observation is that, in experiment after experiment, homohelical interactions always seem to be favored. A chiral host recognizes a guest of the same helical handedness, and the electronic handedness of a chiral catalyst seems to govern the favored direction for its complexation to a pro-chiral substrate that allows it to preserve its helicity in the enantioselection-determining step[15] and, therefore, the stereochemistry of the product it gives. This principle of conservation of helical asymmetry makes stereochemical predictions possible. In asymmetric induction, a reversal of catalyst handedness, which, as shown below, does not necessarily correlate to a reversal of catalyst chirality (configuration and conformation), often results in the reversal of product stereochemistry.

An example is enantioselective allylation catalyzed by chiral Pd-complexes **2a** and **2b**.[16] While the scaffolds in **2a** and **2b** have the same sense of chirality, inverting the orientation of the amide function reverses the sense of the product's chirality (Scheme 2). This can readily be understood on the basis of an analysis of the handedness of the catalyst ring helices which are crucial in executing chiral induction (specifically herein these helices are –N–C^1*–C^2*– at the C^1* center and –C^1*–C^2*–N– at the C^2* center in **2a**, –C(O)–C^1*–C^2*– at the C^1* center and –C^1*–C^2*–C(O)– at the C^2* center in **2b**, respectively. Only these helices need to be considered because they fall into the corresponding catalyst ring structure, therefore, determine the catalyst's handedness). The polarizability sequence around chiral centers flips from N<C* in **2a** to C=O>C* in **2b**, so **2a** is right-handed and **2b** is left-handed. Consequently, they induce opposite chiralities in the products. Particularly interesting are the highly enantioselective hydrogenations of dehydroamino acids catalyzed by the chiral rhodium complexes because, as **3a** and **3b** in Scheme 2 shows, the principle of homohelical interactions again accounts for the directions of enantioselection while steric theories, most notably the so-called quadrant rule, appear to fail.[17] The bulkier phosphorus-substituents in both catalysts occupy the top-left and bottom-right quadrants. However, curiously, **3a** gives (+)-amino acids and **3b** the (−)-enantiomers, both in high ee.[18] These seemingly puzzling results would be expected if helical electronic effects prevail. Since in both catalysts two of the substituents at each phosphorus atom, the CH_2 and Rh, are the same (Rh>CH_2 in polarizability), the different results could be attributed to the opposite handedness of the catalyst ring helices in **3a** and **3b**, that is, –CH_2–P^1*–Rh– at the P^1* center and –CH_2–P^2*–Rh– at the P^2* center. It is the larger of the two diaryl substituents and the smaller of the two dialkyl substituents that has the larger local polarizability. It merits a note that the catalyst handedness-favored product enantiomer correlations reached here are generally applicable to other highly enantioselective catalysts examined in the same reactions.

2.1. Homohelical induction in asymmetric catalysis

Although the principles of this helix theory are applicable to any asymmetric process, in the following discussions we choose to focus on asymmetric hydrogenations for the following considerations: (1) these fields are most fruitfully developed and the several reactions of known mechanisms, established by pioneering studies,[2a] provide a solid platform on which the independent helix analysis, thus the predictive power of the theory, can be tested against numerous experiments; (2) a reaction mechanism itself does not reveal its potential stereochemical bias towards a pro-chiral substrate, so previous stereochemical rationales have largely been applying the steric hindrance into the corresponding enantioselection-determining steps in those known mechanisms and deducing the sense of asymmetric induction by the more sterically favored pathways. Spectacular exceptions to each of these steric rationales exist and it is curious to see whether this electronic theory, specifically helical electronic effects and conservation of helicity, could yield more general catalyst-product stereochemical correlations; (3) these fields encompass both metal-based catalysis and organo-catalysis thus are of exemplary generalities for the theory to illustrate its principles and utilities.

Scheme 3 shows how a molecule is being hydrogenated, the respective mechanism has been established. Case A illustrates ruthenium-catalyzed hydrogenations of functionalized ketones. Func-C_α–(C=O)–R where 'Func' is a functional group, should coordinate to a (*R*)-BINAP-ruthenium catalyst.[19] The left-handed helicity of the (*R*)-BINAP ligand induces a left-handed helicity in the substrate ring Ru–C*–C_α-Func. The essential points are that the ruthenium atom, whose polarizability is much larger than that of any organic C_α fragment, is bonded to the carbonyl carbon and the polarizabilities of the R groups, which could be alkyls or aryls, should all be larger than that of the hard acid OH^+. The enantiomeric excesses achieved in these hydrogenations are all high, and the directions of enantioselection are all in accord with this model. Notably, the direction of



Scheme 3. Homohelical induction in (A) Ru-catalyzed hydrogenations of functionalized ketones; (B) Ru-catalyzed hydrogenations of simple ketones; and (C) Itsuno-Corey reductions using an (*S*)- oxazaborolidine catalyst. The catalysts' helicities are as indicated and the hydrogenations all proceed with the stereochemistries according to the homohelical induction principle. Observed ee is listed under the structure. The ketone substituents of larger polarizability are shown on the left (in blue) and those of smaller polarizability are shown on the right (in red). Notice that hydrogen attaches to the same face of each ketone, even when the larger group is on the right (examples **5a–c**, **5e**, and **6c–e**). Substrates whose substituents do not differ appreciably in polarizability are reduced with low ees (examples **5d**, **5e**). Func=functional group; R=alkyls or aryls. X=O, NH, NR and S; Y=OMe, Br. Z=$CH(CH_3)OSi^tBu(Ph)_2$. Ar=3,5-$(CH_3)_2C_6H_3$, Ar′=*p*-$OCH_3C_6H_4$. Un=unsaturated group. G_L=substituent of larger size; G_S=substituent of smaller size.

enantioselection is reversed in the hydrogenations of *o*-methoxy- and *o*-bromo-benzaldehydes to give **4j**, which is in accord with the theory because deuterium, unlike other R groups, is less polarizable than OH^+.[20]

Case B is ruthenium-catalyzed hydrogenations of unfunctionalized ketones. In the case of simple unfunctionalized ketones, asymmetric hydrogenations are catalyzed by diphosphine-diamine-Ru-compounds, but the mechanisms followed are very different.[21] They involve the pericyclic transfer of hydrogens from ligand nitrogen to substrate oxygen and from ruthenium to carbon. Accordingly, the very large difference between the polarizabilities of Ru and C_α, which dominate the chiralities in the case of functionalized carbonyl hydrogenations, in this case cannot make the chiralities insensitive to the nature of ketone substitutents. Because the polarizability difference between H and O in a partially broken C=O bond is relatively small, it is the polarizability distinction between the two carbonyl substitutents P_L and P_S that determines the twisting of the substrate ring helix –H–C*–O–. Since in both catalysts in Scheme 3, the diphosphine ring and diamine ring both have right-handed helicities, that is, helix -P–C=C–C=C–P- from the atropisomeric skew and helices –N–C^1*–C^2– at the C^1* center and –C^1–C^2*–N– at the C^2* center (both analyzed by two local polarizability sequences: Ph>H; and C*>N. Note also that it is exemplified here that a complete knowledge on the local polarizability ranking of all the four groups is not needed because, as previously emphasized in helicity analyses of **1**–**3**, usually only one helix at a chiral center, that is, the helix that develops along the catalyst/ligand ring structure, is critical for chiral interaction thus is under concern), the homohelical induction principle requires the hydride to attack preferentially as shown, because only with this enantiofacial selection can the substrate ring helix –H–C*–O– also

develop right-handed helicity in the transition state (polarizability sequences: O > H; and $P_L > P_S$). Note that it is not the sizes of the substituents that are important, but their local polarizabilities, which accords with experience, for only aromatic and unsaturated ketones have thus far been found to give high enantioselectivities. Herein, for **5a–d** substituents local polarizabilities are known to follow benzene > pyridine > thiazole > oxazole,[22] and for **5e** benzene is more polarizable than another benzene that is electron-withdrawn by a *para*-CF_3 group. Interestingly, it can also be seen that the higher the local polarizability distinction, the higher the ee. It should be pointed out that application of conventional steric considerations to **5d** is rather hopeless because the substituents are nearly equal in sizes, and to **5a–c** and **5e** yields wrong enantiomers because in each of them the group on the right is larger than that on the left.[19,23]

Case C shows the expected outcomes of oxazaborolidine-BH_3 catalyzed ketone reductions using a so-called Corey–Bakshi–Shibata ('CBS') catalyst.[24] The (*S*)-configured catalyst has right-handed helicity.[10] For **6a–b**, whose substituents are isosteric, it is unclear how steric effects could lead to the large enantiomeric excesses observed. For **6c–e**, whose left-side substituents are less bulkier than the right-side ones, they again seem to give the wrong predictions. However, in each of these cases the homohelical induction principle does lead to the result observed. Particularly important substrates for asymmetric hydrogenations are those represented in **5f** and **6f**. It is well appreciated that the unsaturated group could be generally varied among aromatics, hetero-aromatics, ferrocenes, olefins or acetylenes, despite considerable changes on sizes, without sacrificing the enantioselections, which have been, however, customarily attributed to steric effects.[19,24] It is now clear that these groups share a highly polarizable π-electron component and it is the comparably high π-versus-σ alkyl local electronic polarizability distinctions that ensure their successes. It should be emphasized that molecules employed in the above cases are just illustrative, and as summarized in the Supplementary data, this polarizability rule not only equally effectively applies to all other substrates and other enantioselective catalysts, but also to other asymmetric reactions as well, such as transfer hydrogenations, hydroborations and Heck reactions etc., and perhaps most significantly, it accommodates results that steric theories cannot.[10,25] The above discussions illustrate some utilities of the principle of the conservation of helicity in rationalizing and predicting stereochemical outcomes for asymmetric reactions whose mechanisms in their analogous achiral processes are known. Alternatively, the principle may be also useful for clarifying reactions of unknown mechanisms under the notion that the combination of independent helicity analysis and a reasonable mechanistic proposal should lead to stereochemical results that are in accord with experimental observations.

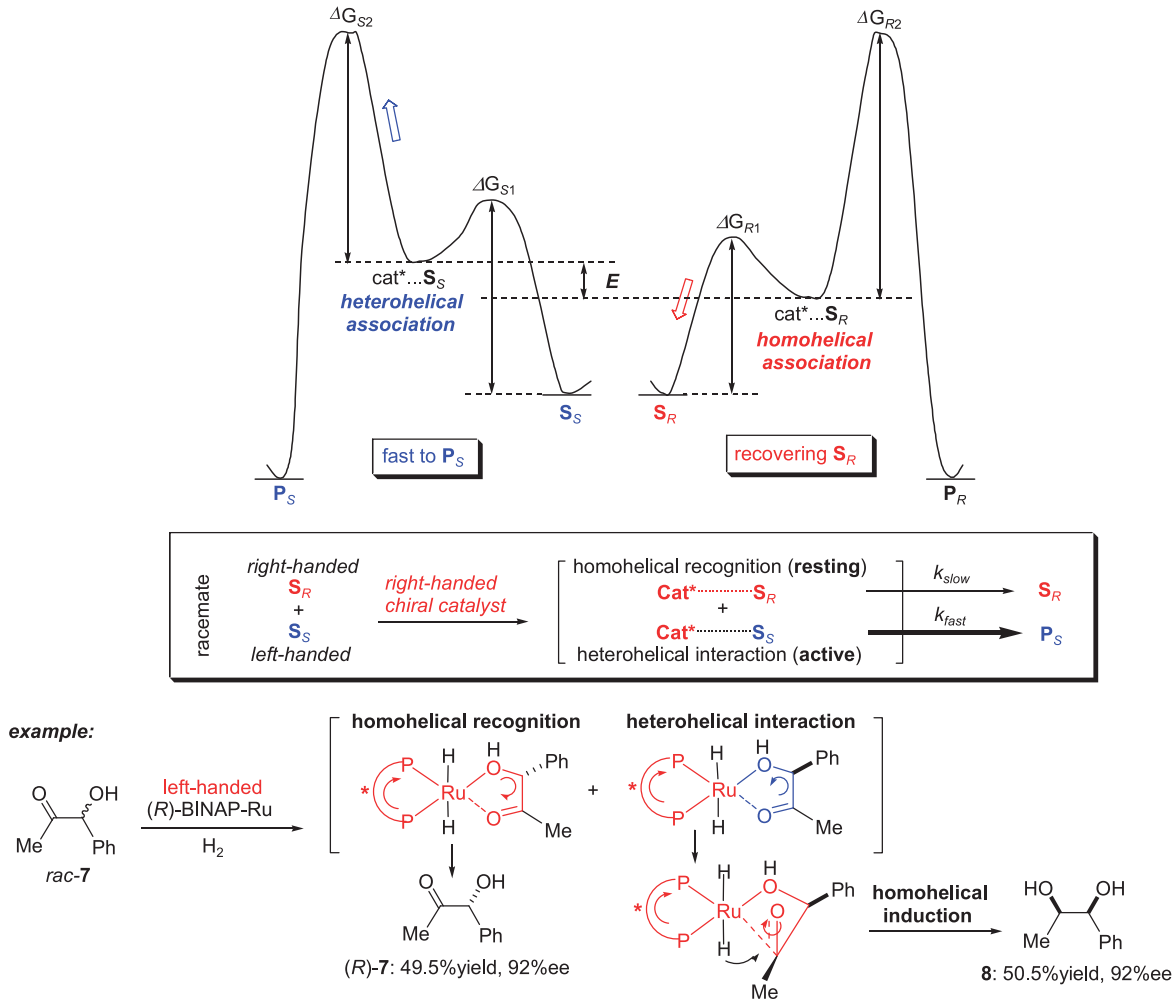
2.2. Homohelical recognition control in kinetic resolution

Kinetic resolutions originate from enantiomers in an asymmetric environment reacting at different rates.[26] They are often achieved by treating racemates with chiral catalysts, which, ideally, leads to the derived product and the recovery of the more slowly reacting enantiomer, both in high yield and enantiomeric excess. Conceptually the realization of a kinetic resolution process is attributed to a chiral catalyst's ability to discriminate the enantiomers, that is, chiral recognition occurs only between one enantiomer and the catalyst.[27] There are two basic stereochemical questions associated with such a process. One, how does a chiral catalyst enantioselectively recognize that enantiomer? Two, does that recognition render a resultant substrate-catalyst combination more reactive, or less?

We have proposed above that chiral molecular recognition electronically follows a homohelical interaction mechanism, in which the chiral host can enantioselectively recognize the guest enantiomer that possesses the same helical handedness in their enantio-discriminating complexations. Applying this homohelical recognition principle to a kinetic resolution system seems to be informative in answering both questions posed above: the catalyst can selectively recognize one enantiomer of the racemate by electronically favorable homohelical interaction and that electronic preference makes the corresponding combination lower in energy and thus less reactive.

The idea is illustrated in Scheme 4. Considered is the kinetic resolution of a racemic substrate **S** by the action of a right-handed catalyst (cat*). The reaction in this simplified picture has two steps: the association of catalyst with substrate, in which both a homohelical pair cat*-$\mathbf{S}_R$ and a heterohelical pair cat*-$\mathbf{S}_S$ are formed; and the subsequent derivatization reaction that is often rate-determining. If, as shown previously, homohelical electronic interactions are favored, intermediate cat*-$\mathbf{S}_R$ is lower in energy than cat*-$\mathbf{S}_S$. This may raise the barrier ΔG_{R2} above that of ΔG_{S2}. In consequence, cat*-$\mathbf{S}_R$ releases $\mathbf{S}_R$, and the cat*-$\mathbf{S}_S$ defines a kinetically active reaction channel that delivers the derived product $\mathbf{P}_S$. At a certain conversion, both $\mathbf{S}_R$ and $\mathbf{P}_S$ would be produced in excess. This conclusion is of practical utilities because a simple examination of helical electronic interactions in the catalyst–substrate associations, whose structures are often more easily inferable than those of the intermediates in the derivatization steps, could suggest useful clues to the reaction stereochemical outcomes.[28]

Kinetic resolution of *rac*-**7** by stereoselective hydrogenation catalyzed by a (*R*)-BINAP-Ru catalyst exemplifies this homohelical recognition control principle (Scheme 4).[29] The catalyst features a left-handed ligand ring helix to which *rac*-**7** complexes as a functionalized ketone. The substrate ring helix –Ru–O–C*–C═O– is left-handed in (*R*)-**7** and right-handed in (*S*)-**7** owing to polarizability sequences C═O > O, and Ph > H. Therefore, (*R*)-BINAP-Ru/(*R*)-**7** is homohelical and (*R*)-BINAP-Ru/(*S*)-**7** is heterohelical. The former, because it is lower in energy, leads to (*R*)-**7** being recovered in a 49.5% yield and 92% ee. The latter leads to hydrogenation and, as already discussed in case A of Scheme 3, the establishment of stereochemistry at the newly formed chirality is controlled by homohelical induction, which yields **8** in a 50.5% yield and 92% ee. This example not only shows that the full stereochemical course



Scheme 4. A simple homohelical recognition control profile for the stereochemical course of a kinetic resolution. When a chiral catalyst interacts with a racemate, the homohelical recognition pair leads to the substrate enantiomer being recovered and the heterohelical interaction pair is reacting. The bottom shows the homohelical recognition control in kinetic resolution of *rac*-**7** by (*R*)-BINAP-Ru-catalyzed stereoselective hydrogenation.

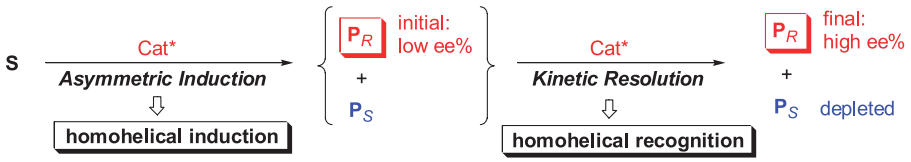
in an efficient kinetic resolution process can be rationally deduced on the basis of homohelical recognition/induction analysis, but it also suggests that the tendency to gain homohelical interaction in an initially unfavorable heterohelical catalyst–substrate association may serve as the driving force for kinetic activity. Thus, homohelical interactions are generally favorable in chiral systems. Systems that enjoy these interactions are less reactive than those that do not.

This electronic theory accounts for the observed results for a wide variety of efficient kinetic resolution systems. It is very predictive. It also accommodates results that conventional steric reasoning cannot. Details are assembled in the supplementary data.[10] Among the systems analyzed are: stereoselective ketone hydrogenations, transfer hydrogenations, ring closing metatheses, sulfides/sulfoxides oxidations, lactones ring openings, kinetic resolution of alkyne-containing substrates, epoxides ring openings (hydrolytic kinetic resolutions), kinetic resolutions of allylic alcohols by dioxirane-catalyzed oxidation, asymmetric epoxidations-based kinetic resolution of secondary allylic, furyl, pyrryl, thienyl and amino alcohols, asymmetric dihydroxylations-based kinetic resolutions, asymmetric alcoholyses of anhydrides, asymmetric ring opening of anhydrides with chiral Lewis acids, Pd-catalyzed aerobic oxidative kinetic resolution of alcohols, kinetic acylations of alcohols by chirally modified DMAPs, and several other processes related to the above systems. Aided by this theory, we also suggest answers to some important questions, such as why dihydroxylations lead to poor kinetic resolutions even though they lead to excellent asymmetric inductions.

Two consequences of homohelical control as the governing electronic factor in efficient kinetic resolutions relate to the stereochemical link between asymmetric induction and kinetic resolution.

1. Since both asymmetric induction and kinetic resolution are both favored by homohelical interactions, enantioselective syntheses should be facilitated by one-pot processes in which the same catalyst or two different catalysts of the same helicity bring about both reactions. This is illustrated in Scheme 5.

Not only does asymmetric catalysis tend to generate an excess of product enantiomer $\mathbf{P}_R$ from pro-chiral substrate **S**, but the subsequent kinetic resolution step tends to



Scheme 5. A 'push–pull' mechanism for product enantio-enrichment in a one-pot asymmetric catalysis-kinetic resolution reaction.

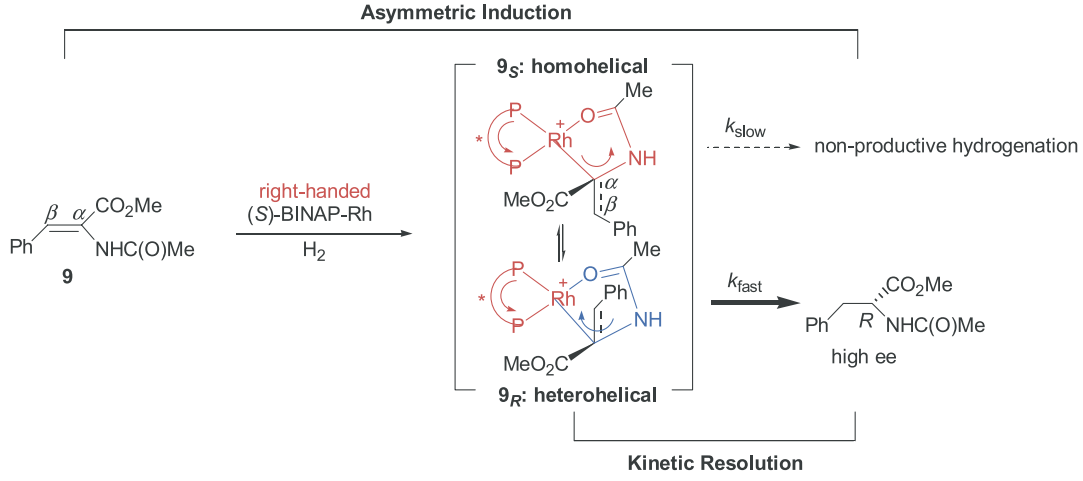
enhance the selectivity by depleting the oppositely handed and more reactive enantiomer $\mathbf{P}_S$ (the latter is more reactive because it forms the heterohelical complex with the catalyst). In other words, while homohelical electronic interaction generates homohelicity in the former, it preserves it in the latter! This suggests that appropriate combinations of asymmetric catalysis and kinetic resolution in a single flask, even with catalysts of mediocre enantio-differentiation ability, should allow reactions that initially give products of low ee to give them, ultimately, in high ee. There should be a 'push–pull' mechanism for enantio-enrichment. Systems employing this strategy, although rare presently, have already proven successful.[10,30]

2. Are asymmetric induction and kinetic resolution stereochemically identical? The fundamental basis for both is clearly homohelical electronic interaction. Consider, for example, asymmetric hydrogenation of enamides **9** catalyzed by chiral diphosphine/Rh complexes. It is known that in this reaction, the minor, not the predominant catalyst–substrate complex, leads to the observed product enantiomer.[31] When the catalyst is, for example, right-handed (*S*)-BINAP-Rh, helical electronic interaction analysis shows that the predominant complex $\mathbf{9}_S$ is homohelical and the minor one $\mathbf{9}_R$, is heterohelical (Scheme 6). Substrate ring helicity is assigned primarily based on the helix –O═C–NH–C_α–Rh– on the C_α center (polarizabilitites: Rh > N, and ester C═O > β-2° CH_2). It has been shown that C_α lies closest to the Rh coordination plane and enantioselectivities in enamide hydrogenations are governed by the nature of the C_α-substituents.[32]

This suggests that there is no clear conceptual boundary between asymmetric induction and kinetic resolution. They share the same homohelical identity in realizing stereochemical control. When viewed as the transformation of an achiral alkene substrate to a chiral amino acid product, the reaction is formally an asymmetric induction. However, when viewed as the transformation of the catalyst–substrate complexes $\mathbf{9}_S$ and $\mathbf{9}_R$ (in which the substrate becomes chiral) to products, it is essentially a kinetic resolution! The key point is that the catalyst-substrate complexes have strong tendency to achieve homohelical electronic interactions that lower the system energy (as compared to the corresponding heterohelical interaction). If the homohelical character acquired in this early-stage complexation is not sufficiently high and more energy lowering can be gained in a late-stage intermediate along the reaction coordinate, as in the vast majority of cases of asymmetric synthesis, the reaction will proceed through this homohelical pathway to deliver the favored product enantiomer. However, if an inversed situation is encountered, such as that found in this type of hydrogenation, the initial homohelical complexation characterizes a resting state which is reluctant to undergo further reaction, and consequently the dominant process is kinetic resolution. This homohelical interaction paradox on asymmetric induction-versus-kinetic resolution essentially exists in all chirality producing processes, and an overwhelming predominance of either one can lead to high levels of enantioselection.

3. Conclusion

In summary, the assumption that there is an electronic interaction between chiral molecules, which we call homohelical interaction or the conservation of helical asymmetry, leads to correct analyses of the outcomes of many asymmetric transformations, even in cases that seem not to be predicted correctly on the basis of prevailing theories, which consider largely steric effects. The applications discussed suggest that helical electronic effects



Scheme 6. The operation of kinetic resolution in asymmetric enamide hydrogenation.

may generally exert greater control than steric effects in enantioselection. In the next paper in this issue, it is further shown that high ees in an asymmetric reaction can be achieved when the characteristics of the interacting helices, such as those of a catalyst and the substrate complexed to it, are matched.[33] Consideration of such interactions could help guide the design of effective chiral catalysts and lead to new theories for electronic control in asymmetric induction. Using this principle, we suggest that homohelical recognition control is the governing electronic factor in kinetic resolutions. The described 'push–pull' mechanism for enantio-enrichment might at a very general level account for the homochirality observed in Nature. The theory is novel, simple, and general, and it possesses predictive power. We believe that generalizing molecular chirality on the basis of inherent helicity and unifying asymmetric induction and kinetic resolution in a single framework of homohelical electronic interaction should facilitate the rational discovery of new efficient asymmetric reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.05.058

General helix structure analyses for molecules of axial-, planar-, and other types of chiralities; detailed helicity assignments for chiral catalysts mentioned in the text; more illustrative examples of homohelical induction analysis in various asymmetric catalytic processes; and homohelical recognition control analyses for all kinetic resolution systems mentioned in the text.

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