Supplementary Material

Conservation of Helical Asymmetry in Chiral Interactions

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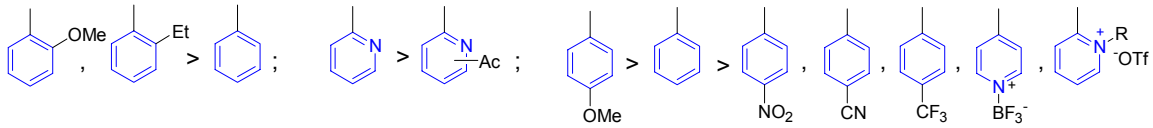
1. Assignments on polarizability sequences

Although polarizabilities of many groups/bonds are unknown, it is important to note that, for the helicity analyses, only the relevant local polarizabilities rankings, but not their values, are primarily concerned. They can be deduced with consistency and reliability on the basis of some general ranking principles summarized in the text. Compiled below is a complete list of polarizabilities sequences used throughtout the work described in the text and in this Supplementary Material.

a. Transition metals > organic groups:
M > C, (M = Rh, Ru, Pd, Ti, Os); Rh > N.

b. Lone pair electrons > bonding electrons:
lone pair electrons > bonding electrons in S-O bond, S=O bond in Ts group, or C=C bond in Ph.

c. Electron-rich groups > electron-poor analogues:



d. The Brewster's refractive indices list, I > Br > SH > Cl > C≡N > C_6H_5 > C=O > CH_3 > NH_2 > OH > H > D > F, is actually an illustration of three polarizability ranking principles: aromatic/π-groups > alkyls, in a period atoms with lower nuclear charges > atoms with higher nuclear charges, and in a group atoms with larger numbers of electron shells > atoms with smaller numbers of electron shells. Applications of these principles herein are: (Ar: aromatic or π-groups; R: alkyls) Ar > R > OH > H, D; C=X > X (X = C, N, O); C≡C > R; C≡C > O; Ph > C=O, C=N; Ph > cyclopropyl; P=O > R; N=C > C; O=Os > C; P in R_3P > C; S > C > N, O; B^- > C.

e. Strained alkyls > unstrained alkyls:
carbons in cyclopropyl > carbons in Me, ^{i}Pr; ***C***H_2 in 5-membered ring > ***C***H_2 in linear $CH_2CH_2{}^{t}$Bu.

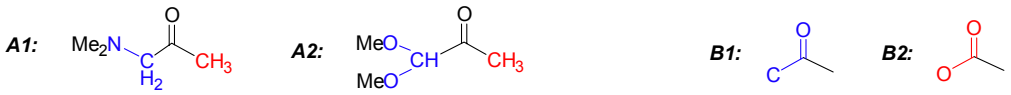
f. In simple alkyls less-substituted carbons > more substituted carbons (due to ***C***-H > ***C***-C):
CH_3 > 1^o ***C***H_2R > 2^o ***C***HR_2 > 3^o ***C***R_3.

g. In a three-membered epoxide ring, the electrons in both the protruding Op_y and Op_z lone-pair electrons orbitals and the two strained O-C σ-orbitals experience much less nuclear attractions thus are more polarizable than electrons in alkyl carbons. In such a special situation, we assign O > C. This polarizability assignment is consistent with the physical helix handedness-rotation sign correlations found in many small epoxides. See Ref. 3 of section 17 in this Supplementary Material.

h. Local polarizabilities of the central carbons [***C***H_2N, ***C***$H(O)_2$, ***C***H_3 in ***A1*** and ***A2***, shown below] and the carbonyls (**C=O** in ***B1*** and ***B2***) are affected by the attaching atoms and are not differentiated in the above polarizability ranking methods. Therefore, polarizabilities of the following groups (highlighted in blue and red colors) are calculated using the additivity methods (Miller, K. J. *J. Am.*

Chem. Soc, **1990**, *112*, 8533-8542. See specifically Table IV on page 8542 therein). They are as follows (α: polarizability):

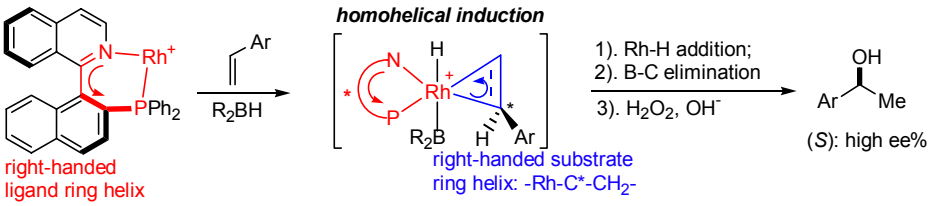
$\alpha(CH_2N) = \alpha(CTE) + 2\alpha(H) + \alpha(NTE) = 1.061 + 2\times0.387 + 0.964 = 2.799 Å^3$;
$\alpha(CH_3) = \alpha(CTE) + 3\alpha(H) = 1.061 + 3\times0.387 = 2.222\ Å^3$;
$\alpha(CH(O)_2) = \alpha(CTE) + \alpha(H) + 2\alpha(OTE) = 1.061 + 0.387 + 2\times0.637 = 2.722\ Å^3$;
$\alpha(C\text{-}C{=}O) = \alpha(CTR) + \alpha(OTR4) + \alpha(CTE) = 1.352 + 0.569 + 1.061 = 2.982\ Å^3$;
$\alpha(O\text{-}C{=}O) = \alpha(CTR) + \alpha(OTR4) + \alpha(OTE) = 1.352 + 0.569 + 0.637 = 2.558\ Å^3$;



On the basis of these values, we assign $\boldsymbol{C}H_2N > \boldsymbol{C}H_3$, $\boldsymbol{C}H(O)_2 > \boldsymbol{C}H_3$, and ketone carbonyl C-**C=O** > ester carbonyl O-**C=O**. It is important to note that the additivity methods use empirical atomic and bond polarizabilities that are refined from a large set of experimental molecular polarizabilities. Therefore the methods are successful for comparing groups of similar structures and atomic hybridization states (typically in 2.8% error).

2. How can enantioselections arise electronically? Some illustrative analyses

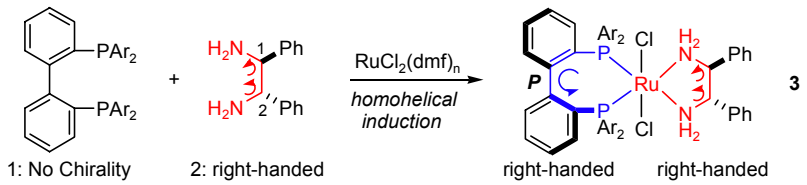
a. ***Asymmetric hydroboration:*** Shown below is selective recognition of an enantiotopic face in a *pro*-chiral vinylarene in the hydroboration catalyzed by a chiral Rh-Quinap complex.[1] Because the (*S*)-configured catalyst ring has a right-handed helicity (in red), homohelical induction should favor addition to the *Re*-face of the C=C bond because the substrate ring -Rh-C*-CH_2- (in blue) would also define a right-handed helical twist owing to the polarizability sequences: Rh > $\boldsymbol{C}H_2$, and Ar > H. The subsequent steps give the alcohol product of expected absolute stereochemistry.



Reference:

1. Doucet, H.; Fernandez, E.; Layzell, T. P.; Brown, J. M. *Chem. Eur. J.* **1999**, *5*, 1320-1330.

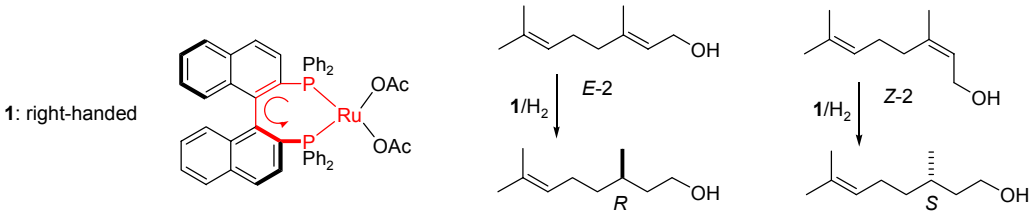
b. ***Point-to-axial chirality induction:*** the following scheme considers the induction by chiral ligand **2** of axial chirality in the conformationally flexible **1**.[1] The diamine ligand ring -H_2N-C*-C*-NH_2- have synergistic right-handed twists at the two chiral centers, i.e., -N-C^1*-C^2*- at C^1 and -C^1*-C^2*-N- at C^2, owing to the polarizability sequences Ph > H, and C* > N. This ring helix thus preferentially induces a right-handed helix, or *P*-configuration, in the diphosphine moiety of **3**.[2]



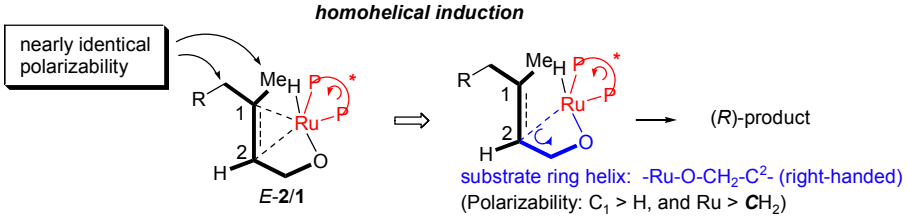
References:

1. (a) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem. Int. Ed*. **1999**, *38*, 495-497; (b) Aikawa, K.; Mikami, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 5455-5458.
2. For another interesting example of homohelical induction controlling point-to-axial chirality transfer, see: Superchi, S.; Casarini, D.; Laurita, A.; Bavoso, A.; Rosina, C. *Angew. Chem. Int. Ed.* **2001**, *40*, 451-454.

c. *Asymmetric hydrogenation of functionalized alkenes*: The influence of C=C bond geometry on the sense of asymmetric induction can be profound. For example, in **1**-catalyzed hydrogenation of **2**, the *Z*/*E* isomers give opposite senses of induction with the same catalyst. This can be easily rationalized on the basis of homohelical induction.[1]



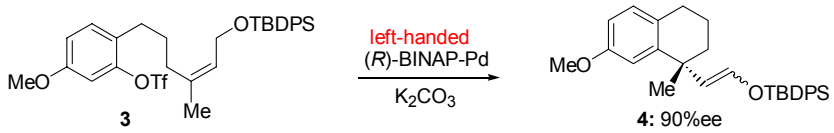
In *E*-**2**/**1** complexation shown below, the right-handed **1** attaches to the C=C at its back face because only with this facial selection can the substrate ring helix -Ru-C_2*-CH_2-O- be right-handed (note that the helix at the C_1 center doesn't contribute appreciably to homohelical induction because of the nearly identical polarizability of ***C***H_3 and ***C***H_2). Hydrogen delivery to this face therefore leads to (*R*)-product. Clearly, in *Z*-**2**/**1** complexation, homohelical induction requires the right-handed **1** to attach to the front face of C=C, which yields (*S*)-product. Opposite *Z*/*E* alkenes enantiofacial recognitions by homohelical inductions with the same catalyst also occur similarly in other systems, such as asymmetric isomerizations[2] and allylic alkylations.[3]



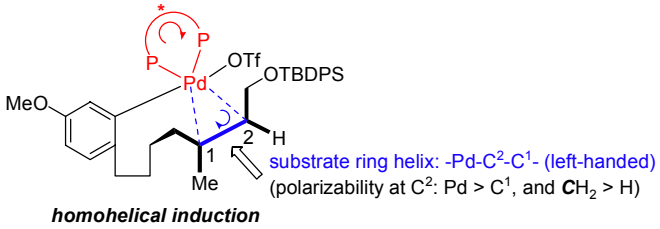
References:

1. Noyori, et.al. *J. Am. Chem. Soc.* **1987**, *109*, 1596.
2. Akutagawa, S. chapter 41.4 of of *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, **1999**.
3. Trost, B. M.; Shen, H.C.; Dong, L.; Surivet, J-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276-9277.

d. *Asymmetric Heck reaction*: The (*R*)-BINAP-Pd complex-catalyzed cyclization of **3** leads to efficient construction of **4** that features a quaternary chiral center.[1] Suggest a stereochemical rationale.

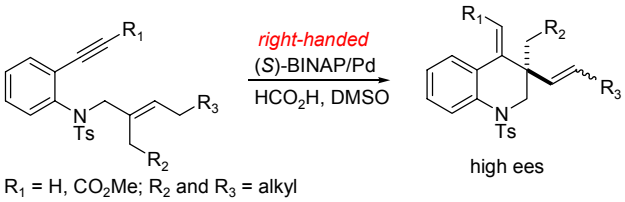


The transition state is shown below. The enantioface of the double bond is recognized through homohelical induction by the left-handed catalyst: the substrate ring helix can be left-handed only when the Pd catalyst attaches to the back-face of the C=C bond (note that the substrate ring helix twisting largely comes from the C^2 chirality; the substituents at the C^1 center, i.e., ***C***H_2 and ***C***H_3, differ little in polarizability thus make little contribution).[2]

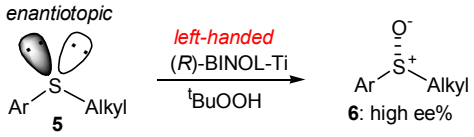


References:

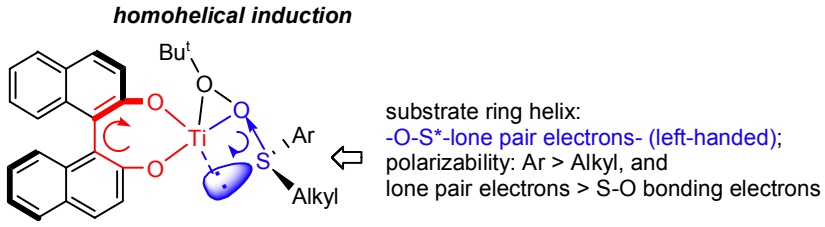
1. (a) Kojima, A.; Takemoto,T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 4876-4877; (b) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477-8478. Note that in this reference the Heck product (i.e., compound of **17** in Scheme III) stereochemistry was incorrectly assigned as (*S*) due to an earlier mis-assignment of the absolute configuration of natural product (-)-Eptazocine. The correct Heck product configuration was shown in compound **90** in Scheme 26, on page 479, of the review article: Shibasaki, M.; Vogl, E. M. "*Asymmetric Heck Reactions*" in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, **1999**.
2. Using the right-handed nature of a (*S*)-BINAP-Pd catalyst, the reader are encouraged to rationalize the stereochemical courses in the following highly enantioselective ene-type cyclizations by homohelical induction. See: Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704-4705.



e. *Asymmetric sulfide oxidation:* Oxidation of **5** with a left-handed (*R*)-BINOL-Ti catalyst gives **6** in high ees. Suggest a stereochemical rationale.



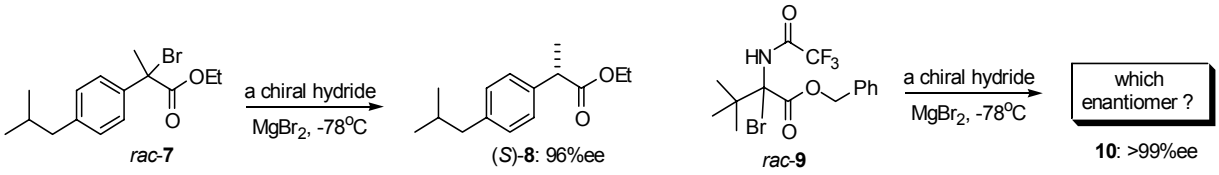
The observed enantiofacial selection may be explained on the basis of homohelical induction. The analysis is show below. An interesting feature in this system is the operation of tandem asymmetric induction-kinetic resolution of the sulfoxides: the ees of initially formed **6** (~50%ee) was improved to a much higher level at the final stage of reaction (>99%ee). Both steps are shown to be under homohelical interaction control.[2]



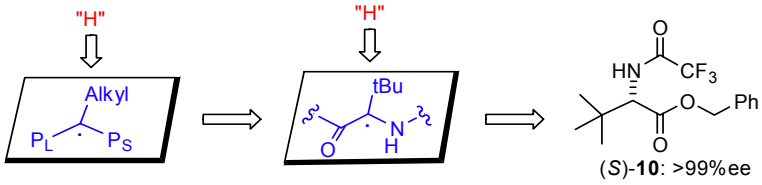
Reference:

1. Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529-4533.
2. See specifically Scheme 5 in the text and section 14.

f. *Asymmetric radical reaction*: *C&EN* recently highlighted a free-radical chemistry for practical chiral synthesis:[1] *rac*-**7** is transformed by this technique into (*S*)-**8** in 96%ee. Question: without knowing any mechanistic details of the reaction, deduce the stereochemical outcome of *rac*-**9** under identical conditions by making a simple analog of homohelical induction between reactions of **7** and **9**.

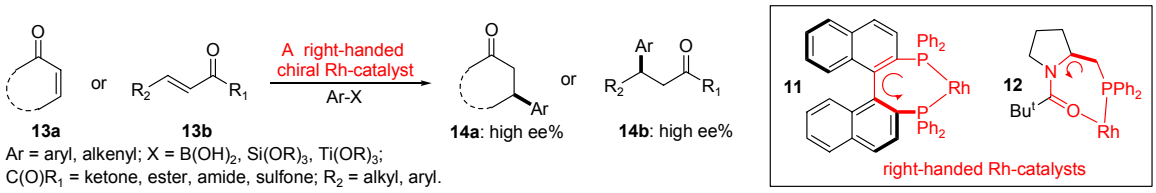


The chiral hydride has a certain helicity that allows it to recognize one of the enantiofaces of the *pro*-chiral radical intermediate by a certain homohelical induction mechanism. Inspection of the enantiofacial selection of hydrogen delivery to the radical generated from *rac*-**7** reveals the trajectory shown in below in which P_L = more polarizable phenyl and P_S = less polarizable ester carbonyl. This selection must be followed in the reaction of *rac*-**9** in which, accordingly, the P_L = carbonyl and P_S = NH. Consequently, (*S*)-**10** is produced.

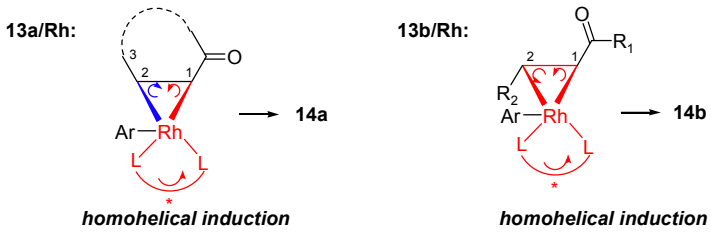


References: Rouhi, A. M., *Chem & Eng News*, July 14, **2003**, 34-35.

g. ***Asymmetric conjugate addition:*** Right-handed Rh-complexes **11** and **12** (polarizabilities: ***C***H_2 > H; and ***C***H_2P > N) catalyze efficient 1, 4-addition of a range of Ar-X to substrates **13a** or **13b** in high ees. Suggest an enantiofacial recognition mechanism on the substrate double bonds that accounts for the observed absolute configurations of products **14a** and **14b**.



The correspnonding homohelical induction models, **13a**/Rh and **13b**/Rh, are shown below. Both chiral centers, C^1 and C^2, contribute to the helix twisting in the substrate ring structure -Rh-C^1*-C^2*-Rh-. The ring helix at the C^1 cneter, i.e., -C^2-C^1*-Rh-, is right-handed in both models. Note that the ring helix at the C^2 center, i.e., -C^1-C^2*-Rh-, is left-handed in **13a**/Rh (polarizabilities: C^3 > H; and Rh > C^1), but is right-handed in **13b**/Rh (polarizabilities: R_2 > H; and Rh > C^1). The C^1-helix in **13a**/Rh dominates the substrate ring twist because the π-electronic C=O is significantly more polarizable than the aliphatic C^3. Because of this handness reversal of the C^2-helix between the cyclic substrate **13a** and linear **13b** upon their complexations to a chiral Rh-catalyst in an enantioselection-determining step, their substrate ring helical characters differ. This leads to, from a helical electronic effect perspective, an implication that the same chiral catalyst under the same reaction conditions would induce different ees in **14a** and **14b**, which is indeed often observed experimentally.

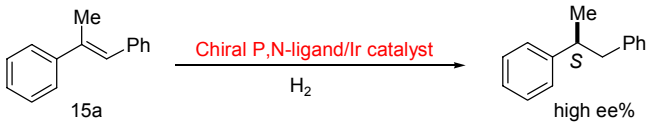


References: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829-2844.

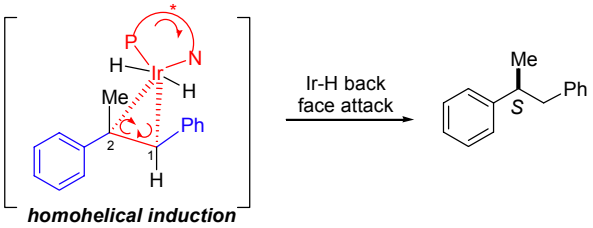
h. ***Asymmetric hydrogenation of unfunctionalized alkenes:*** The above discussion in section **2g** on the homohelical induction origin of enantiofacial selection on a *pro*-chiral C=C bond reveals a critical "*trans*-effect" of the alkene substituents polarizabilities on the corresponding substrate ring helix twisting, that is, the substituents that are *trans*- to each other define helices of the same handedness (see the substituents R_2 and C(O)R_1 in the above structure **13b/Rh**), thus they contribute synergistically to the substrate ring twisting. In other words, this *trans*-geometry has essentially a local *pseudo*-C_2 symmetry, its consequences on enantioselectivity therefore resemble the often-seen beneficial effects of the so-called C_2-symmetric chiral ligands in asymmetric catalysis,[1,2] in which the C_2-symmetry ensures that the helices from the chirality sources are synergistic to each other.

Some chiral P, N-ligand/Ir complexes catalyze highly enantioselective hydrogenation of a variety of unfunctionalized alkenes.[3] The hydrogenation of **15a** shown below is an example. Question: without

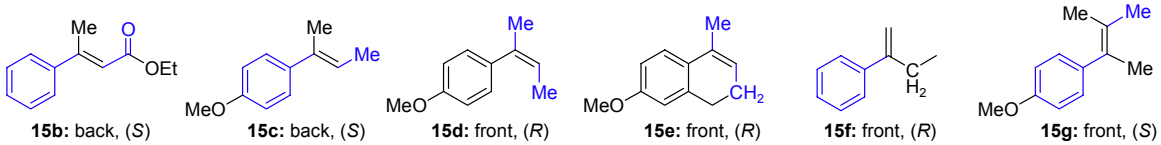
knowing any further information on the catalyst structure and the reaction mechanism, rationally deduce the products absolute configurations of substrates **15b-m** under the action of the same chirl catalyst on the basis of the reaction of **15a** and considerations on the substituents "*trans*-effect".



Upon complexation with the chiral catalyst, the *trans*-phenyls in **15a**, highlighted below in blue, should dominate the substrate ring twisting. An inspection on the product's (*S*)-configuration reveals that the catalyst selectively delivers the hydride to the back face of the double bond, suggesting its having a left-handed helicity.[4] The corresponding homohelical induction model may be constructed as below.[4] Polarizabilities for assigning the helicity of the substrate ring -Ir-C^1*-C^2*-Ir- are the following: at the C^1 center (ring helix -Ir-C^1*-C^2-), Ph > H, and Ir > C^2; at the C^2 center (ring helix -C^1-C^2*-Ir-), Ph > Me, and Ir > C^1.

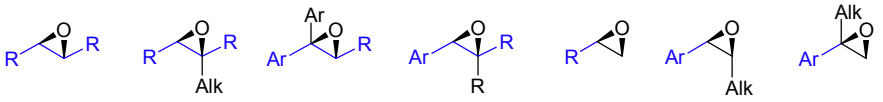


Clearly, this model shows that, simply by identifying the *trans*-substituents around the double bond of a substrate and then comparing it to **15a** in the model, one can readily tell the favored hydride attack trajectory therefore the product stereochemistry. The results are summarized below (note that in **15g** there are two pairs of *trans*-substituents, the pair of higher polarizabilities, i.e., phenyl/methyl, should be used; in **15f** the *trans*-substituents are absent, again the more polarizable phenyl is used). It merits attention here that geometrical substrate isomers, such as **15c/d**, **15j/k**, and **15l/m**, lead to the same product of opposite configurations as a natural consequence of such a "*trans*-effect" in determining substrates ring helicities.



This *trans*-effect is widely seen in alkene substrates in other catalytic asymmetric processes as well, such as in chiral ketones-catalyzed epoxidations[5] and chiral Os complexes-catalyzed asymmetric dihydroxylations.[6] The key implication of it is that the *trans*-substituents usually can cooperatively establish significant helical twisting in the relevant substrate ring, thus facilitating efficient catalyst/substrate homohelical interactions. It is generally true that in asymmetric catalysis it is usually easier to achieve high ees with substrates capable of defining significant helical twistings

(examples **15a-c**, **15h-m**) than with substrates of relatively weak helical twistings (examples **15d-g**).[2] Traditionally, discussion on the effects of alkene substrates' structures on their performances in asymmetric inductions focuses on their sizes and substitution patterns, i.e., whether they are mono-, di-, tri-, or tetra-substituted. The above analysis, however, suggests that *it may be generally more useful to consider the alkenes' substituents polarizabilities and their distribution patterns around the double bonds*. Summarized below are a range of epoxides produced from chiral ketones-catalyzed epoxidations.[5] The substituents that dominate the corresponding substrate ring twistings are highlighted in blue. With the same or similar catalysts, these epoxides are produced in the same enantiofacial selection when good-to-high ees are achieved. In accord with the relative degrees of their substrates ring twistings, epoxides **I-IV** are generally of very high ees; epoxides **V-VII** are of moderate-to-high ees; epoxides having *cis*-diaryl, *cis*-dialkyl, 1,1-diaryl, or 1,1-dialkyl substituents, not shown here, are usually of low ees.



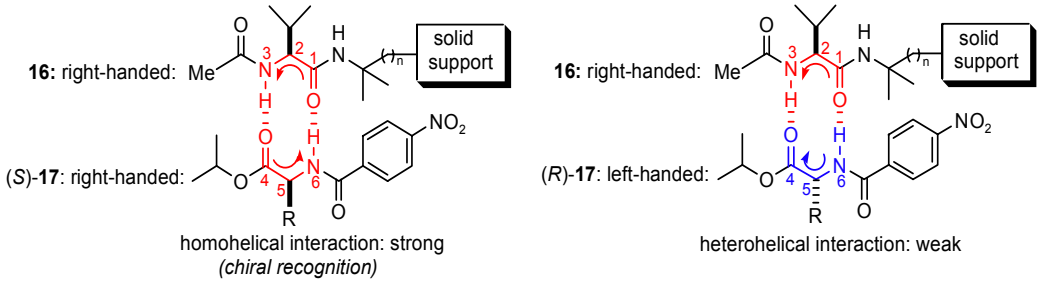
Ar: aryl, alkenyl, alkynyl; Alk: alkyl; R: either an Ar or Alk

References:

1. Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581-1590.
2. Although this *trans*-effect in a substrate and the C_2-symmetry in a catalyst are often beneficial for achieving high ees. It should be emphasized, however, that the magnitude of enantioselectivity in an asymmetric reaction is, on an electronic control sense, ultimately determined by the corresponding catalyst/substrate helical character matching in an enantioselectivity-determining step. For detailed treatments, see: (a) Wang, D. Z. the following *Tetrahedron* paper in this issue; (b) Wang, D. Z. *Chirality*, **2005**, *17*, S177-S182.
3. (a) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33-43. and references therein; (b) McIntyre, S.; Hörmann, E.; Menges, F.; Smidt, S. P.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 282-288.
4. Since the transition state structure in this reaction is unknown, the model is constructed purely for an illustration purpose, and it essentially still represents an early-stage catalyst-substrate association. It is assumed here that a Halpern-type mechanism (see Scheme 6 in the text) is not operating, that is, with a left-handed catalyst, the model leads to the observed product enantiomer. But note that this mechanistic obscurity does not interfere with the analysis since, whatever the exact mechanism is, it is reasonable to expect that substrates **15a-m** would all undergo hydrogenations in the same mechanism.
5. (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488-496; (b) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497-505.
6. For analysis on the importance of alkenes' substituents polarizabilities in achieving high ees in Sharpless asymmetric dihydroxylations, see section 20a.

i. ***Homohelical interactions in chiral recognition:*** The Scheme below considers the resolution of derivatized racemic amino acids **17** by HPLC on chiral stationary phase **16**.[1] If the molecules interact by the dual hydrogen-bonding mechanism as previously suggested, the helix involved in **16**, $O{=}C^1$-C^2-N^3H, is right-handed because the group polarizability sequences around C^2 are: $O{=}C^1 > N^3$, and

local carbon in ***C***HMe_2 > H. The helix in (*S*)-**17**, O=C^4-C^5-N^6H, is also right-handed because the R group is always more polarizable than H (its enantiomer is left-handed). Thus the observed stronger retention of (*S*)-**17** is in accord with a favored homohelical interaction.[2]

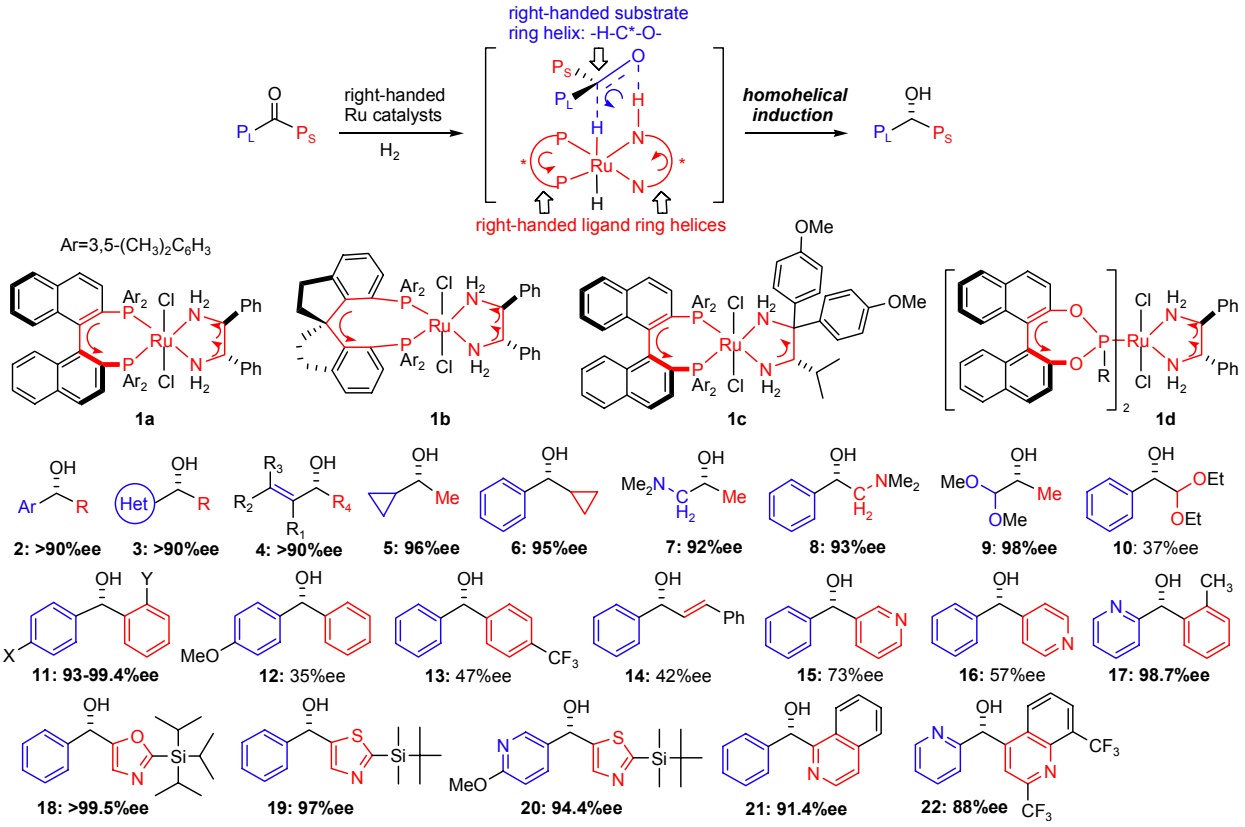


References:

1. (a) Dobashi, A.; Hara, S. *Anal. Chem.* **1983**, *55*, 1805-1806; (b) Dobashi, A.; Hara, S. *Tetrahedron. Lett.* **1983**, *24*, 1509-1510.
2. Noteworthy is that this simple homohelical recognition mechanism, when applied to a wide variety of chiral HPLC systems, is found to be capable of rationalizing and predicting enantiomers retention behaviors. See: Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347-362.

3. Ruthenium-catalyzed hydrogenations of unfunctionalized ketones

The diphosphine diamine Ru-catalysts are all shown in enantiomers of right-handed helicities. In each of them the right-handed physical helix of the diphosphine ligand ring is obvious from its axial- or spiro-configuration, and that of the diamine ligand ring is a simple consequence of local polarizability sequences around each chiral center: Ph > H, and C* > N. Note that the handedness matching between the diphosphine and the diamine rings are important. The hydrogenations all proceed with the expected stereochemistries.[1] The 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. Substrates whose substituents do not differ appreciably in polarizability are reduced with low ees.



Scheme 1. Homohelical induction in Ru-catalyzed hydrogenations of simple ketones. The ketone substituent of larger polarizability are shown on the left (in blue) and those of smaller polarizability are shown on the right (in red). Ar: aromatics; R: alkyls; Het: heterocycles or ferocenes; X = H, CH_3; Y = Me, F, Cl, Br, OCH_3.

The polarizability sequence of aromatic or π-substituent > cyclopropyl > alkyl is among those used to make the assignments for **2-6**, **8** and **10** in Scheme 1. Polarizabilities of heterocycles are known to follow the sequence benzene > pyridine > thiazole > oxazole (for **15**, **16**, and **18-21**),[2] and benzene is more polarizable than an alkene (for **14**). Amine- and oxygen-substituted alkyls are more polarizable than a methyl group (for **7** and **9**).[3] Assumed also is that electron-donating OMe groups in *para* positions enhance polarizabilities, while electron-withdrawing *p*-CF_3-groups diminish polarizabilities, of benzene rings (for **12** and **13**). *Ortho*-substituents all diminish polarizability by interfering with π-orbital co-planarity between a benzene ring and the attached carbonyl that is being reduced, not by exerting steric effects as usually assumed (for **11**).[4] This *ortho*-effect also efficiently operates in **17**, **21** and **22**. Notably the conventional steric arguments would predict wrong stereochemistries for **10**, **11**, **13**, **17-22** because the substituents at left are smaller than those at right.

References and Notes:

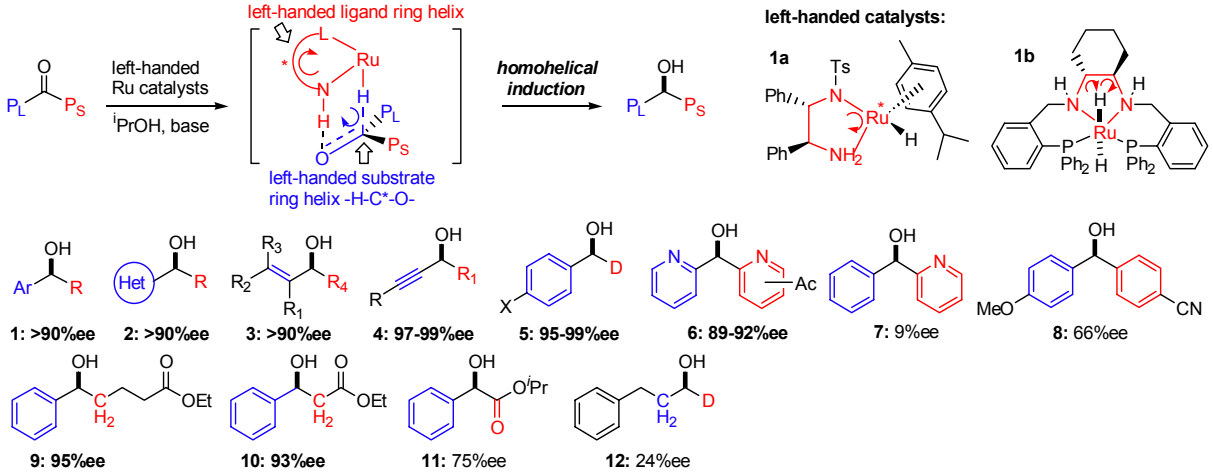
1. (a) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed*. 2001, *40*, 40-73; (b) Xie, J., Wang, L., Fu, Y., Zhu, S., Fan, B., Duan, H., Zhou, Q. *J. Am. Chem. Soc.* 2003, *125*, 4404-4405; (c) Chen, C-Y.; Reamer, R. A.; Chilenski, J. R.; McWilliams, C. J. *Org. Lett.* **2003**, *5*, 5039-5042. This paper reported highly enantioselective hydrogenations of a variety of aromatic hetero-aromatic ketones in which the stereochemical outcomes can be understood by polarizability analysis and

homohelical induction, but not by conventional steric arguments. Using this new theory, we had previously predicted on them successfully. See: Rouhi, A. M. *Chem & Eng News*, **2003**, *81*, 34-35, September 29. (d) Xu, Y. J.; Alcock, N. W.; Clarkson, G. J.; Docherty, G.; Woodward, G.; Wills, M. *Org. Lett.* **2004**, *6*, 4105-4107.

2. See Ref. 22 cited in the text.
3. See calculations in section 1h.
4. Corey, E. J.; Helal, C. J. *Tetrahedron. Lett.* **1996**, *37*, 5675-5678.

4. Ruthenium-catalyzed transfer hydrogenations of unfunctionalized ketones

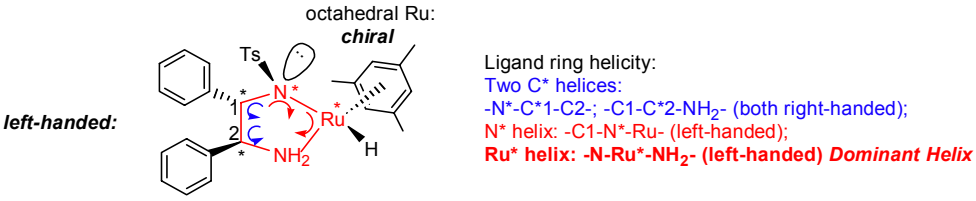
Ru-catalyzed transfer hydrogenations operate by a similar mechanism to that of direct hydrogenation.[1] One catalyst, generated *in situ*, is **1a**, and its left-handed helicity resides directly at the Ru-center.[2] Another is **1b**, whose left-handed helicity arises from the diamine ring and is assigned on the basis of the polarizability sequences C* > N and ***C***H_2 > H.[3] Homohelical induction would then have hydride attack the carbonyl groups as shown, in agreement with the experimental observations. Again, the ketone substitutes must differ appreciably in polarizability for ee to be high.



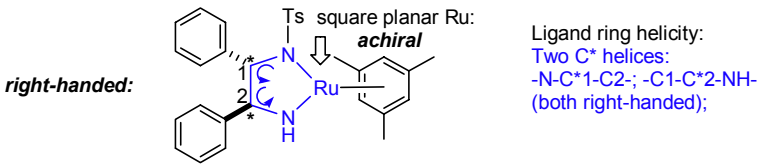
Scheme 1. Homohelical induction in transfer hydrogenations. The notations and abbreviations are the same as in Scheme 1 of section 3.

The catalyst ring helicity of **1a** is analyzed as follows: The ^{1}H-NMR in $CDCl_3$ shows this *in-situ* prepared complex exists as a single diastereomer and its structure is further confirmed by *X*-ray study. Thus, with the chiralities on the newly formed Ru* and N* centers clearly defined, the helical structures in the five-membered ligand ring that are responsible for homohelical induction can be assessed unambiguously: while both carbon chiral centers tend to generate right-handed helical twisting in the ligand ring, the ring helix around the Ru* center, -N*-Ru*-NH_2-, is left-handed because of bond twisting along the less polarizable N*-Ru* to the more polarizable Ru*-NH_2 that is triggered by the highly polarizable Ru*-arene bond (arene > H). Since this transition metal-containing left-handed -N*-Ru*-NH_2- helix is the one that is of high helical twisting and also is closest to the reaction site, and since the Ru*-H attack to *pro*-chiral carbonyls defines the product

stereochemistry, it is no doubt that this Ru*-centered helix will be the dominant factor that actually executes the homohelical induction from the ligand ring to the corresponding substrate ring.



Overall, the superb efficiency of this catalytic system in transfer hydrogenation may be a synergistic consequence of several remarkable features: (1). The introduction of strong electron-withdrawing -Ts group makes the nitrogen atom to which it attaches electron-deficient thus differentiates the polarizabilities on the two nitrogen centers; (2). The steric repulsion between the bulky -Ts and the two adjacent -Ph groups fixes the orientation of -Ts group relative to the rigid five-membered chelate ring and this, in conjunction with the concurrent repulsion between -Ts and bulky arene ligand, in turn defines the Ru* stereochemistry as *R* solely;[4] (3). The -Ts and lone pair electrons make the nitrogen another newly formed chiral center,[5] and the left-handed -C^1-N*-Ru*- helix (Note that electrons in a lone pair orbital are generally more polarizable than electrons in a bonding orbital, such as those in local S of -Ts group; and Ru is much more polarizable than C^1) enhances the left-handed helical twisting in the ligand ring; (4). The highly polarizable arene moiety (thus large arene-Ru *versus* H-Ru polarizability difference) helps set up the catalyst ring helix -N-Ru*-NH_2- that lies directly at the junction between the ligand ring and the six-membered substrate ring; (5). The N-H moiety participates in a hydrogen bond with the substrate that not only helps locate the orientation of the carbonyl in a pericyclic transition state but also facilitates the delivery of hydrogen from nitrogen to carbonyl oxygen via a metal-ligand bifunctional mechanism.[1] All of the above factors may contribute to the observed high level of reactivity and enantiocontrol in these hydrogenations.



In contrast, the precursor of the above active catalyst features a square planar Ru center that is achiral! This complex is an active catalyst in kinetic resolution of racemic secondary alcohols.[6] In this latter case the catalyst ring helicity comes solely from the two carbon chiral centers: -N-C*^{1}-C^2- and -C^1-C*^{2}-NH-, which are both right-handed (polarizabilities: Ph > H, and C* > N). This handedness, as will be shown in the kinetic resolution part of this supporting material, is in accord with its chiral recognition behaviors in the kinetic resolution of a variety of racemic alcohols.

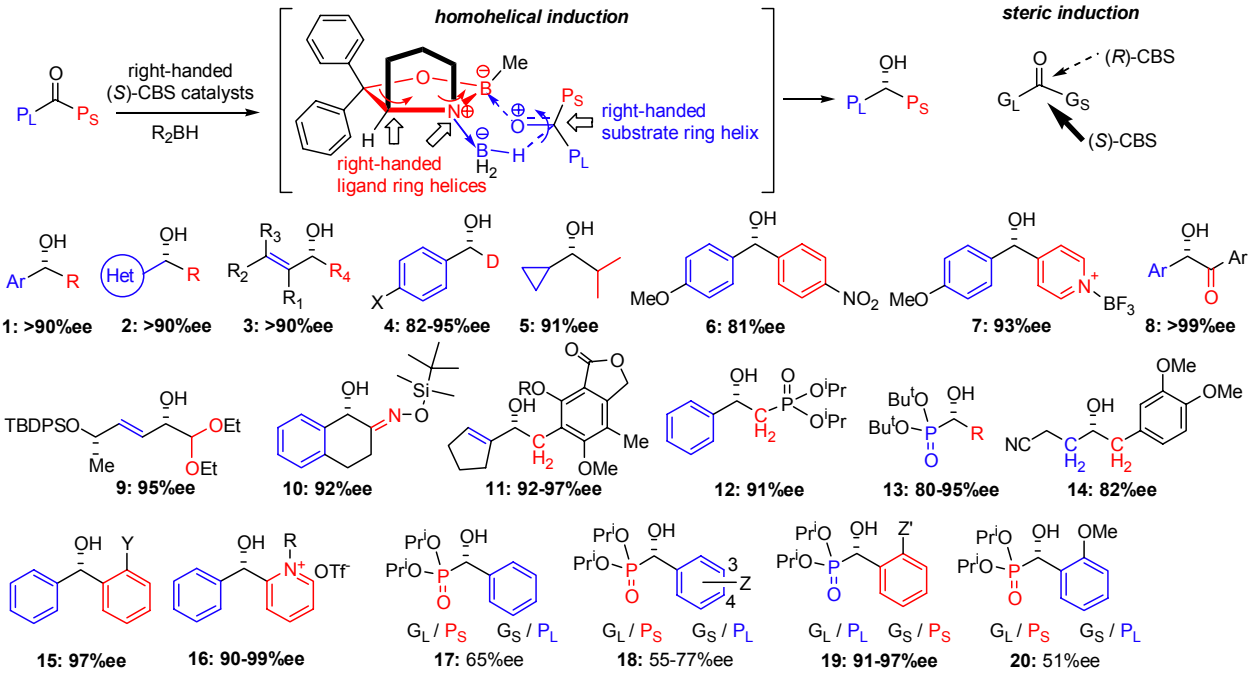
References:

1. Noyori, R., Yamakawa, M., Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931-7944.
2. Haack, K. J., Hashiguchi, S., Fujii, A., Ikariya, T., Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 285-288.
3. Noyori, R., Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97-102.
4. For the *X*-ray structure evidence, see Figure 3 on page 286 of Ref. 2.

5. The *in-situ* generated heteroatom-chiralities have not received serious attentions despite their profound influence on the steroechemical course of an asymmetric reaction. These heteroatoms often coordinate directly to metal center thus bring their helical structures to a closest proximity to the reaction site; and these helices also often have high helical characters due to the involvement of the highly polarizable electrons in lone pair and transition metal *d* orbitals. For a recent fascinating disclosure of such a heteroatom chirality-in-enantioselection issue, see: Evans, D. A., Michael, F. E., Tedrow, J. S., Campos, K. R. *J. Am. Chem. Soc*. **2003**, *125*, 3534-3543.
6. Hashiguchi, S.; Fujii, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 288-290.

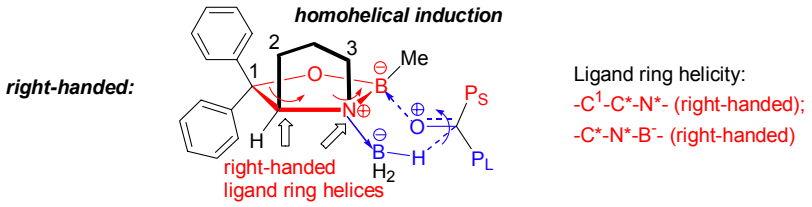
5. Itsuno-Corey Hydrogenation

Scheme 1 shows the expected outcomes of Corey-Bakshi-Shibata ("CBS") reagent-catalyzed ketone reductions, on the top left if the homohelical induction principle applies, and on the top right if steric effects prevail.[1] The (*S*)-configured reagent has right-handed helicity. For **1**–**3** it is unclear how steric effects apply with R groups of varied sizes, and for **6**–**7** how they could lead to the large enantiomeric excesses observed. For **5**, **9**, **10** and **14**–**16** they seem to give the wrong results. However, in each of these cases the homohelical induction principle does lead to the result observed. In cases in which the two substituents attached to the carbonyl do not differ significantly in polarizability but do differ greatly in size, steric effects appear to prevail. Methyl alkyl ketones in which the alkyl groups are *t*-butyl and triphenylmethyl are examples. Both are reduced in 97% ee.[1] Aryl diisopropylphosphono ketones seem to balance between the two effects.[2] The reductions yielding **17** and **18** suggest that the tetrahedral $(^{i}PrO)_2P{=}O$ group is much bulkier but the local P=O bond slightly less polarizable than a phenyl ring, so that steric effects dominate but are attenuated by the polarizability effects. In cases **19**, *ortho* substituents, by interfering with phenyl-carbonyl π orbital co-planarity (as in cases **11** in Scheme 1 of section 3), would make $(^{i}PrO)_2P{=}O$ surpass *ortho*-Z'-C_6H_4 in both size and polarizability. Thus they contribute synergistically to enantio-control. The ees are now high. However, a powerfully donating *ortho* substituent, as in **20**, seems to overcome this effect. The attenuated steric effect gives rise to a low ee.[3]



Scheme 1. Homohelical induction in Itsuno-Corey reductions using an (*S*)-CBS catalyst. The top shows the expected directions of reduction according to both homohelical and steric induction principles. The notations and abbreviations are the same as in Scheme 1 of section 3. X = H, OCH_3, Br; Y = Br, Me; Z = Cl, Me, OMe; Z' = F, Cl, Br, I, Me; G_L: ketone substituent of larger size; G_S: ketone substituent of smaller size.

The (*S*)-CBS catalyst ring helicity analysis is as follows: In the oxazaborolidine ring two critical structural characters merit comments: One, when the boron center acquires electrons from both the ring oxygen and the ketonic oxygen atoms, it becomes significantly electron rich and the B-O bond has a substantial π-bonding nature (bond distance: 1.335Å; the B-N bond is also considerably short: 1.486Å).[4] Two, due to the 5-membered rigid bicyclic rings, the N atom becomes a new stereogenic enter when its lone pair electrons are donated to BH_3. Therefore, the oxazaborolidine ligand ring is featured by a right-handed helix -C^1-C*-N^+- around C* (polarizability sequences: $C^1 > N^+$, and $C^2 >$ H) and a right-handed helix -C*-N*-B- around N* (polarizability sequences: $B^- >$ C*, and $H_3B^- > C^3$) chiral centers as indicated below.



The latter *in situ*-generated N* helix is particularly significant because it positions at the closest proximity of the reaction site thus exerts more influence on homohelical induction than does the original C* helix. Moreover, the handedness consistence between the C* helix and the N* helix highlights the critical importance of the *syn*-relationship between C^2- and C^3-CH_2s relative to the

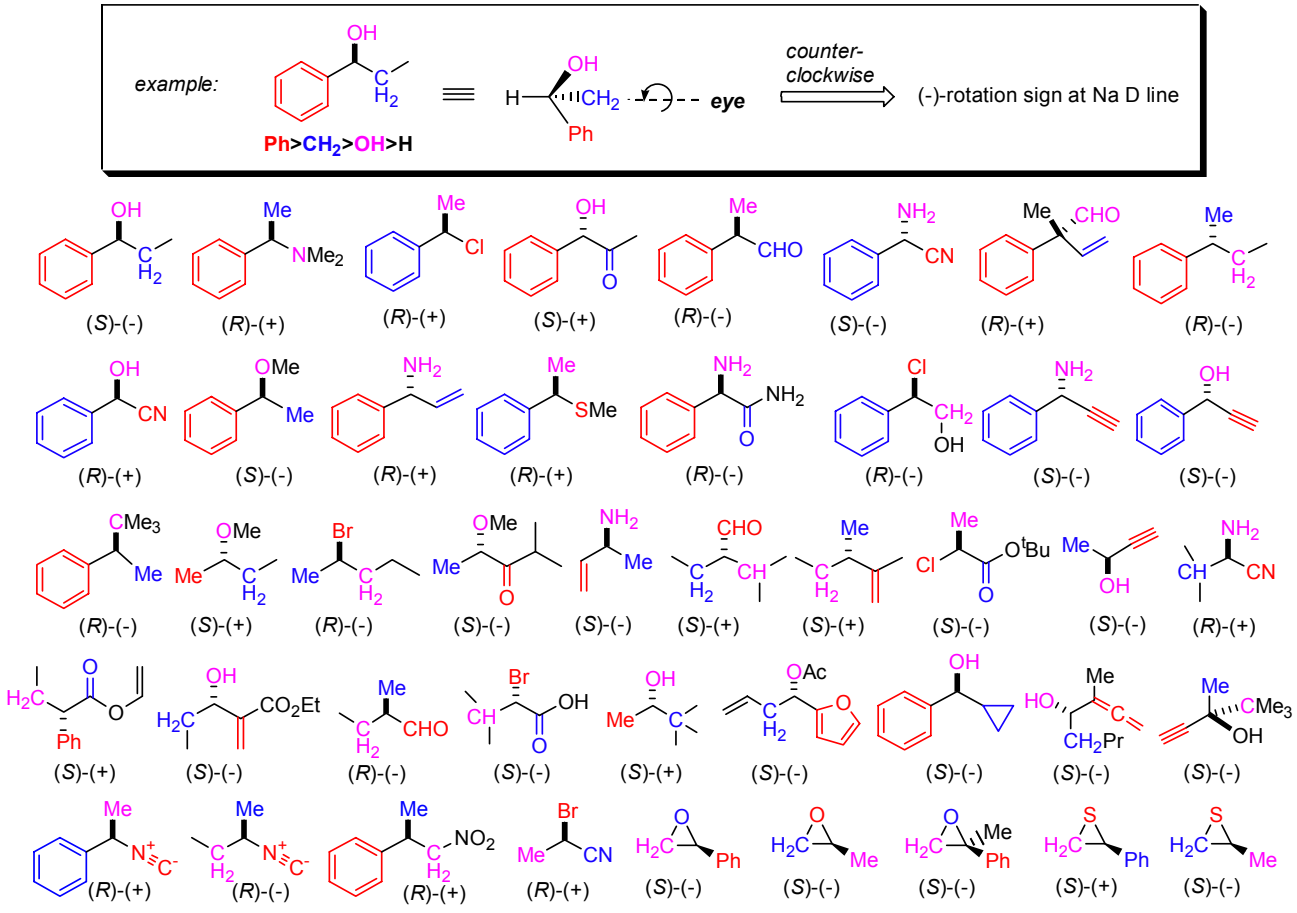
oxazaborolindine ring. This may account for two important empirical appreciations on catalyst design in this asymmetric reduction, i.e., that in bi- or poly-cyclic CBS type ligands the C*-C^2-$(CH_2)_n$-C^3-N* moiety must be a rigid small ring structure (three-, four- or five-membered but not six- or higher),[2] and that in monocyclic oxazaborolidines ligands an *N*-alkylation is often detrimental for attaining high ees.[1,5]

References:

1. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012.
2. Meier, C.; Laux, W. H. G. *Tetrahedron: Asymmetry*, **1995**, *6*, 1089-1092. The polarizability of a P=O bond has been reported to be 0.5-1.52 $Å^3$, depending on the environment (Arbuzov, B. A.; Arshinova, R. P. *Dokl. Akad. Nauk SSSR*, **1976**, *227*, 1361-1364.), that is less than that of a C=C bond (1.643 $Å^3$, see: Miller, K. J. *J. Am. Chem. Soc.* **1990**, *112*, 8533-8542) or a phenyl ring but more than that of a C-C single bond (0.531 $Å^3$) in simple alkyls. These polarizability sequences are consistent with the positive rotations observed in a wide range of point-chiral small molecules of a general structure (*R*)-ArC*H(XH)P(O)$(OR)_2$ and (*S*)-RC*H(XH)P(O)$(OR)_2$ where Ar is an aryl or alkene; X = O or NH; and R is an alkyl. These would require a polarizability sequence of Ar > P=O > R > XH > H for a right-handed helicity. See ref. 7 in the text. Examples: (a) Rowe, B. J.; Spilling, C. D. *Tetrahedron: Asymmetry*, **2001**, *12*, 1701-1708; (b) Spropeta, D.; Schmidt, R. R. *Tetrahedron: Asymmetry*, **2003**, *14*, 265—274; (c) Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757-1760; (d) Meier, C.; Laux, W. H. G. *Tetrahedron: Asymmetry*, **1996**, *7*, 89-94.
3. Not treated here are the reductions of acetylenic ketones $R_1C{\equiv}C$-C(O)-R_2, where R_1 can be either an alkyl or aryl but R_2 is an alkyl. The carbonyl substituents C≡C and R_2 display a very large polarizability difference but the reaction stereochemical outcomes are not dominated by homohelical induction, and in contrast, more tunable by steric size of R_1 and R_2 groups (See: Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem.. Soc.* **1996**, *118*, 10938-10939; and Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214-3217). During the course of our homohelical induction analysis, we have already come across several other interesting issues such as that the extraordinary tolerance of R group in functionalzied ketone hydrogenations (Scheme 3 in the text); that the homo-helicity in the diphosphine and diamine ligands of catalysts **1a-c** seems to be essential in those reactions for achieving high ees (Scheme 1 in section 3) but might be not always needed in other reactions (for example: Ohkuma, T.; Ikehira, H.; Ikariya, T.; Noyori, R. *Synlett* **1997**, 467-468.); and that a relatively small Ph-*versus*-C=O polarizability difference seems to be tolerated in Itsuno-Corey reduction (>99%ee in **8** of this section) but not in transfer hydrogenation (75%ee in **11** of section 4). All these issues are connected to another critical aspect of homohelical interaction: *the catalyst / substrate helical character matching*. In general, it is the catalyst handedness that electronically defines the sense of asymmetric induction, but for the magnitude of enantioselection to be high, the helical characters of the catalyst and the substrate complexed to it in the enantioselection-determining step must be matched. This topic is developed in the following *Tetrahedron* paper in this issue, and in: Wang, D. Z. *Chirality*, **2005**, *17*, S177-S182.
4. Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron. Lett.* **1992**, *33*, 3429-3430.
5. Jiang, Y. Z.; Feng, X. M. *HuaXue* (Taiwan), **1997**, *55*, 67-79.

6. Application of physical helix handedness-rotation sign correlation: determination of absolute stereochemistry

Both physical helices and geometrical helices in a chiral molecule may contribute to its optical rotation. At long wavelengths, a molecule of a net right-handed helicity is dextrorotatory, and a molecule of a net left-handed helicity is levorotatory.[1] For small and conformationally flexible molecules, the net geometrical helicity is effectively absent, thus the helicity comes largely from the physical helices. This suggests that the net physical helix can be correlated to rotation sign, which provides a new method of assigning molecular absolute stereochemistry. The net handedness can be analyzed by the procedure illustrated in Scheme 1 of the text, but alternatively can be more efficiently accessed by inspecting the arrangement of the three more polarizable groups from the opposite side of the least polarizable group. If the arrangement is counter-clockwise, the molecule is left-handed thus levorotatory at sodium D line; if the arrangement is clockwise, the molecule is right-handed thus dextrorotatory. The following molecules are illustrative. Local polarizability sequence of the three more polarizable groups in each molecule is indicated as red > blue > pink.



It should be noted that, since this method considers only the rotation contributions of the physical helices, it is only applicable to *small and conformationally flexible molecules that don't possess geometrical helices*.[2] Preferably, *the molecules should also have minimal polar functionalities and the rotations are measured in non-polar solvents*. Under such conditions, complications from non-

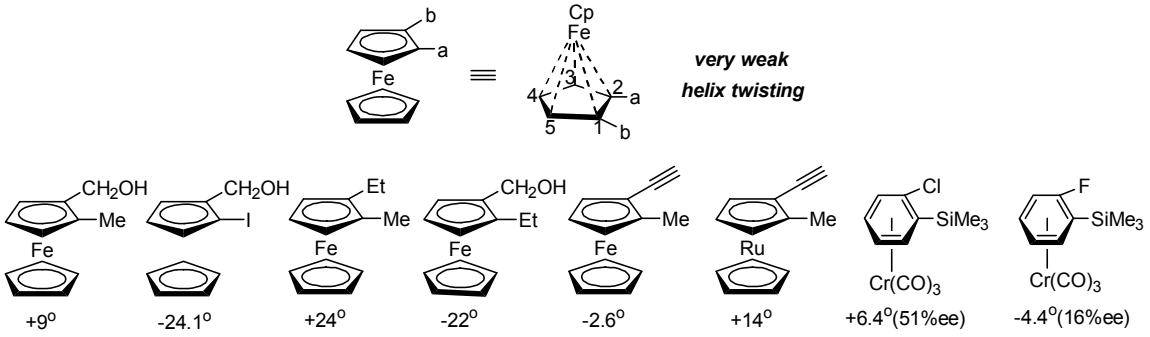
structural factors, such as inter- and intra-molecular associations and solvent effects, may be effectively minimized.[3]

References and Notes:

1. (a) Brewster, J. H. "Helix Models for Optical Activity", *Top. Steroechem*. **1967**, *2*, 1-72; (b) Caldwell, D. J.; Eyring, H. "*The Theory of Optical Activity*", Wiley Interscience, **1971.**
2. For more practice and checking of this method, see (a) Klyne, W.; Buckingham, J. *Atlas of Stereochemistry: Absolute Configurations of Organic Molecules*, Volumes I and II, second edition, Oxford University Press, **1978**; and their supplement by Buckingham, J and Hill, R. A., Chapman and Hall Ltd., in **1986**; (b) The *Graphical Stereochemical Abstract* in each issue of *Tetrahedron: Asymmetry*.
3. The influences of such factors as polar group, solvent, concentration, and temperature on a molecule's rotation sign and magnitude can be all attributed to their influences on the molecular helical structures.

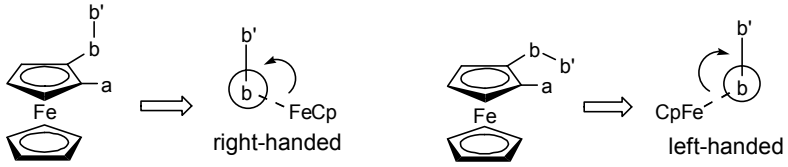
7. Helix structures in planar-chiral molecules

Physical Helices: physical helices in representative planar-chiral molecules, such as *ortho*-disubstituted optical active ferroecnes, could be most easily visualized by formally reducing the η^5-bond to five single bonds, which transforms the system into a point-chiral situation. The conjugation in the Cp ring makes the polarizabilities of the five carbon centers nearly identical and, simultaneously, strongly counters any helix twisting within the ring. These two factors lead to very weak physical helices in such molecules (another helix, i.e, -*a*-C-C-*b*-, not shown below, may be resulted by repulsions from the bottom FeCp moiety, and is presumably also weak when the *a*-C and *b*-C bonds do not differ significantly in their polarizabilities). Consequently, when substituents *a* and *b* are atoms or linear groups, the molecules should show very small optical rotations, and in fact, they are.[1] Examples are shown below.

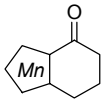
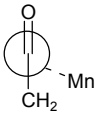
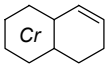
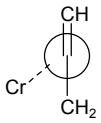
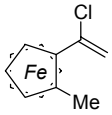
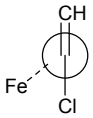
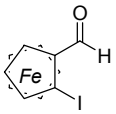
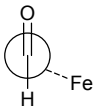
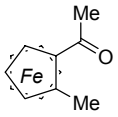
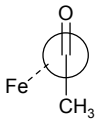
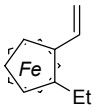
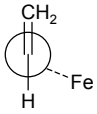
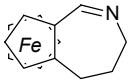
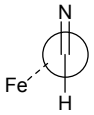
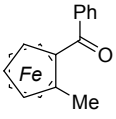
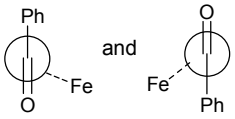
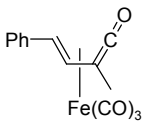
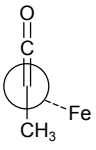
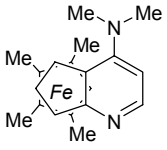
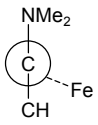


Geometrical Helices: when substituents *a* and *b* are not linear, the molecules may develop favorable conformations thus give rise to significant geometrical helices. In such cases, molecular rotations could be very large. Visualized below are the geometrical helices formed between one of the non-linear substituent *b-b'* and the CpFe moiety. They are identified by inspecting the relative orientation of the metallocene residue and the *b-b'* moiety that is placed directly upwards in the Newman projection. If the metallocene residue lies to the right of the observer, a right-handed helix is defined and the molecule is dextrorotatory, and *vice versa*. This essentially serves as a basis for a successful

empirical rule proposed earlier by Schlögl et.al that correlates sign of rotation with absolute configuration in optically active metallocenes.[2]



Some illustrative molecules are shown in the table below.

chiral Metallocene (preferred comformation)	Newman projection	handedness of dominant geometric helix	$[\alpha]_D$	Ref.
		right	+454°	3
		left	-51°	3
		left	-500°	3
		right	+484.5°	4
		left	-544°	3
		right	+660°	3
		left	-450°	3
		right, left	+258.2°	5
		right	+1492°	6
		right	+1560°	7

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1. (a) Schlögl, K.; Fried, M.; Falk, H. *Monatsh. Chem*. **1964**, *95*, 577-597; (b) Schlögl, K. *Top. Stereochem*. **1967**, 39-91.
2. Falk, H.; Schlögl, K. *Tetrahedron*, **1966**, *22*, 3047-3053.

3. (a) Figure 19 on page 86 of Ref 1b; (b) Figure on page 3052 of Ref 2.
4. Riant, O.; Samuel, O.; Flessner, T. Taudien, S.; Kagn, H. B. *J. Org. Chem.* **1997**, *62*, 6733-6745.
5. Enders, D.; Peters, R.; Lochtman, R.; Runsink, J. *Eur. J. Org. Chem*. **2000**, 2839-2850.
6. Benyunes, S. A.; Gibson, S. E.; Ward, M. F. *Tetradhedron: Asymmetry*, **1995**, *6*, 2517-2520.
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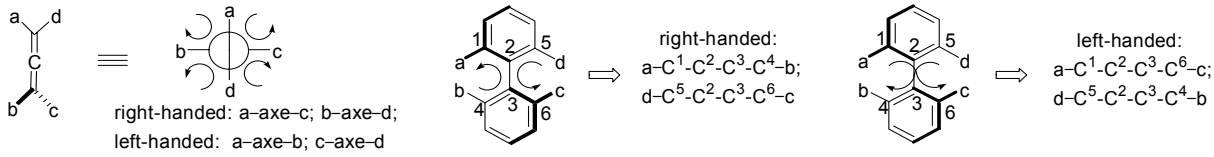
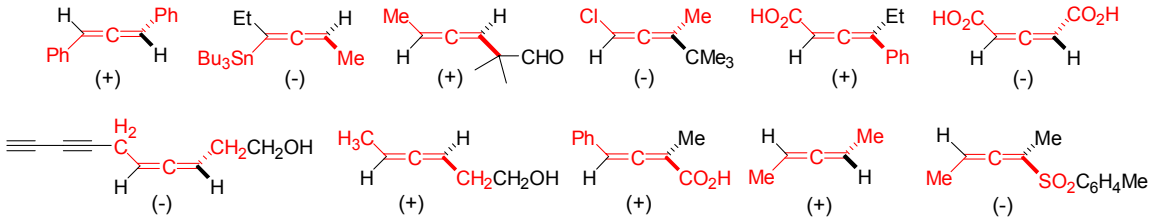
8. Helix structures in axial-chiral molecules

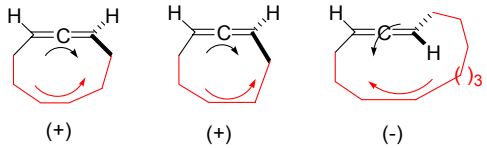
Helix analyses for axially chiral molecules are performed on two representative cases: allenes and atropisomeric biaryls. For the allene model molecule the following helical structures are visualized by its Newman-type projection: *a*-axis-*c* (right-handed); *b*-axis-*d* (right-handed); *a*-axis-*b* (left-handed) and *c*-axis-*d* (left-handed). In the biaryl model model, four helices are of practical interest: *a*-C^1-C^2-C^3-C^4-*b* (right-handed); *d*-C^5-C^2-C^3-C^6-*c* (right-handed); *a*-C^1-C^2-C^3-C^6-*c* (left-handed) and *d*-C^5-C^2-C^3-C^4-*b* (left-handed). *Each of them is both physical helix and geometric helix.*



For both allenes and biaryls, there are two right-handed and two left-handed helices, the molecular rotation sign is determined by the net helicity. For biaryls, such a net helicity is often difficult to assign because the rotational contribution of each helix is markedly modulated by not only the substitutents' polarizabilities but also the atropisomeric dihedral angle. For rigid allenes, however, such a net helicity can be easily accessed because the rotation contribution of a helix only depends on its substituents' polarizabilities, i.e., the net helicity is determined by the helix that possesses two most polarizable substituents. Previously there has been a very influential empirical rule, called "*Lowe's rule*", that correlates an allene's absolute stereochemistry to its rotation sign.[1] Lowe's rule states that "an allene is viewed along its orthogonal axis with the more polarizable substituent in the vertical axis uppermost. If the more polarizable substituent in the horizontal axis is to the right, then this enantiomer will be dextrorotatory and *vice-versa*". Clearly, by this definition Lowe's rule works essentially because it links the rotation sign to the handedness of the dominant helix. Some illustrative molecules are shown below (dominant helix highlighted in red).



It is interesting to note that some cyclic allenes reported to violate the Lowe's rule, in which the handedness of the dominant helix along the allene backbone contradicts to the observed rotation sign, can also be rationalized by this helix rule. The following molecules are representative: in them the cyclic structures define large geometrical helices (in red) that govern the rotation sign.[2]

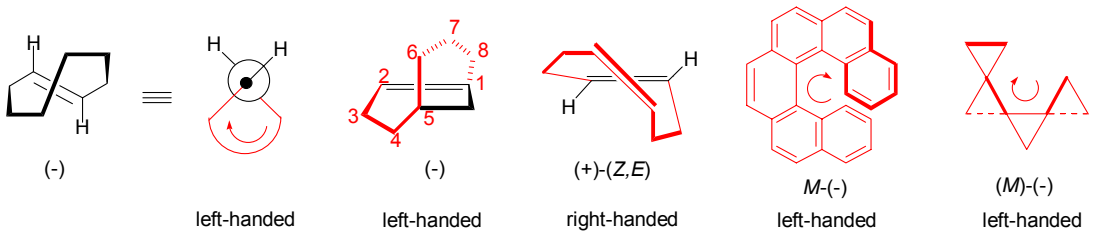


References:

1. (a) Lowe,G.; *Chem. Comm*. **1965**, 411-412; (b) Krow, G.; *Top. Stereochem*. **1970**, *5*, 31-68; (c) Crabbe, P.; Velarde, E.; Anderson, H. W.; Clark, S. D.; Moore, W. R.; Drake, A. F.; and Mason, S. F. *Chem. Comm*. **1971**, 1261-1262.
2. (a) Moore, W. R.; Anderson, H. W.; Clark, S. D.; Ozretich, T. M. *J. Am. Chem. Soc*. **1971**, 4932-4934; (b) Bach, R. D.; Mazur, U.; Brummel, R. N.; Lin, L. H. *J. Am. Chem. Soc*. **1971**, 7120-7121; (c) Bertrand, M.; Gras, J. L.; Gore, J. *Tetrahedron*, **1975**, *31*, 857-862.

9. Helix structures in other chiralities

Some representative structures are show below.[1] The corresponding dominant helix is highlighted in red: without exception, a net right-handed helicity gives rise to dextrorotation and a left-handed helicity leads to levorotation, respectively. Noteworthy is the so-called π- and σ-helicenes, which have long been regarded as "special cases of chirality".[2] It is clear now that helicity is actually the most general form of molecular chirality. *It is based on this inherent helicty that complex molecular chiralities can be generalized, and fundamentally there are only two types of chiralities: right- and left-handed helicities.*



References:

1. (a) Cope, A. C.; Mehta, A. S. *J. Am. Chem. Soc.* **1964**, *86*, 1268-1269; (b) Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* **1979**, *44*, 2438-2441; (c) Cope, A.; Howell, C. F.; Knowles, A. *J. Am. Chem. Soc.* **1962**, *84*, 3190-3191; (d) Newman, M. S.; Lednicer, D. *J. Am. Chem. Soc*. **1956**, *78*, 4765-4770; (e) de Meijere, A.; Khlebnikov, A. F.; Kostikov, R. R.; Kozhushkov, S. I.; Schreiner, P. R.; Wittkopp, A.; Yufit, D. S. *Angew. Chem. Int. Ed.* **1999**, *38*, 3474-3477;
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10. Some general considerations on kinetic resolution analysis:

In the context of the homohelical control analysis, the focus is placed on the kinetic resolution systems that meet the following criteria:[1]

(1) The reactions must be generally highly enantioselective so the homohelical electronic control on enantioselectivity is ensured and complications from other less significant factors, such as steric or solvent effects etc, are minimized. The selectivity factor $\boldsymbol{s} = k_{rel}$, the ratio of the rate of the fast reacting enantiomer to the slow reacting enantiomer, should be generally larger than ten.[2]

(2) The reactions must show a relatively broad tolerance on substrate structures, which should further demonstrate the helical electronic control in chiral discriminations.

(3) Both the substrates and the catalysts employed must be structurally defined and tailored so helical structure analysis can be straightforward and unambiguous.

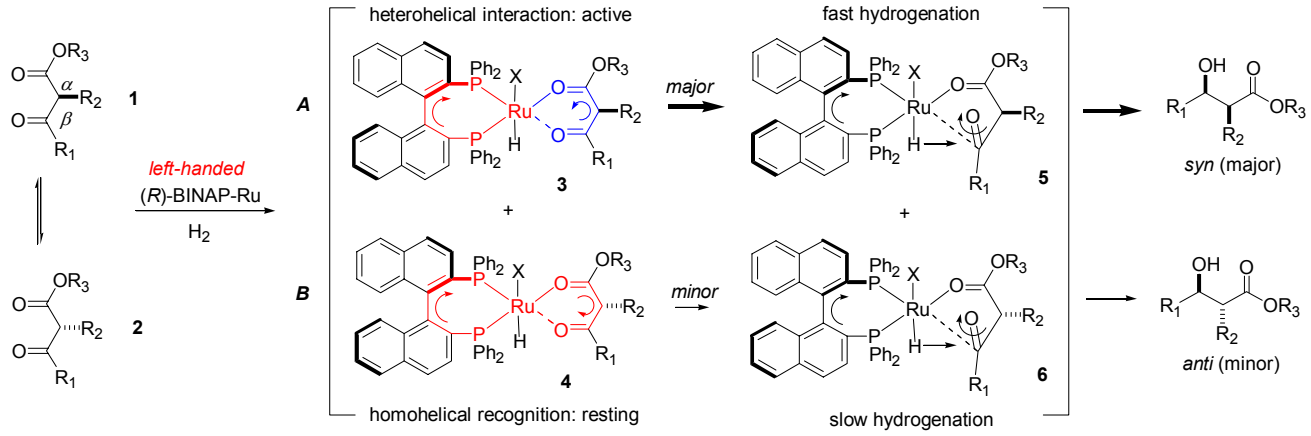
Based on these criteria, some outstanding kinetic resolution processes catalyzed by enzymes and chiral pool-derived agents, and some in which outstanding ees are achieved only in selected substrates under optimized conditions, are out of our attention. As might be expected, the successful systems developed so far that meet all of the above criteria are numbered. Nonetheless, they overall should provide a solid platform on which the validity of the homohelical recognition control principle can be examined. Although the general helical structure method has been previously described,[3] the identifications of helix structures in the relevant ligands/catalysts and substrates have been illustrated throughout the analyses in order to minimize possible confusion. The systems discussed here include the following: stereoselective ketone hydrogenations, transfer hydrogenations, ring closing metatheses, sulfides/sulfoxides oxidations, lactones ring openings, kinetic resolutions of alkyne-containing substrates, kinetic resolutions of allylic alcohols by dioxirane-catalyzed oxidation, epoxides ring openings (Hydrolytic Kinetic Resolutions), asymmetric ring opening of anhydrides with Lewis acids Ti-TADDOLates, asymmetric epoxidation (Sharpless AE)-based kinetic resolutions of secondary allylic, furyl, pyrryl, thienyl and amino alcohols, asymmetric dihydroxylation (Sharpless AD)-based kinetic resolutions, asymmetric alcoholysis of anhydrides, Pd-catalyzed aerobic oxidative kinetic resolutions of alcohols, and asymmetric acylations of alcohols by chirally modified DMAPs. Several systems related to the above are also discussed.

References:

1. For a critical analysis of contemporary most important kinetic resolution processes, see: (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5-26. For a comprehensive treatment of kinetic resolutions using non-enzymatic catalysts, see: Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry*, **2003**, *14*, 1407-1446.
2. It should be noted that a judgment based on this k_{rel} parameter is rather qualitative since accurate determination of its value under the reaction conditions requires a detailed knowledge of the reaction kinetics, which is, unfortunately, rarely investigated in literature.
3. See specifically Scheme 1 of the text and sections 6-9.

11. Kinetic resolution by stereoselective hydrogenation

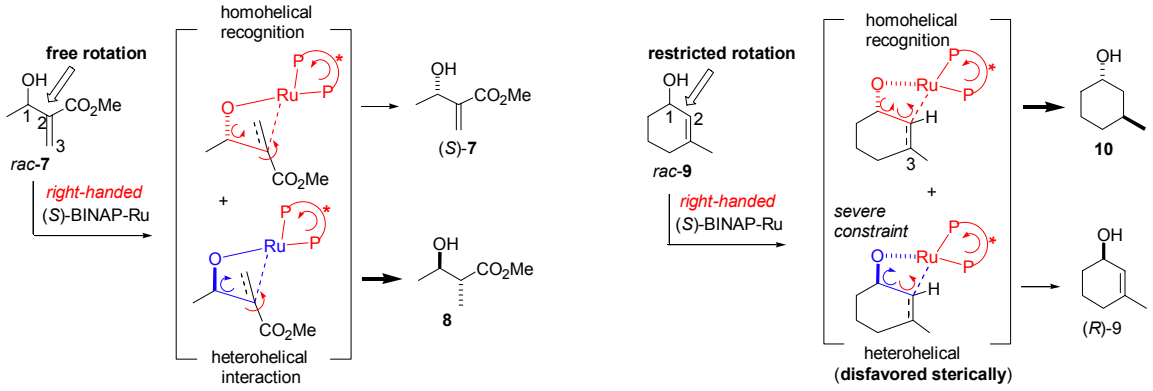
Asymmetric hydrogenation of chirally labile α-substituted β-keto esters is of central importance in this field.[1] The racemate comprises of two rapidly equilibrating enantiomers **1** and **2**, which gives a homohelical catalyst-substrate complexation **4** and a heterohelical complexation **3**, respectively, when complexed with a left-handed (*R*)-BINAP-Ru(II) catalyst (polarizabilities: R_2 > H, and ketone carbonyl **C(O)**C (2.982 Å^3) > ester carbonyl **C(O)**O (2.558 Å^3).[2] As expected, **3** should be kinetically more active than **4** thus pathway ***A*** should be dominant. The subsequent ketone hydrogenation is controlled by homohelical induction,[3] which determines the absolute stereochemistry at the R_1 termini as shown and the reaction consequently delivers *syn*-isomer as a major product in both high enantiomeric and diastereomeric excesses (Scheme 1). The step of ketone hydrogenations in **5** and **6** merit further comments: one, the newly generated helicity at the alcoholic chiral center in **5** counters the opposite helical twisting of C_α chirality, and immediately followed, the hydrogenation saturates the highly polarizable carbonyl into an alcohol (less polarizable than -CO_2R_3) thus left-handed C_α ring helix is generated in the final product. These changes transform the originally unfavorable heterohelical catalyst-substrate electronic interaction in **3** into a homohelical one in a late intermediate that disassociates to yield *syn*-isomer; two, ketone hydrogenation in **5** and **6** requires the initial σ-type Ru-O=C binding shifts to a π-facial Ru-C=O mode,[3] which is strongly sterically prohibited in **5**, but not in **6**, when the substituents R_1 and R_2 form a cyclic structure. The reason is straightforward: R_1 and R_2 are *syn*-oriented in **6** but *trans*- in **5**. A direct consequence for this appreciation is that asymmetric hydrogenation of chirally labile α-substituted β-keto esters in which R_1 and R_2 define a ring (particularly a small ring) structure under otherwise similar conditions makes pathway ***B*** favorable and therefore gives *anti*-isomer as major product. This is again in line with the experimental observations.[1a]



Scheme 1. Homohelical recognition control in dynamic kinetic resolution of chirally labile α-substituted β-keto esters.

Similar to hydrogenation of chirally labile α-substituted β-keto esters in which R_1 and R_2 define a small ring structure, kinetic resolution of allylic alcohols **7** and **9** by (*S*)-BINAP-Ru-catalyzed hydrogenation represents another interesting case where the electronic effect-driven kinetic preference of the heterohelical pathway is simultaneously countered by the disfavored sterics resulted in it due to severe constraint posed by a cyclic structure. Consequently, under these special conditions, the

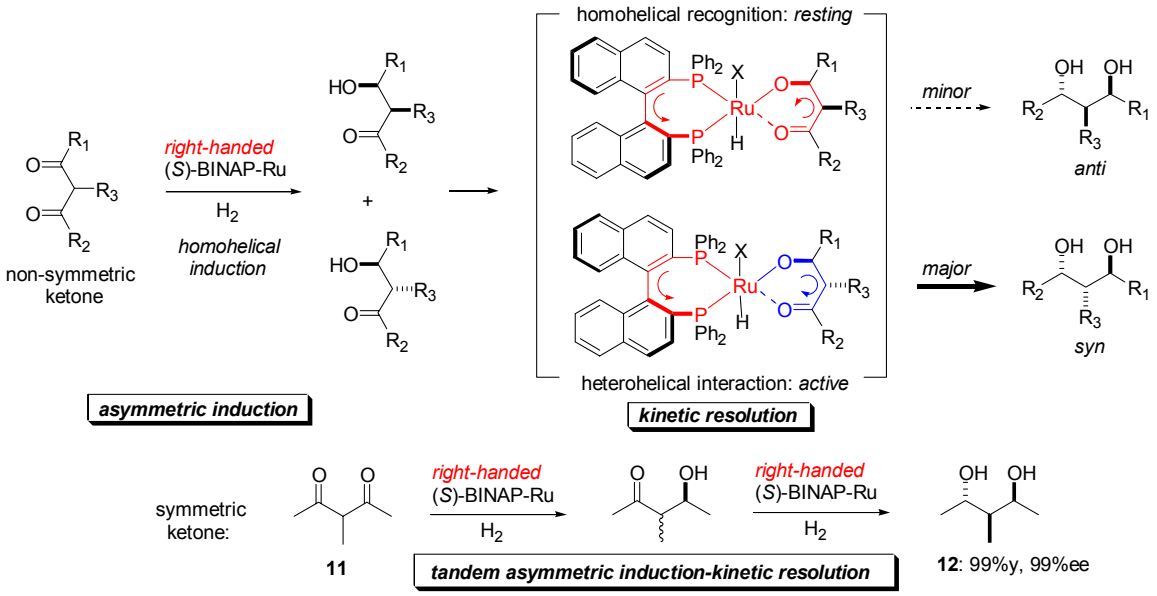
homohelical pathway delivers the derived product. The critical structural difference between **7** and **9** lies at the rotation freedom of the C_1-C_2 bond in them: in acyclic **7** such a rotation is free but in cyclic **9** it is restricted. Upon coordination to a right-handed (*S*)-BINAP-Ru catalyst, the homohelical induction requires a right-handed helical twisting newly established at C^2 center in the substrate ring helix -Ru-O-C^1-C^2- thus a *Si*-facial selection on the olefin double bond in both homohelical and heterohelical complexations (polarizabilities at C^1 of **7**: $\boldsymbol{C}H_3$ > H, and C^2 > O; at C^2 of **7**: Ru > C^1, and C=O > C^3; at C^1 of **9**: $\boldsymbol{C}H_2$ > H, and C^2 > O; and at C^2 of **9**: Ru > C^1, and C^3 > H).[4] This is easily satisfied in the hetero-helical (*S*)-BINAP-Ru/(*R*)-**7** and its kinetic resolution behaviors are thus in agreement with those expected from the homohelical recognition control; However, this is strongly disfavored in the heterohelical (*S*)-BINAP-Ru/(*R*)-**9** association because the (*R*)-configuration at C^1 and the concurrent *Si*-facial double bond selection generate a severe steric constraint on the Ru coordination sphere (a 4-membered ring). This significantly retards the reactivity of the heterohelical pathway and forces the originally kinetically disfavored homohelical pathway to undergo hydrogenation, and not surprisingly, in a slower rate (ca. 56 h, other allylic alcohols complete reactions in 0.5-11h). Consequently, kinetic resolutions of racemic **7** and **9** with the same catalyst display opposite stereochemical sense: with a similar OH/C=C spatial relationship, (*S*)-**7** is recovered but (*S*)-**9** is hydrogenated to **10** (Scheme 2).[5]



Scheme 2. From acyclic to cyclic substrate: a formal "violation" to the homohelical recognition control in kinetic resolution.

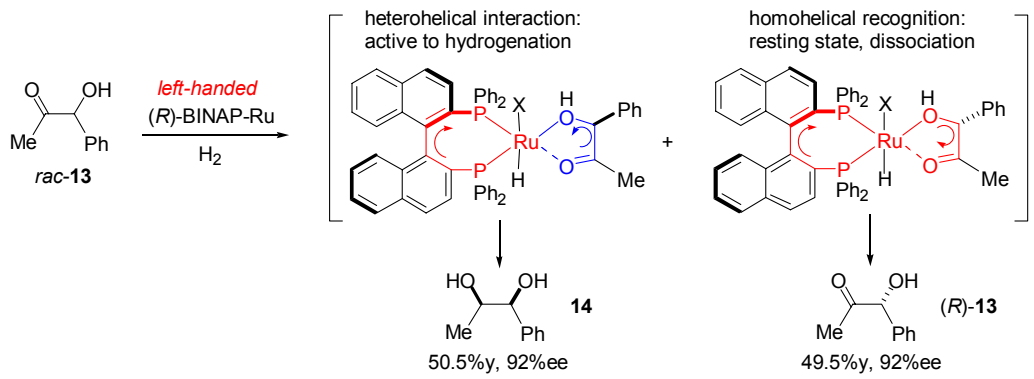
As an extension, similar homohelical recognition analysis is also applied to a more complicated situation: stereoselective hydrogenation of 1, 3-diketones of a general structure $R_1C(O)CHR_3C(O)R_2$ where both carbonyls are subject to hydrogenation. Assuming a certain regio-control directs the first step hydrogenation at the $R_1C(O)$ terminus, the homohelical induction during this hydrogenation should generate a mixture of two diastereomeric α-hydroxy ketones of the indicated absolute stereochemistries when the catalyst is a right-handed (*S*)-BINAP-Ru complex (Scheme 3). At this stage the $R_2C(O)$ terminus remains active towards hydrogenation thus the second step reaction represents a typical kinetic resolution process. A homohelical recognition control analysis yields a prediction that the *syn*-product should be predominant. Imaginably, such 1, 3-diketones are much less attractive substrates as compared to β-keto esters since the lack of high carbonyl regioselectivity could render the reactions synthetically useless as a variety of stereo-isomers are expectable. However, remarkably, the issue of regio-control could be completely eliminated when symmetric ketones (R_1 = R_2) are employed, and the reactions become tremendously useful not only because the products stereochemistries could be effectively controlled, but also because the *syn*- and *anti*- isomers share the

same structure, which eliminates the isolation problem! Indeed, 3-Methyl-2, 4-pentanedione **11** has been subjected to such a hydrogenation process, yielding **12** as the single product in a 99%ee.[6] It merits comments here that this reaction has been previously interpreted briefly as a "triple stereodifferentiation" process. Reduction of **11** into **12** may in fact represent the first literature demonstration of a tandem asymmetric induction-kinetic resolution process in asymmetric hydrogenation catalysis.[7]



Scheme 3. Application of homohelical recognition control in kinetic resolution: origin of very high stereoselection in 1, 3-diketone hydrogenation.

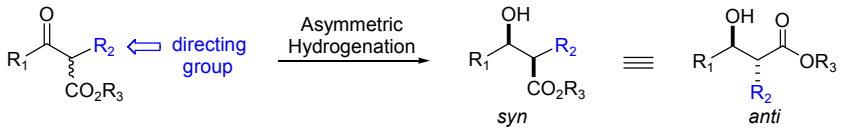
Stereochemistry in kinetic resolution of configurationally stable functionalized ketones by stereoselective hydrogenation could be also understood on the basis of this simple homohelical recognition control rationale. An illustrating example is the hydroxyl ketone **13**. The left-handed (*R*)-BINAP-Ru catalyst can effectively differentiate the enantiomers through the homohelical and heterohelical complexiation, respectively. The heterohelical one undergoes rapid hydrogenation to give 1,2-diol product **14** in 92%ee and the unreacted (*R*)-**13** is recovered with a 92%ee (Scheme 4).[1b] It is again worthy of noting that in **14** the newly established chiral center by means of asymmetric hydrogenation is controlled by left-handed (*R*)-BINAP/Rh helix via the homohelical induction mechanism previously discussed for functionalized ketones.[3,8]



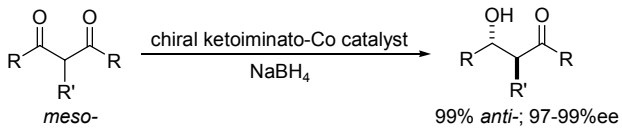
Scheme 4. Homohelical recognition control in the kinetic resolution of a configurationally stable functionalized ketone.

References:

1. (a) Noyori, R., Tokunaga, M., Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36-56; (b) Noyori, R. chapter 2, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**. It should be noted that this inherent *syn*-selectivity may be used to produce *anti*-products in reactions where, as shown below, a properly chosen R_2 in the substrate, such as an amino substituent, coordinates to the metal center thus effectively functions as the directing group. Examples: (c) Makino, K., Goto, T., Hiroki, Y., Hamada, Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 882-884; (d) Lei, A., Wu, S., He, M., Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626-1627; (e) Mordant, C.; Dünkelmann, P.; Ratovelomanana-Vidal, V.; Genêt, J-P. *Chem. Commun.* **2004**, 1296-1297; (f) Mordant, C.; Dünkelmann, P.; Ratovelomanana-Vidal, V.; Genêt, J-P. *Eur. J. Org. Chem.* **2004**, 3017-3026; (g) Makino, K.; Hiroki, Y.; Hamada, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5784-5785.



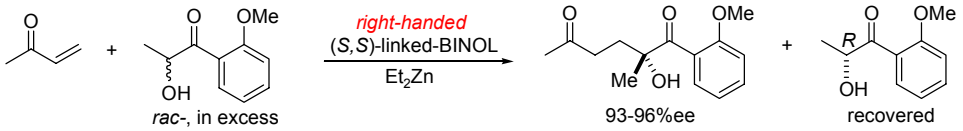
2. See: (a) Calculations in Section 1h; (2) Miller, K. J. *J. Am. Chem. Soc.* **1990**, *112*, 8533-8542.
3. See specifically Scheme 3 in the text.
4. For an illustration of facial selection by homohelical induction on an allylic system similar to **9**, see section 2c.
5. Kitamura, M., Kasahara, I., Manabe, K., Noyori, R., Takaya, H. *J. Org. Chem.* **1988**, *53*, 708-710.
6. Kitamura, M., Ohkuma, T., Inoue, S., Sayo, N., Kumobayashi, H., Akutagawa, S., Ohta, T., Takaya, H., Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629-631. For a related system, see: Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 2543-2546. Using a chiral *β*-ketoiminato-Co/$NaBH_4$ catalyst, several *meso*- 2-alkyl-1,3-diaryl-1,3-propanediones are reductively desymmetrized in extremely high stereoselectivities (see below).



7. Tandem asymmetric induction-kinetic resolution in asymmetric oxidation catalysis has been

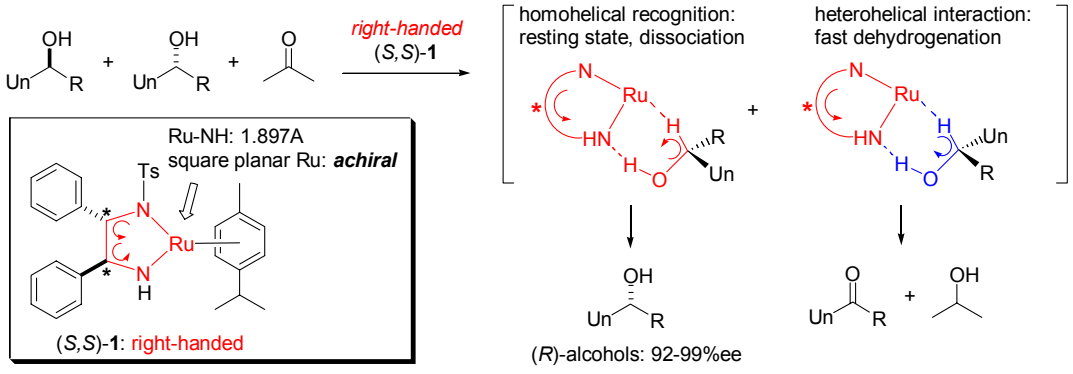
observed earlier in allylic alcohol epoxidation, see: (a) Hatakeyama, S.; Sakurai, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759-1760; (b) Hafele, B.; Schroter, D.; Jager, V. *Angew. Chem. Int. Ed.* **1986**, *25*, 87-89; (c) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525-1529; and later in enantioselective sulfoxides syntheses, see: (d) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529-4533.

8. It may at first seem surprising that in the following 1, 4-addition reaction the right-handed catalyst enantiospecifically reacts with the right-handed (*S*)-hydroxyl ketone enantiomer (substrate ring helix -HO-C*-C(O)-. Polarizabilities: ***C***H_3 > H; and C=O > OH) and leaves the left-handed (*R*)-enantiomer (that is, heterohelical to the catalyst) sequentially enriched to >99%ee. See: Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582-2590. Note that in this system the substrate-catalyst interaction in their association step, i.e., that between the (*S*)-enantiomer and the catalyst, is *irreversible*, therefore it does not conform to the normal kinetic resolution situations generally illustrated in Scheme 4 of the text.



12. Transfer hydrogenation-based kinetic resolution of alcohols

(*S,S*)-**1** and its dihydrogen adduct, a Ru-hydride species, characterize a truly exceptional transfer hydrogenation system in which they are unambiguously identified as catalyst and reactive intermediate, respectively.[1] We have previously shown that that hydride species, containing a distorted octahedral chiral Ru* center, features a dominant left-handed ligand ring helicity.[2] Unlike that Ru*-chiral complex, the Ru center in (*S,S*)-**1** adopts a square-planar geometry and the corresponding NH-Ru bond has double bond characters (bond length 1.897Å), thus Ru center here is achiral and makes no contribution to catalyst helicity: (*S,S*)-**1** is therefore right-handed simply because of the carbon backbone helicities.[2] As expected, helix analysis predicts that (*S*)-alcohol enantiomers will be dehydrogenated more rapidly via heterohelical pathways (polarizabilities: Un > R; and O > H), which is in accord with the experimental observations in efficient kinetic resolution of a variety of secondary alcohols.[3] In all the cases, (*R*)-alcohols are recovered in high ees (Scheme **1**).



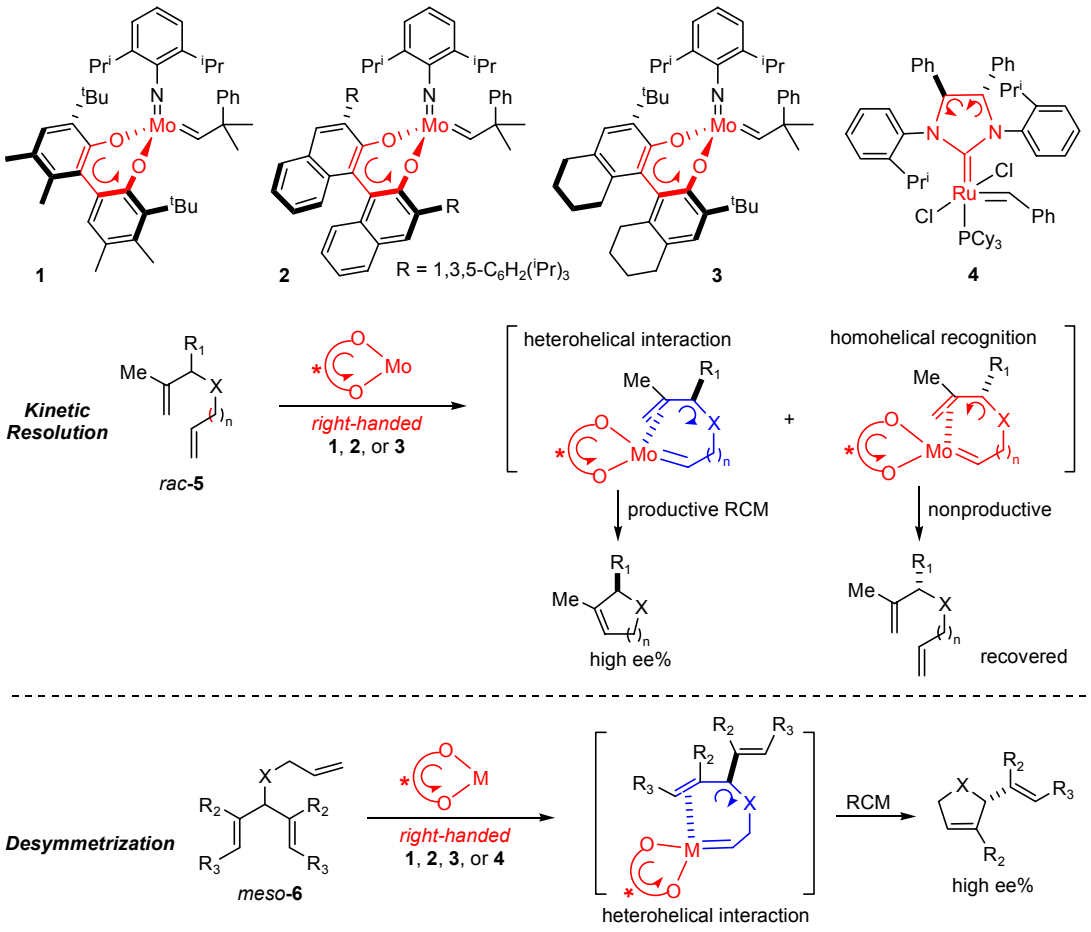
Scheme 1. Homohelical recognition control in kinetic resolution of alcohols by transfer hydrogenation. Un: unsaturated substituents, R: simple alkyls.

References:

1. (a) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T, Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 285-288; (b) Hashiguchi, S.; Fujii, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 288-290.
2. See specifically section 4.
3. The reaction's unique pericyclic mechanism has been established: (a) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931-7944; (b) Haack, K. J., Hashiguchi, S., Fujii, A., Ikariya, T., Noyori, R. *Angew. Chem. Int. Ed*. **1997**, *36*, 285-288; (c) Yamakawa, M., Ito, H., Noyori, R. *J. Am. Chem. Soc*. **2000**, *122*, 1466-1478; (d) Alonso, D. A., Brandt, P., Nordin, S. J. M., Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9280-9588; (e) Casey, C. P., Johnson, J. B. *J. Org. Chem.* **2003**, *68*, 1998-2001.

13. Kinetic resolution and desymmetrization in asymmetric ring closing metathesis (ARCM)

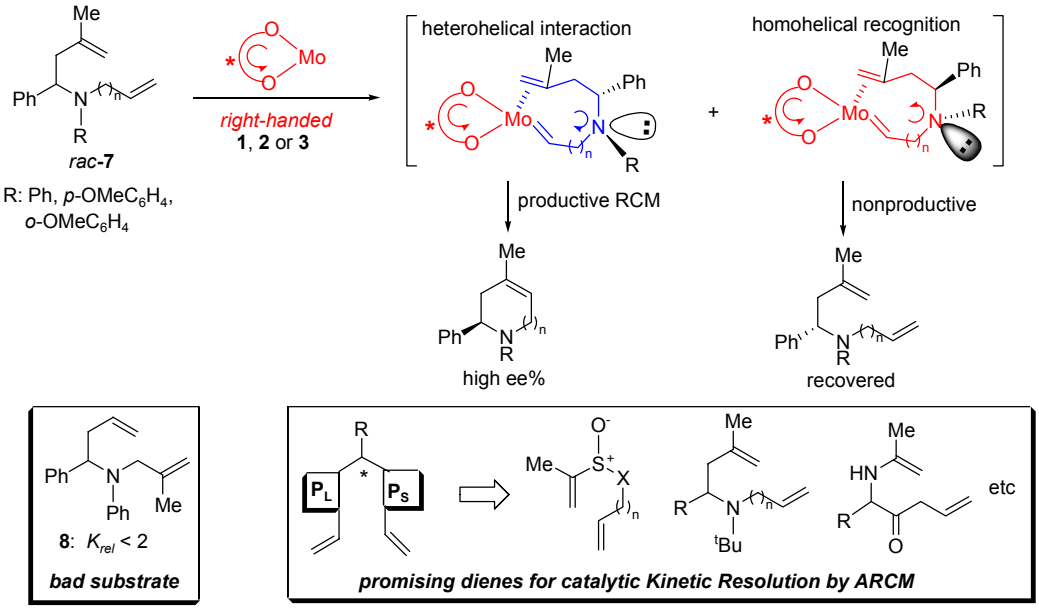
Complexes **1**-**4** are the representative members of the chiral Mo- and Ru-based metathesis catalysts developed so far.[1] They are shown in Scheme 1 as their right-handed enantiomers (polarizabilities in **4**: C* > N, and Ph > H). The appropriate diene substrate, *rac*-**5** or *meso*-**6**, often has a double bond α- to the chiral center, a polarizability character that helps build the substrate ring helix twisting. A homohelical recognition control analysis is presented in Scheme 1 (polarizabilities: C=C > X; and R > H): the slow-reacting enantiomer is the one that forms a homohelical substrate-catalyst association, and productive ARCM occurs preferentially through the heterohelical association. This sense of stereochemistry is generally obeyed in various ARCM-based kinetic resolutions and desymmetrizations.[2]



Scheme 1. Homohelical recognition control in ARCM. R_1: OR, alkyls; R_2 and R_3: alkyls; X = O, CH_2, or $SiMe_2$; M = Mo, Ru; *n* = 1, 2, 3.

ARCM based-kinetic resolution of N-containing substrates **7**, however, as originally emphasized,[3] is characterized by fine tuning between N-substituent R and substrate reactivity and reaction enantioselectivity thus should not be viewed as simple extensions of their hydrocarbon or oxygen-containing analogues. Homohelical recognition analysis suggests an insight why this may be the case: in the catalyst-substrate association a new chiral N* center in the substrate ring is established as a consequence of steric repulsions between Ph and R (in this regard, to facilitate the formation of N* chirality, R must be a bulky group; Experimentally all successful R groups have been bulky aryls).[3] Two critical structural features in **7** may ensure that this *in-situ* generated N* chirality plays a more important role than the original carbon chirality does in the substrate-catalyst stereochemical communication: one, the lone pair electrons are highly polarizable (N* substituents poalrizabilities: lone pair electrons > bonding electrons of the local carbon in R; and 2^o ***C***H_2 > 3^o ***C***H), therefore, in the substrate ring the helical twisting around N* could be more significant than that around the C* center; two, the N-terminus double bond is set to be mono-substituted thus to facilitate the formation of Mo-alkylidene at this site, which brings N* chirality closer to the catalyst ring helix. These factors lead to that it is the N* chirality, but not the original C* chirality, that is the major contributor in the substrate-catalyst stereochemical interactions. The chirality communication between the N* helix and the catalyst helix is so decisive that it can make the amines' reactivity profiles towards achiral and chiral

Mo catalysts completely different. It has been previously reported that amines that readily react with the achiral catalyst (thus without such a homohelical *versus* heterohelical stereochemical bias) can be completely unreactive with chiral catalysts.[3] As shown in Scheme 2, reaction of (*R*)-**7** with the right-handed catalyst leads to a (*S*)-configured N* of a left-handed substrate ring helix thus the corresponding substrate-catalyst association is heterohelical. It undergoes fast ring closing metathesis to give cyclic unsaturated amines in high ees. The (*S*)-**7**/catalyst association characterizes a resting homohelical recognition intermediate which leads to the recovery of the substrate enantiomer.[4] The operation of such a N* chirality-modulated homohelical/heterohelical interactions in these cases suggests that the ARCM should be considerably faster than the inversion of N* configuration in the rate-determining step (Scheme 2).



Scheme 2. An N*-chirality modulated homohelical recognition control in ARCM.

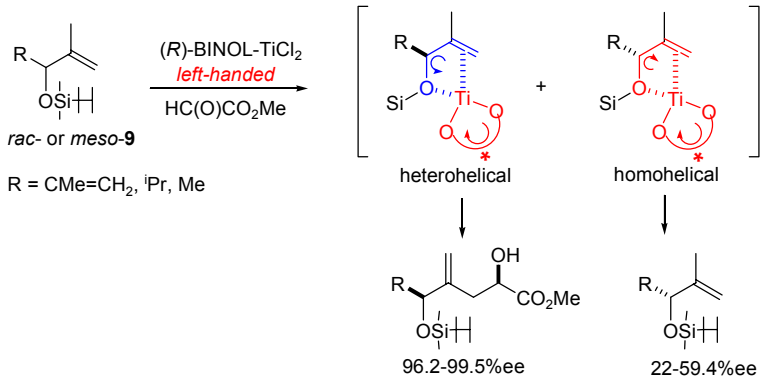
In light of the above appreciation, it seems to be readily understandable why no kinetic resolution was observed for amine **8**: the N*-terminus double bond is di-substituted thus the formation of Mo-alkylidene preferentially occurs at the mono-substituted C*-terminus double bond, which brings the C* substrate ring helicity to a closer vicinity to the catalyst ring helix thus enables it to compete effectively with the oppositely handed N* ring helix. These two competing helices markedly diminish the substrate ring helical twisting. Consequently, **8** functions like an achiral diene and its enantiomers show essentially no bias towards the chiral Mo-catalysts in RCM. In summary, the above analysis suggests that promising diene substrates for ARCM-based kinetic resolutions should be those featuring both a large (P_L) and a small (P_S) polarizability substituent around the stereogenic center, therefore ensuring a significant substrate ring helical twisting. Some of those promising dienes predicted by this helix theory are highlighted in the bottom box of Scheme 2. They invite experimental explorations.

References:

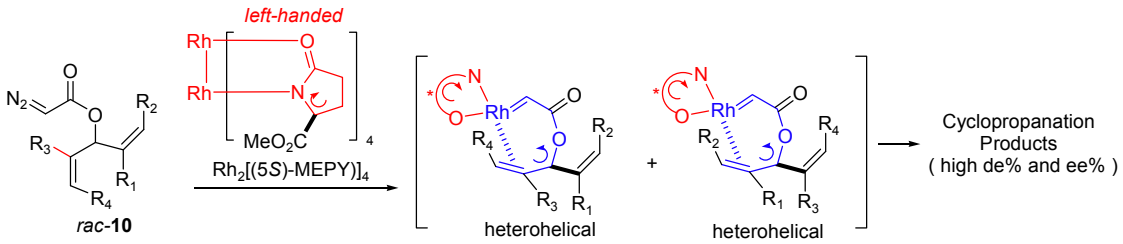
1. For **1-3**, see: (a) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945-950; (b) Hoveyda, A. H.; Schrock, R. R. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592-4633; for **4**, see: (c) Seiders, T. J.; Ward,

D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225-3228. Not included here is a Ru-based catalyst whose helicity analysis is complicated by its possessing chiralities at both the Ru center and the ligand moiety. The catalyst induces moderate ees in ARCM reactions. See: (d) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502-12508.

2. Similarly, the homohelical recognition control principle, as summarized below, also accounts for the stereochemical profiles observed in kinetic resolution or desymmetrization of: (1). olefinic substrates **9** by means of asymmetric carbonyl-ene and hydrosilation reactions. See: (a) Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566-6568; (b) Tamao, K.; Tohma, T.; Inui, N.; Ito, Y. *Tetrahedron Lett* **1990**, *31*, 7333-7336.

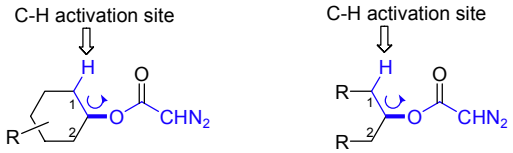


And (2). olefinic substrates **10** by means of asymmetric cyclopropanations catalyzed by left-handed complex Rh_2[(5*S*)-MEPY]$_4$ (ligand ring helix is marked below in red. Polarizabilities: C=O > H; and ***C***H_2 > N). Both double bonds in **10** are potential reaction sites, therefore, as shown below, there are two heterohelical catalyst/substrate associations that kinetically lead to products of high yields and high diastereomeric and enantiomeric purities (polarizabilities used in assigning the substrate ring helices: C=C > H; and C=C > O). See: (a) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493-4494.



Likewise, the stereochemical matching and mismatching between Rh_2[(5*S*)-MEPY]$_4$ and enantiomers of **11** may be also understood: the kinetically active heterohelical association (*S*)-**11**/ Rh_2[(5*S*)-MEPY]$_4$ leads to product in high yield and diastereomeric excess, constituting formally a "matched" case. The resting nature of the homohelical association (*R*)-**11**/ Rh_2[(5*S*)-MEPY]$_4$ jeopardizes both the reaction yield and stereochemical control, constituting formally a "mismatched" case (for more discussion on such chirality matching and mismatching, see section 19f).

The left handedness of $Rh_2[(5S)\text{-MEPY}]_4$ also allows for a rationalization of its stereochemical behaviors in stereoselective C-H activations in substrates **12** and **13**: the favored site in each case, as highlighted below in blue, is the one that lies within a right-handed substrate ring helix (that is, heterohelical to the catalyst. Polarizabilities: $C^2 > H$; and $C^1 > O$). See: (b) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021; (c) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Caňas, F.; Pierson, D. A.; van Basten, A.; Müller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507-4508; (d) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837-8846.

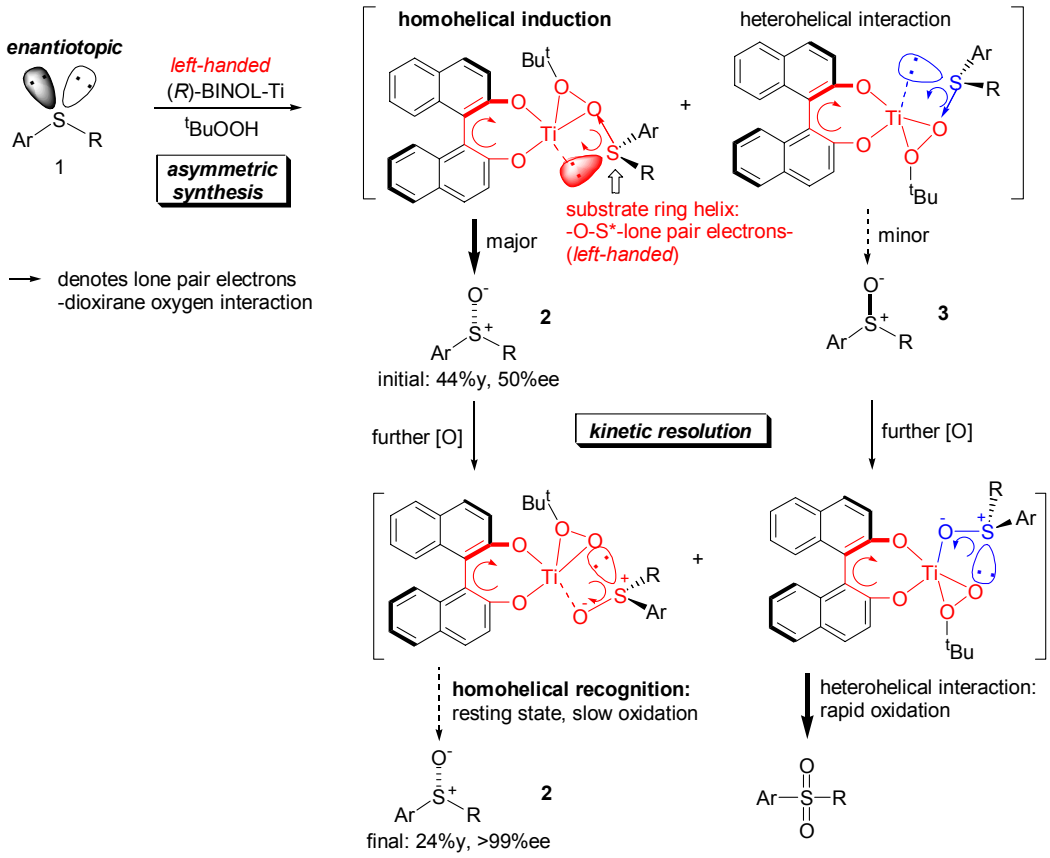


12 *meso*-**13**

3. (a) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991-6997; (b) Dolman, S. J.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2003**, *5*, 4899-4902.
4. It should be noted that when the R substituent on the nitrogen atom is a small group incapable of generating such an N*-chirality, such as H, Ac, or Cbz, the stereochemical outcomes in the relevant highly enantioselective ARCM reactions again conform to those expected from the homohelical recognition control as illustrated in Scheme 1. See: Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, ASAP.

14. Enantioselective synthesis of sulfoxides via asymmetric catalysis and kinetic resolution

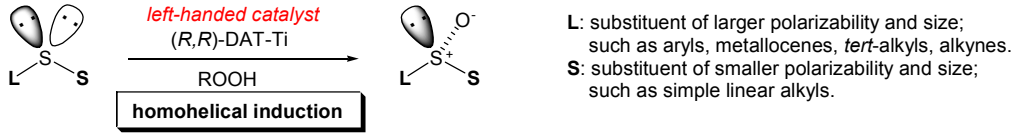
On the basis of the analysis illustrated in Scheme 5 of the text for a consecutive asymmetric catalysis-kinetic resolution system employing two catalysts of the same electronic helicity (but not necessarily the same structure or configuration), it could be expected that highly enantioselective synthesis of a compound could be assisted by such a “push-pull” mechanism even with a mediocre chiral catalyst. This is, unfortunately, often difficult to realize experimentally. One major reason is that the catalyst in the asymmetric induction step and that in the subsequent kinetic resolution step usually have to work under rather different conditions, therefore it is practically challenging to carry these two reactions in a one-pot fashion. However, oxidative resolution of sulfoxides turns out to be such an outstanding system: the asymmetric synthesis of aryl alkyl sulfoxides by a chiral BINOL-Ti catalyst starts from pro-chiral sulfides, and it is revealed that enantiopurities of the sulfoxides increase with the reaction time, and the reaction is accompanied by the formation of sulfones. This suggests that the BINOL-Ti complex catalyzes not only the first step asymmetric oxidation but also the subsequent kinetic resolution (Scheme 1).[1]



Scheme 1. A homohelical "push-pull" mechanism for product enantioenrichment in a consecutive asymmetric induction-kinetic resolution system. Ar: aryls; R: alkyls.

The sulfide **1** is characterized by a large aryl-*versus*-alkyl substituent polarizability distinction and two pairs of enantiotopic lone pair electrons. Both are potentially sites for oxidation. In the first oxidation step, homohelical induction executed by the left-handed (*R*)-BINOL-Ti catalyst leads to selective delivery of oxygen to pro-*R* position of **1** because only with such a facial selection could the corresponding substrate ring helix in the transition state be also left-handed (polarizabilities: Ar > R, and lone pair electrons > bonding electrons), the ee is moderate in this step; In the second oxidation step, the major product enantiomer **2** complexes to the catalyst to form a homohelical resting state and the minor product **3** is further consumed via a kinetically active heterohelical pathway. Consequently, the enantiopurity of **2** is synergistically enriched to >99%ee.

Prior to this helix theory, there has been an influential, purely steric effect-based rationale that predicts empirically the sulfoxides' absolute stereochemistries in dialkyl tartrate (DAT)-Ti/ROOH -catalyzed oxidation of sulfides (Scheme 2).[2] Substrate survey shows that the **L** groups not only need to be bulkier, but more generally and significantly, need to be more polarizable than the **S** groups.[3] Therefore, with consideration on electronic control in these homohelical inductions, the catalyst structure-product configuration stereochemical correlation is re-formulized as shown below in Scheme 2: when a (*R,R*)-DAT/Ti catalyst (which is left-handed, see the following section 19 for the helicity identification) is used, the oxygen atom is always delivered backward to the **L**-S-**S** plane. This new rationale holds generally.



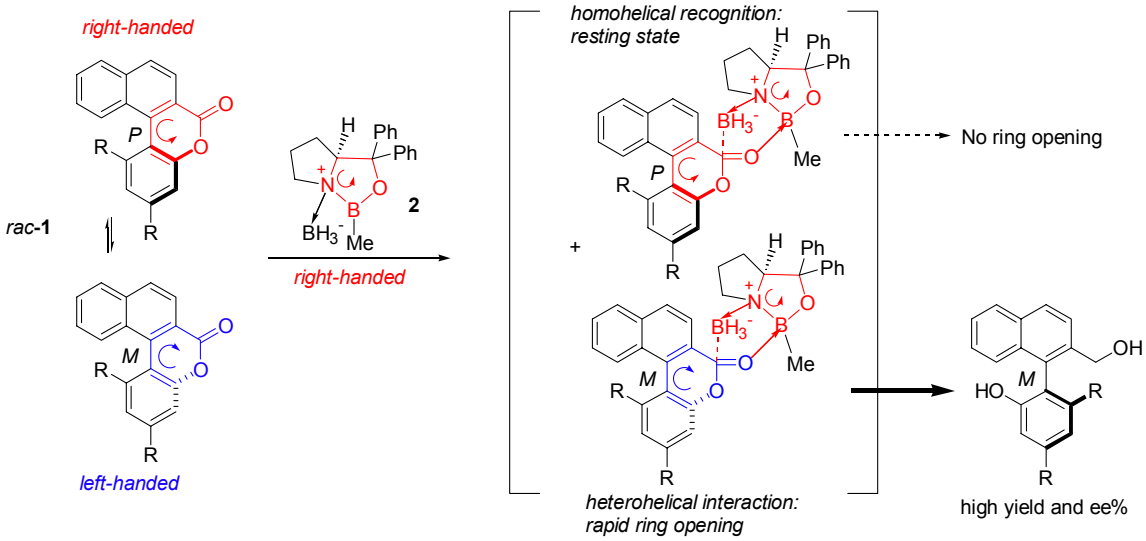
Scheme 2. A general stereochemical predictor for asymmetric sulfides oxidations.

References:

1. (a) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529-4533. For some similar observations, see: (b) Scettri, A.; Bonadies, F.; Lattanzi, A.; Senatore, A.; Soriente, A. *Tetrahedron: Asymmetry*, **1996**, *7*, 657-658; (c) Lattanzi, A.; Bonadies, F.; Senatore, A.; Soriente, A. Scettri, A. *Tetrahedron: Asymmetry*, **1997**, **8**, 2473-2478; (d) Jia, X.; Li, X.; Xu, L.; Li, Y.; Shi, Q.; Au-Yeung, T. T-L.; Yip, C. W.; Yao, X.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 723-726.
2. (a) Pitchen, P.; Deshmukh, M.; Dunach, E.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188-8193; (b) Zhao, S.; Samuel, O.; Kagan, H. B. *Tetrahedron*, **1987**, *43*, 5135-5144; (c) Bolm, C.; Muniz, K.; Hildebrand, J. P. in chapter 19 of *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, **1999**.
3. A recent triumph in sulfoxide asymmetric synthesis is the oxidation of ^{t}Bu-S-S-^{t}Bu (production at kg scale in 99%ee), which could be attributed to the significant substrate ring helix characters defined by a very large S-*versus*-tertiary carbon polarizability distinction. See: Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317-1320.

15. Asymmetric lactone ring opening via dynamic kinetic resolution

Dynamic kinetic resolution of a configurationally labile biaryl lactone **1** by a (*S*)-CBS catalyst **2** represents an interesting case of homohelical recognition control in enantioselective ring opening reactions. The mechanism of the ring opening was examined.[1] The catalyst has been previously identified as a right-handed boron hydride source.[2] The catalyst should form a heterohelical association with the left-handed (*M*)-**1** in which their ring helices are jointed together as shown in Scheme 1. Thus, it rapidly opens the (*M*)-isomer to give the reduction products in both high yields and ees.



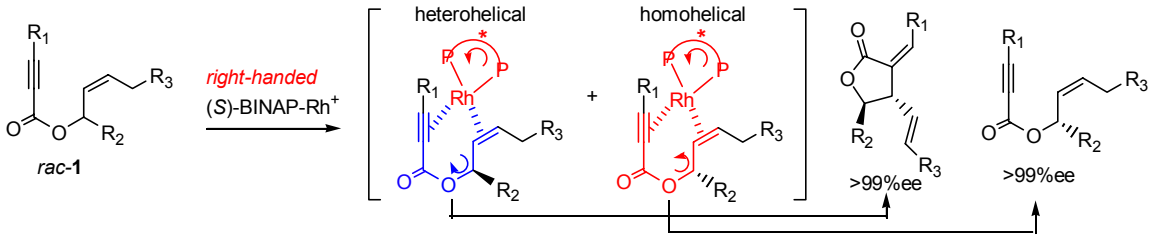
Scheme 1. Homohelical recognition control in lactones ring opening via dynamic kinetic resolution. R= H, Me, Et, ^{i}Pr, ^{t}Bu, OMe.

References:

1. (a) Bringmann, G.; Hinrichs, J.; Kraus, J.; Wuzik, A.; Schulz, T. *J. Org. Chem.* **2000**, *65*, 2517-2527, and references cited therein; (b) Bringmann, G.; Hartung, T. *Angew. Chem. Int. Ed.* **1992**, *31*, 761-762. Just as expected, for configurationally stable binaphthyl lactones, kinetic resolution with right-handed **2** yields (*M*)-diols and unreacted (*P*)-substrate enantiomers with a remarkable k_{rel} = 50, see: (c) Bringmann, G.; Hinrichs, J. *Tetrahedron: Asymmetry*, **1997**, *8*, 4121.
2. See section 5.

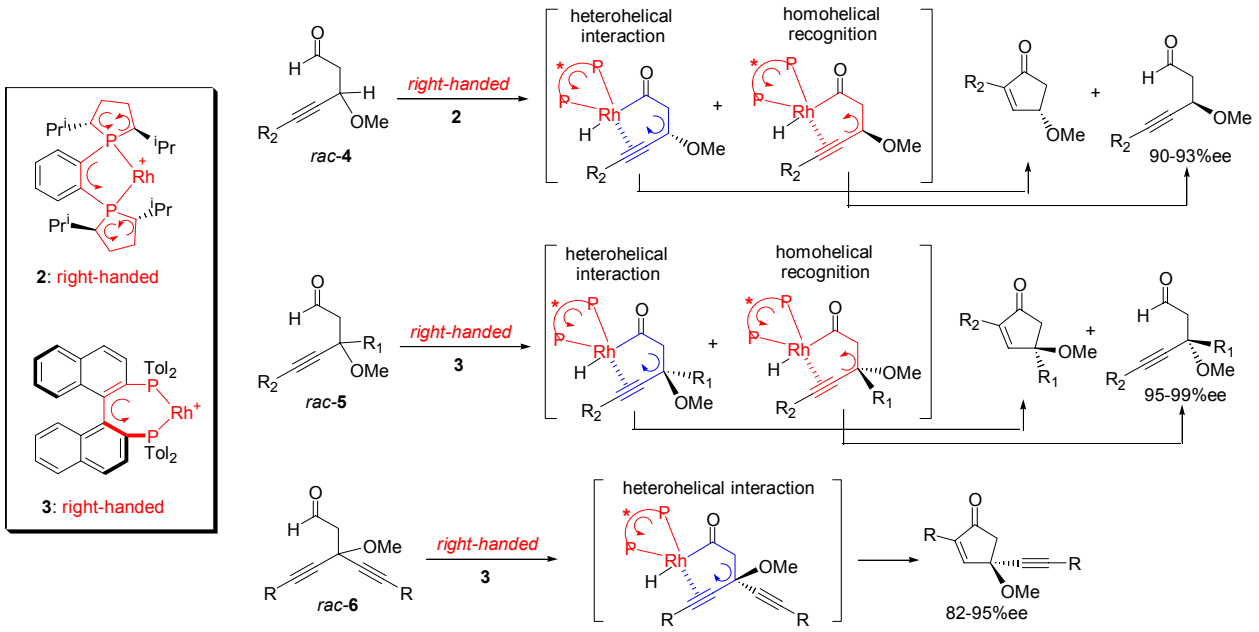
16. Kinetic resolution of alkyne-containing substrates

These successful substrates have included enyne esters **1** and 4-Alkynals (**4**, **5** and **6**). The interactions between **1** and the right-handed (*S*)-BINAP-Rh catalyst may involve coordination of both alkyne and alkene moieties of **1** to the Rh center, which brings the catalyst ring helix and the substrate ring helix into homohelical and heterohelical interactions (polarizabilities: C=C > O, and R_2 > H). As shown in Scheme 1, for a variety of substrates, the corresponding heterohelical intermediates lead to lactone products and the homohelical intermediates lead to recovery of the (*S*)-enantiomers, all in >99%ee.[1]



Scheme 1. Homohelical recognition control in kinetic resolution of enyne esters.

In 4-Alkynals the C≡C polarizability is much higher than that of CH_2 that is α-to the electron-withdrawing C=O. Upon complexation to the Rh catalyst, the handedness of the helical twisting in the substrate ring is controlled by the polarizabilities of the rest two substituents around the chiral center. The substituents R_2 in **4** and **5**, and R in **6**, are not in the corresponding substrate ring helices thus make little electronic contribution to the enantioselection, therefore, not surprisingly, in these kinetic resolutions they can be varied considerably among aryls or alkyls, without significantly scarifying the ees. For **4**, in which H < ***O***Me in polarizability, the (*S*)-enantiomer features a left-handed substrate ring helix -C≡C-C*-CH_2-C=O-. It interacts with the right-handed catalyst **2** (catalyst ring helices are deduced based on polarizabilities: Me_2***C***H > H; and electron-rich phosphine > ***C***H_2) heterohelically and readily cyclizes to yield a cyclopentenone. The homohelical (*R*)-**4**/**2** complexation characterizes a homohelical intermediate that leads to the recovery of (*R*)-enantiomer in high ees. For **5**, the substrate ring helicity is inversed as a consequence of polarizability ranking alkyls R_1 > ***O***Me. Accordingly, when treated with the right-handed catalyst **3**, the (*R*)-**5**/**3** define a heterohelical pathway to yield the cyclopentenone product and (*S*)-**5** is recovered in high ee. Lso as expected, desymmetrization of **6** by this cyclization occurs via a heterohelical substrate-catalyst intermediate: when the catalyst is right-handed **3**, (*R*)-cyclopentenones are produced in high yields and ees (Scheme 2).[2]



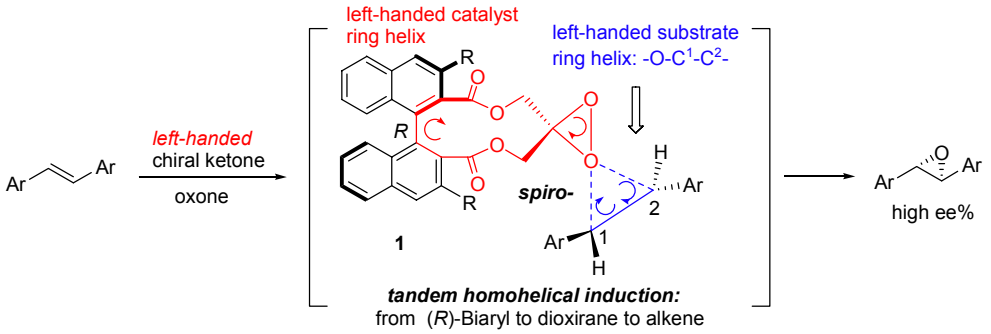
Scheme 2. Homohelical recognition control in kinetic resolution and desymmetrization of 4-Alkynals. R_1 = H, Me, ^{i}Pr; R_2, R: aryls, alkyls.

References:

1. Lei, A.; He, M.; Zhang, X. *Abstracts of Papers, 226th Acs National Meeting*, Sept 7-11, No. ORGN-050. See also: Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11472-11473.
2. Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296-10297.

17. Kinetic resolution of allylic alcohols by dioxirane-catalyzed epoxidation

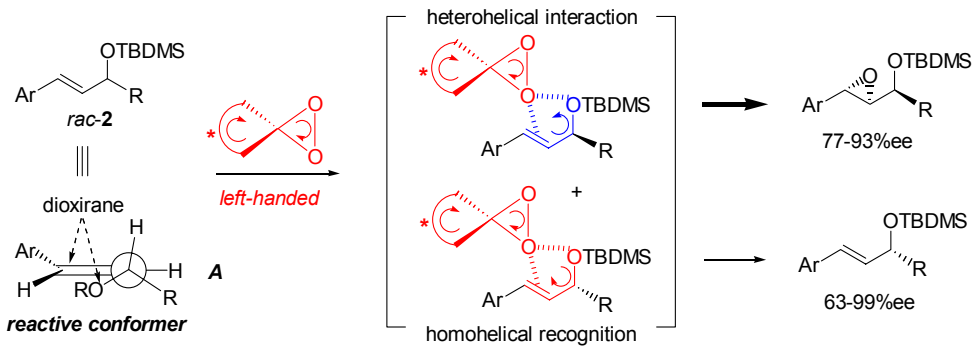
The proposed mechanistic picture of dioxirane **1**-catalyzed epoxidation of olefins is depicted in Scheme 1.[1] A prominent feature in this system is the operation of what might be termed "tandem homohelical induction": the original chiral biaryl backbone first transmits its helical twisting information into the dioxirane ring, and this dioxirane ring in turn executes homohelical induction in epoxidation.[2]



Scheme 1. Homohelical induction in dioxirane-catalyzed epoxidation.

In accord with the left-handed catalyst ring helicity, the dioxirane adds the oxygen atom to the double bond in the indicated facial selection so that the substrate ring helix is also left-handed (polarizabilities at C^1: Ar > H; and O in strained 3-membered ring > C^2. The same sequences hold at C^2 center).[3] It is important that the double bond is substituted by *trans*- phenyls which ensures the helicities at C^1 and C^2 have the same handedness thus contribute synergistically to the substrate ring helix twisting.[4]

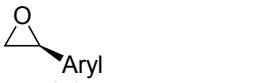
Kinetic resolution of TBDMS-protected allylic alcohols **2** by means of dioxirane **1**-catalyzed epoxidation is shown in Scheme 2. It has been previously identified that the low-energy conformer ***A*** is involved in epoxidation.[5] When the dioxirane approaches to the double bond from the top face as indicated, a spiro-trajectory that is electronically required by homohelical induction (see Scheme 1),[1] concomitant orbital interactions between the dioxirane O_P and the C=C π electrons, and between the dioxirane O_P and OR group's O_P electrons, would occur. These interactions may couple the left-handed catalyst ring helix with the substrate ring helix -C=C-C*-O- into homohelical or heterohelical interaction (polarizabilities: C=C > O; and R > H). As illustrated, for various substrates **2** the corresponding heterohelical intermediates undergo fast epoxidation (whose senses are predictable based on Scheme 1) and the homohelical intermediates return the starting material enantiomers.



Scheme 2. Homohelical recognition control in kinetic resolution of allylic alcohols by dioxirane-catalyzed epoxidation. Ar = *p*-X-C_6H_4 where X is ^{t}Bu, OMe, H, Et. R = CCl_3, ^{t}Bu, CF_3, TBDMS = $Si^tBu(Me)_2$.

References:

1. (a) Yang, D., Wang, X. C., Wong, M., K., Yip, Y., C., Tang, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 11311-11312; (b) Yang, D., Wong, M. K., Yip, Y. C., Wang, X. C., Tang, M. W., Zheng, J. H., Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943-5952; (c) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497-505.
2. Such a tandem homohelical induction mode is also seen in other catalysts, such as those based on DuPHOS- and BPE-type ligands. See: Burk, M. J. *Acc. Chem. Res.* **2000**, 6, 363-372.
3. In a three-membered ring the electrons in both the protruding Op_y and Op_z lone-pair orbitals and the two constrained O-C σ-orbitals experience less nuclear attraction thus are more polarizable than electrons of alkyl carbons. This polarizability assignment is consistent with the physical helix handedness-rotation sign correlation found in many small epoxides (summarized below, see: Klyne, W.; Buckingham, J. *Atlas of Stereochemistry: Absolute Configurations of Organic Molecules*, Volumes I and II, second edition, Oxford University Press, **1978**; and their supplement by Buckingham, J and Hill, R. A., Chapman and Hall Ltd., in **1986**; see also section 6).



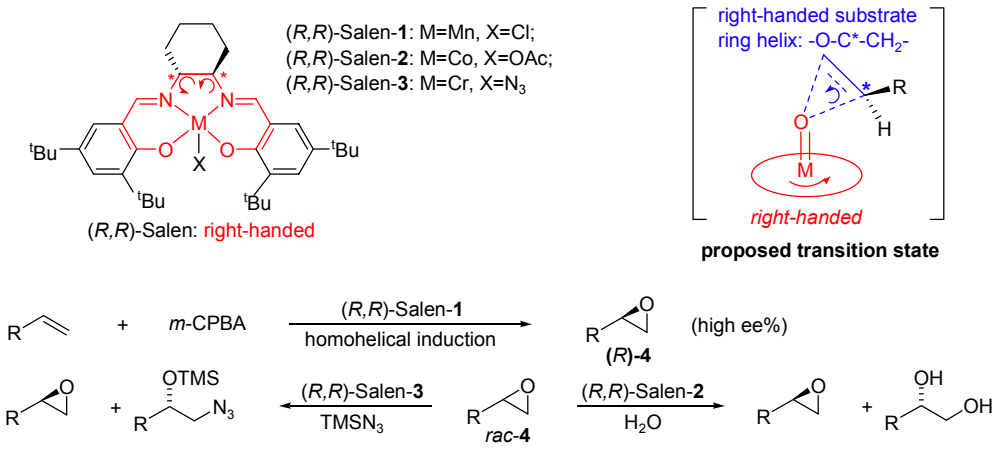
Levorotatory
Aryl > strained O > strained CH_2 > H

Levorotatory
strained O > strained CH_2 > Alkyl >H

4. Such a beneficial *trans*-effect of the double bond substituents on enantioselectivity has been discussed previously in section 2h.
5. Yang, D.; Jiao, G. S.; Yip, Y. C.; Lai, T. H.; Wong, M. K. *J. Org. Chem.* **2001**, *66*, 4619-4624.

18. Kinetic resolution of terminal epoxides

It has been established that Salen-**1** catalyzes the asymmetric epoxidation of terminal olefins to give epoxides **4** in high ees. The role of the two *ortho*-^{t}Bu substituents is crucial for achieving high ees, which, in addition to sterically blocking the olefin trajectories from the achiral side of the salen ring, presumably also helps build up the catalyst ring helix twisting (by enhancing the non-planarity of the salen ring) that is triggered by the diamine chiralities.[1] The right-handed helical twisting in the Salen ring is homohelically transferred to (*R*)-epoxide (the shown homohelical induction transition state is constructed on the basis of mechanistic model proposed by Jacobsen et. al, polarizabilities used here for deducing the substrate ring helix are consistent with those used earlier in sections **7** and **9**, i.e., R > H, and O in strained 3-membered ring > ***C***H_2).[1] Changing the metal from Mn to Co or Cr, and the axial ligand X from chloride to nucleophiles OAc or CN, doesn't change the catalysts' helical handedness (polarizabilities at either C*: N=C > C*; and ***C***H_2 > H), but transforms the epoxidation catalyst **1** into two efficient asymmetric ring opening catalysts **2** and **3**, respectively, that effect remarkable kinetic resolution of *rac*-**4** (Scheme 1).



Scheme 1. Homohelical recognition control in kinetic resolution of terminal epoxides. R: alkyls.

The stereochemical interactions between **2** (or **3**) and an epoxide in their associations should resemble those of the epoxidation transition state.[2] Therefore, the (*R*)-epoxide enantiomers bind to the right-handed **2** or **3** in a homohelical fashion and should be less susceptible to nucleophilic ring opening. It is indeed observed that it is always the heterohelically associated (*S*)-epoxides that undergo facile ring opening to yield enantioenriched 1,2-diols and 1-azido-2-siloxy products.

References:

1. Jacobsen, E. N. in chapter 18.2 of *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, **1999**.
2. Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421-431.

19. Kinetic resolutions based on Sharpless asymmetric epoxidation (Sharpless AE)

Kinetic resolution of secondary allylic alcohols by Sharpless (*R*,*R*)-DAT-Ti (DAT: dialkyl tartrates) catalysts is perhaps the most widely used kinetic resolution process in organic synthesis.[1] Despite intensive studies, the detailed mechanistic picture and the origin of high enantioselection in this system remain issues of much debate, due largely to the complex structures of several equilibrating Ti-species involved in the reaction.[2] Therefore, compared to structurally well-defined synthetic catalysts, it is not immediately visible in this natural pool-derived catalyst which particular helix twisting at the chiral center is actually responsible for its asymmetric induction. Remarkably, in contrast to steric effect-based stereochemical rationales which must be examined on a case-by-case basis, that characteristic helix twisting is the only information needed to analyze the catalyst/substrate helical electronic interactions; and once identified, it should succeed generally in all kinetic resolution systems associated with Sharpless AE. Thus the simple strategy employed here is to first identify the catalyst helix twisting and then to use it to understand the reactions stereochemical behaviors. As detailed below, kinetic resolutions of not only allylic alcohol, but also furyl, pyrryl, thienyl alcohols and amino alcohols, together with desymmetrizations of dialkenyl and *meso*-diallylic alcohols, are all under strict homohelical recogntion control. More significantly, this homohelical recognition rationale not only explains the results that appear to fit with the previous empirical models,[1b] but also accommodates results that conventional steric effect-related considerations do not.

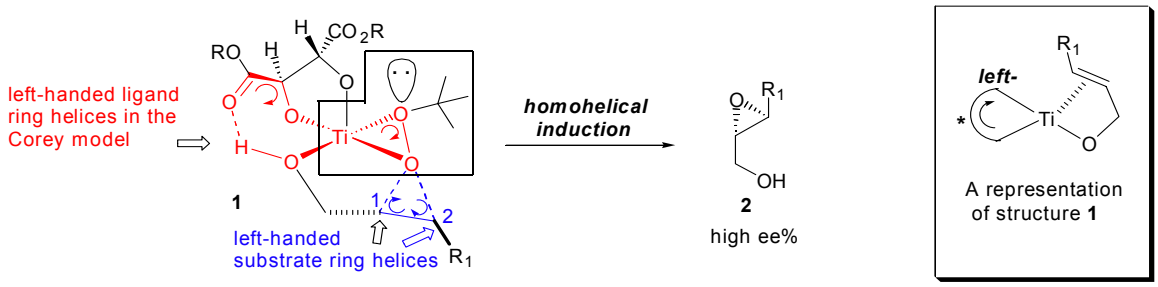
(a) Catalyst handedness and substrate structure

The (*R,R*)-DAT ligand can potentially interact with the Ti center and the substrate via dihydroxyl (***A***) or hydroxyl ester (***B***) mode (Scheme 1).[1,2] The former defines a right-handed ring helix, and the latter defines a left-handed ring helix (polarizabilities in ***A***: C=O > H; and C* > O; in ***B***: C=O > O; and C* > H).

Scheme 1. Possible helices in (*R,R*)-DAT-Ti catalysts.

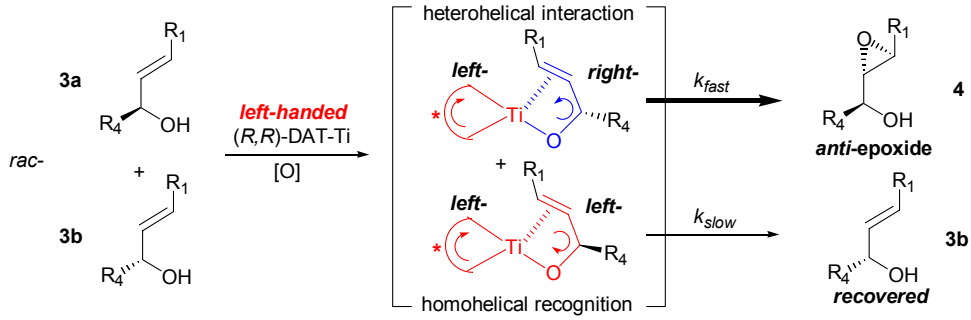
Although these two oppositely handed helices may exist concomitantly in a catalytically active intermediate, their respective roles in controlling the enantioselection are clearly not comparable, and there is evidence that strongly suggests that it is the hydroxyl ester mode ***B*** that actually controls asymmetric induction. Using structurally similar chiral 1,2-diols, such as 2,3-butanediol or 1,2-diphenyl-1, 2-ethanediol, to effect asymmetric epoxidation in place of the DAT ligands leads to essentially racemic products, which highlights the critical function of the ester moiety in the DAT ligands in enantioselections.[3] Is it hydrogen-bonding to the allylic alcohol substrates, or is it coordinative to the Ti center, or both, in the actual enantioselection-determining species? There is no definite answer although a preference may be placed on the former (note that these catalysts can not effect enantioselective epoxidations on allylic ethers). However, in either case ***B*** should bring left-handed helical twisting character to the catalyst. In this light, it is concluded here that *(R,R)-DAT-Ti is a class of catalysts featuring left-handed helical twisting*.[4]

An appealing rationale for origin of enantiocontrol has been the Corey model **1** (Scheme 2).[3] In addition to the left-handed helix from mode ***B*** that connects to both the Ti center and the substrate OH group, in this model there is another important left-handed catalyst ring helix that is readily recognizable, i.e., the helix centered on the oxygen atom in the dioxirane ring (highlighted in the box. Polarizabilities: Ti > O; and lone pair electrons > bonding electrons of the local tertiary carbon in ^{t}Bu). It should be noted that the latter is probably not independent from the former in that its establishment could well be the consequence of the synergistic action of both the homohelical induction from the original hydroxyl ester helix and the steric interactions between the ligand and the bulky ^{t}Bu group. This might help account for the observations that the steric bulkiness of R group in an achiral oxidation agent ROOH often affects the reaction ee significantly.[1c] In other words, asymmetric induction in this system likely operates through a *tandem homohelical induction* mechanism:[5] the original hydroxyl ester helix helps set up a left-handed helix in the dioxirane ring which is in direct contact with the substrate double bond, and subsequently it is this dioxirane helix that controls the delivery of the oxygen atom to the double bond with an enantiofacial selection defined by homohelical induction (left-handed substrate ring helices at C^1 and C^2 centers are defined by the following polarizabilities: at C^1, $\boldsymbol{C}H_2$ > H, and strained O > C^2; at C^2, R_1 > H, and strained O > C^1). Consequently, **2** is produced in high ee. In the following discussion, a simplified representation of structure **1**, highlighted in the box, will be used for clarity. As will be shown, this left-handed helical character in the (*R,R*)-DAT-Ti catalysts and the homohelical recognition control principle lead to a simple and general rationale for a wide variety of stereochemical observations in these systems.



Scheme 2. Homohelical induction in (*R,R*)-DAT-Ti catalyzed epoxidation of allylic alcohols.

(b) General stereochemical picture of kinetic resolution of allylic alcohols

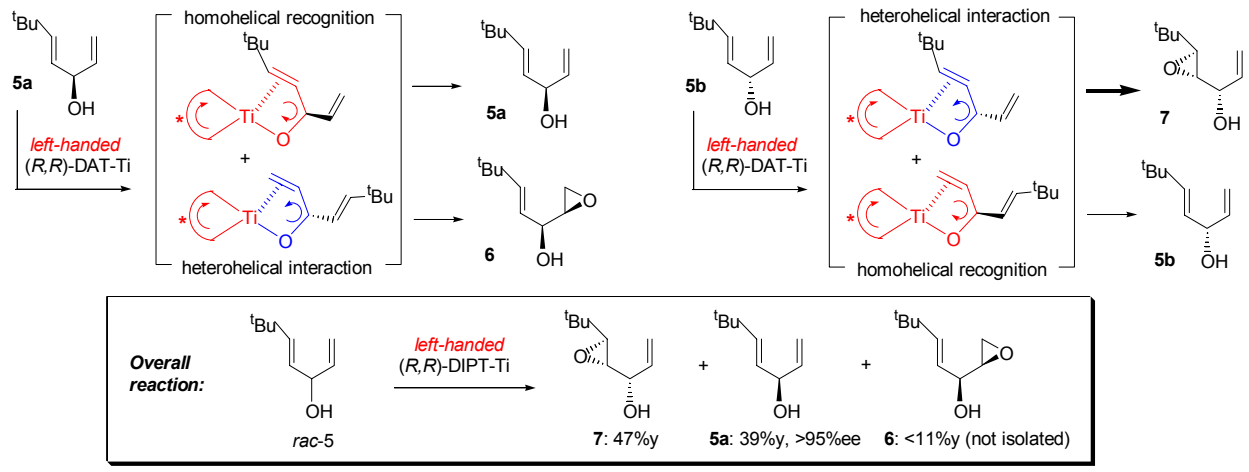


Scheme 3. Homohelical recognition control in kinetic resolution of allylic alcohols.

Upon coordination to the Ti center, an allylic alcohol enantimer **3a** establishes a right-handed substrate ring helix -O-C*-C=C- and its enantiomer **3b** establishes a left-handed helix (polarizabilities: C=C>O, and R_4>H). In line with the left-handed helical twisting in the (*R,R*)-DAT-Ti catalysts, kinetic resolution of racemic **3** generally yields *anti*-epoxide **4** from the kinetically active heterohelical (*R,R*)-DAT-Ti/**3a** intermediate with concomitant recovery of the slow-reacting enantiomer **3b** from the homohelical intermediate (*R,R*)-DAT-Ti/**3b** (Scheme 3).[1]

(c) Kinetic resolution of diallylic alcohols of electronically biased double bonds

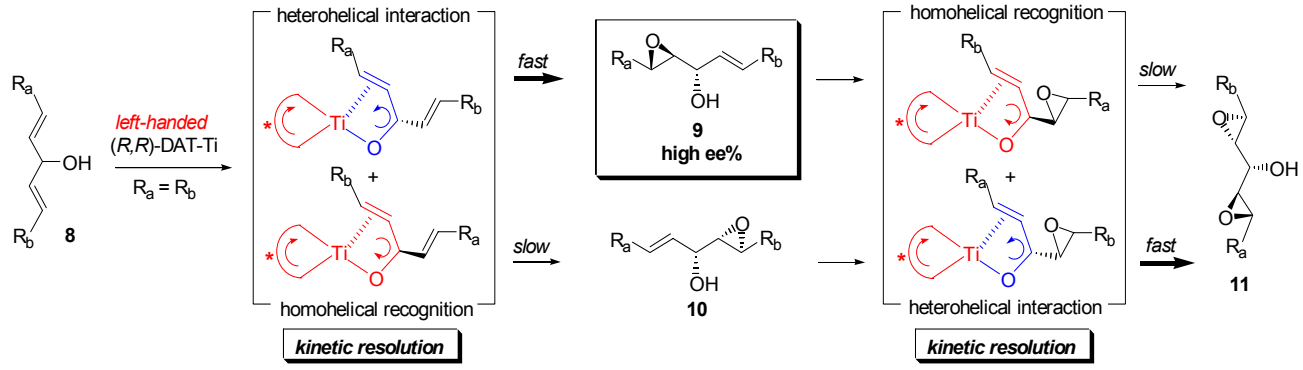
Kinetic resolution of **5** is a fascinating example in which both double bonds are potential sites for asymmetric epoxidation.[6] For its enantiomers **5a** and **5b**, a helical structure analysis is performed on each of the four possible catalyst-substrate associations. For **5b**, compound **7** should be expected as the sole product because it is from a kinetically active heterohelical intermediate and also the electron richness of the ^{t}Bu-substituted double bond further enhances its rate towards epoxidation; for **5a**, the situation is a little more complicated: while epoxidation product **6** is favored by the heterohelical pathway, its formation is retarded by the relative electron deficiency of the terminal double bond; Consequently, both production of **6** and recovery of unreacted **5a** may be expected. In agreement with this analysis, the overall kinetic resolution outcome for *rac*-**5** is exclusive formation of **7** in 47% yield from **5b** and recovery of **5a** in 39% yield. The minor product **6**, whose yield must be lower than 11%, was not reported (Scheme 4).



Scheme 4. Homohelical recognition control in kinetic resolution of diallylic alcohol **5**.

(d) Epoxidation of prochiral dialkenyl carbinols

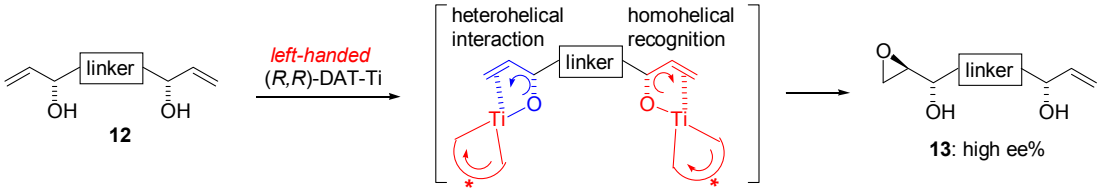
Epoxidation of prochiral **8** of two equivalent substituents (labeled as R_a and R_b), is formally a process involving consecutive kinetic resolutions, each of which is under homohelical recognition control, thus in each of which the fast-reacting pathway is associated with a heterohelical intermediate (Scheme 5). The remarkable feature is the inversed reactivity profiles in these two kinetic resolution steps: the epoxide **9** preferentially produced in the first step is consumed in a slower rate in the second step due to homohelical recognition, and the minor product **10** reacts in a faster rate towards further epoxidation because it forms a heterohelical intermediate with the catalyst. Both end up with the diepoxide **11**. This stereochemical characteristic leads to an important consequence, that is, **9** is furnished in extremely high ee, especially at longer reaction time.[7]



Scheme 5. Homohelical recognition control in a consecutive kinetic resolution process.

(e) Epoxidation of *meso*-secondary diallylic alcohols

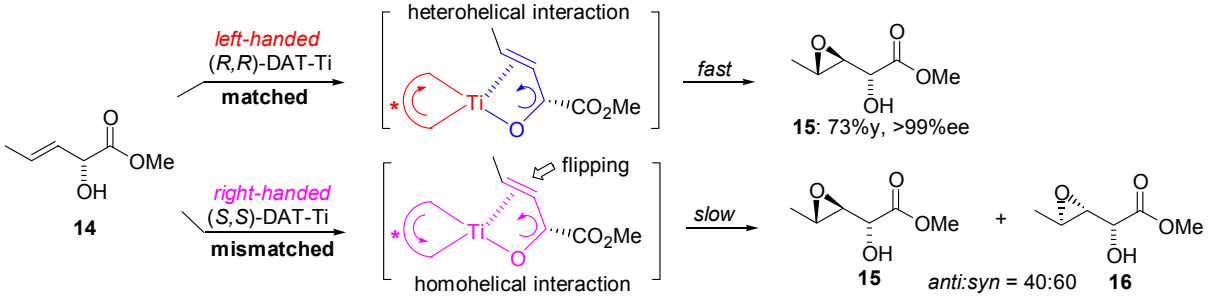
These epoxidations may be viewed as an intramolecular version of kinetic resolution. As expected from the homohelical recognition control, epoxidation of *meso*-**12** occurs selectively at the terminal double bond that defines a heterohelical complexation with the left-handed catalyst, leaving the other double bond untouched. This provides desymmetrized product **14** in high ees (Scheme 6).[8]



Scheme 6. Homohelical recognition control in epoxidation of *meso*-diallylic alcohols.

(f) Chirality matching and mismatching effects in epoxidation of optically pure allylic alcohols

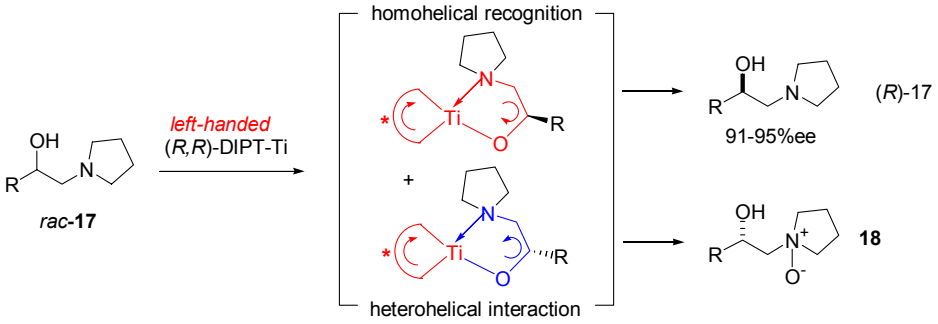
The principle that homohelical recognition leads to an energetically resting intermediate could also be used to understand the stereochemical matching profiles in epoxidations. An excellent example is the epoxidation of **14**, which, upon coordination to the Ti center, communicates an inherent right-handed substrate ring helix to the catalyst. When the catalyst is left-handed (*R,R*)-DAT-Ti, the resulted heterohelical catalyst/substrate association undergoes rapid epoxidation to give *anti*-epoxide **15** as the single product in 99%ee, constituting formally a catalyst-substrate chirality matching case;[9] In contrast, when the catalyst is right-handed (*S,S*)-DAT-Ti, a homohelically resting intermediate is formed, in which the double bond flipping occurs to some extents in the course of slow epoxidation. Consequently, although *syn*-epoxide **16** expected from homohelical induction is indeed formed as the major product, it is accompanied by a significant amount of **15** (Scheme 7).[10] On a more general conceptual perspective, it merits comments here that the terminologies "stereochemical matching" and "mismatching", although widely used, merely carry descriptive meanings, the helix analysis exemplified here may help appreciate the underlying stereochemical implications.



Scheme 7. A stereochemical correlation between chirality matching/mismatching and homohelical recognition control.

(g) Kinetic resolution of amino alcohols via asymmetric oxidation

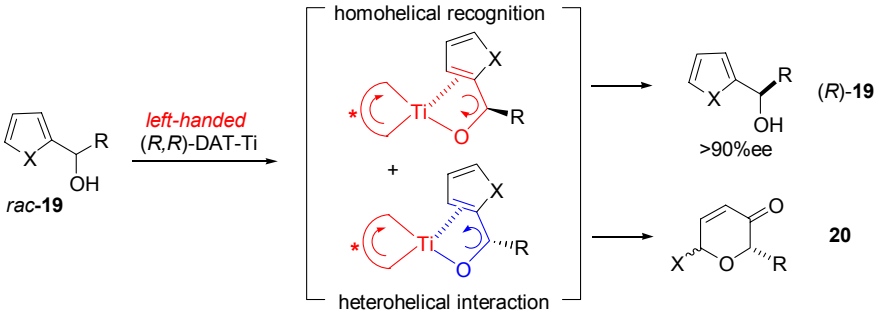
Oxidative kinetic resolutions of amino alcohols **17** are certainly different reactions from the allylic alcohols epoxidations, but their catalyst/substrate interactions are presumably similar. The stereochemical courses are without exception under the homohelical recognition control: the homohelical pathways lead to the recovery of slow-reacting (*R*)-enantiomers in high ees, and the heterohelical pathways have the (*S*)-enantiomers oxidized rapidly to **18** (polarizabilities: R > H; and $\boldsymbol{C}H_2$ > O, Scheme 8).[11]



Scheme 8. Homohelical recognition control in kinetic resolution of amino alcohols. R: alkyls, aryls.

(h) Kinetic resolution of furyl, pyrryl and thienyl alcohols and their derivatives

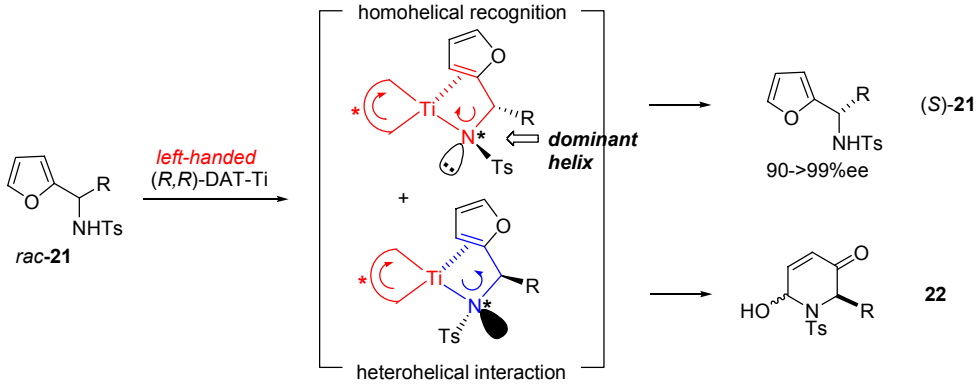
Similar to secondary allylic alcohols, 2-(1-hydroxyalkyl) derivatives of heterocyclic compounds of a general structure **19** also function as good substrates for DAT-Ti catalyzed kinetic resolutions because they contain an electron-rich double bond that is α- to the OH group, formally an allylic alcohol system.[12] Homohelical recognition control yields predictions on the stereochemical outcomes that are in full agreement with the experiments: (*R*)-enantiomers are recovered from slow-reacting homo-helical pathways, and (*S*)-enantiomers are epoxidized rapidly via the heterohelcial intermediates to give final products pyranones **53** after a rearrangement. Both are in high yields and ees (Scheme 9).



Scheme 9. Homohelical recognition control in kinetic resolution of **19**. X= O, S, NH, NTs; R= Ph, alkyls, alkenes.

The scope of this kinetic resolution process can be extended to substrates of a structure **21** since the amino groups in them may mimic the -OH in **19**. The reactions proceed with comparable efficiency. Remarkably, in these reactions the stereochemical outcomes are opposite to those found in kinetic

resolutions of **19**: for a racemic substrate **21**, the (*R*)-enantiomer reacts at a faster rate to give **22**, and the (*S*)-enantiomer is always recovered in high yield and ees (Scheme 10)![13]



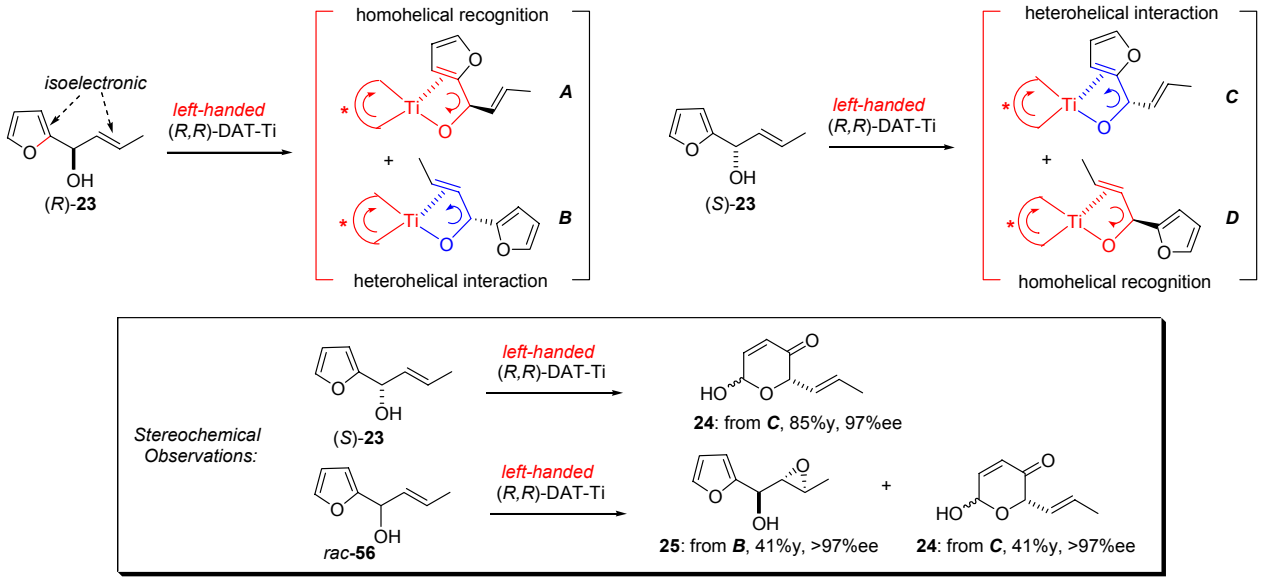
Scheme 10. Homohelical recognition control in kinetic resolution of **21**. R = alkyls, alkenes.

These seemingly surprising behaviors, however, may be deduced from the homohelical recognition control principle. The critical element of this specific system is the *in-situ* generated N* chirality when **21** complexes to the Ti center. In an (*R,R*)-DAT-Ti/(*S*)-**21** association, the steric repulsion between the bulky -Ts and the -R groups may establish a new N* chirality in the substrate ring structure, on which the lone pair electrons orbital is projected as indicated (note that in this system the deprotonation of NH is assumed since the catalyst is modified with calcium hydride and silica gel for effectiveness). This may generate a significant left-handed substrate ring helix -C*-N*-Ti- (polarizabilities: Ti > C*; and lone pair electrons > bonding electrons of S in -Ts) whose handedness is opposite to the original C*-centered right-handed substrate ring helix -C=C-C*-N*- (polarizabilities: C=C > N; and R > H). This new N*-helix is apparently dominant due to two reasons: one, electrons in a lone pair orbital and a transition metal Ti are both highly polarizable, therefore the large polarizability distinctions in the pairs of lone pair electrons-*versus*-bonding electrons and of Ti-*versus*-C* create a helical twisting in the N*-helix that may outweigh that of the original C*-helix;[14] two, this left-handed N*-helix is directly attached to the Ti center thus should exert more influence on the catalyst/substrate interactions than the C*-helix. As a result, the (*R,R*)-DAT-Ti/(*S*)-**21** association characterizes a homohelical recognition resting state that leads to the recovery of (*S*)-**21**, and the (*R,R*)-DAT-Ti/(*R*)-**21** association is heterohelical thus it undergoes a rapid epoxidation-rearrangement sequence to yield **22** (Scheme 10).

(i) Kinetic resolution of substrates of isoelectronic allylic double bonds

Oxidation of **23** is another interesting case in which the stereochemical outcomes can be rationalized by the homohelical recognition control principle. It has been previously recognized that the furan ring double bond and the (*E*)-disubstituted double bond are isoelectronic thus are oxidized in comparable rates by DAT-Ti catalysts, the high chemoselectivity in such a system is therefore controlled by the chirality of the catalyst.[15] However, the origin of such a catalyst-controlled chemoselectivity has not been understood. Homohelical recognition control suggests a rationale here. The homohelical (intermediates ***A*** and ***D***) and heterohelical (***B*** and ***C***) (*R,R*)-DAT-Ti/**23** associations for both enantiomers are shown in Scheme 11. Oxidation product for each enantiomer should be derived from

the kinetically active heterohelical pathway, which is ***B*** for (*R*)-**23** and ***C*** for (*S*)-**23**. Therefore, when the substrate is optically pure (*S*)-**23**, **24** is produced from ***C*** exclusively in 97%ee; when the substrate is racemic **23**, both **24** and **25** are formed in high yields from ***C*** and ***B***, respectively, also in >97%ee.



Scheme 11. Homohelical recognition control in epoxidation of isoelectronic allylic double bonds.

References:

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14. In asymmetric catalysis the stereochemical roles of the *in-situ* generated chirality on some heteroatoms have often been overlooked. It should be emphasized that they may exert critical influences on the stereochemical course of an asymmetric reaction for the reasons stated in the text: these heteroatoms often coordinate directly to a metal center thus bring their helical structures to close proximities to the reaction site; and their helices often have high helical characters due to the involvement of highly polarizable metal-*d* and lone pair electrons. For an excellent example of in-situ generated S*-chirality, see: (a) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534-3543; N*-chirality, see: (b) Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron. Lett.* **1993**, *34*, 5563-5566; O*-chirality, see the above Ref. 3.
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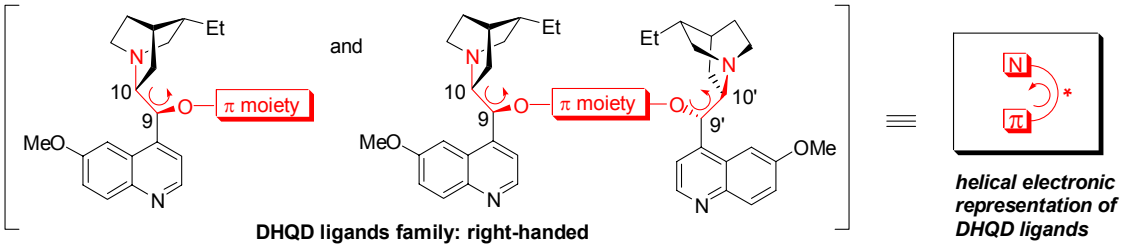
20. Kinetic resolution of olefinic substrates by asymmetric dihydroxylation (Sharpless AD)

(a) Catalyst handedness, homohelical induction and substrate structural requirements

The asymmetric dihydroxylation catalysts are generally derived from Cinchona alkaloid ligands, dihydroquinidine (DHQD) and dihydroquinine (DHQ), which are *pseudo*-enantiomers.[1] To reach a general understanding of the origin of stereoselections in these reactions, i.e., the mechanism of enantiofacial selections on the double bonds, and the relevant kinetic resolution behaviors, we must first identify which helix (helices) in these structurally untailored ligands is actually responsible for the ligand-to-substrate homohelical induction. We focus the discussion on the DHQD ligands (Scheme 1). There are several empirically yet well established structural appreciations on this system that can guide us to the answer: (1). The tertiary amine binds to the Os catalytic center; (2). Configurations of C^9 and $C^{9'}$ are critical in controlling the reaction absolute stereochemical course; (3). Oxygen of 9-OR group is essential and can't be replaced by a carbon substituent; (4). In both monomeric or dimeric DHQD ligands 9-OR group must be a π-moiety (aromatic or hetero-aromatic rings or C=O bonds) to allow for high enantioselections; (5). The ligand structure-reaction ceiling rate constants correlation shows that variations in the 9-OR substituent have much more profound effects upon the ceiling rate constants than almost any other variations in the ligand structure.[2]

These facts lead to the conclusion that *the physical helices linking the N coordination site and the π-moiety, i.e., -N-C^{10}-C^9-O-π moiety- in monomeric DHQDs and -N-C^{10}-C^9-O-π moiety-O-$C^{9'}$-$C^{10'}$-N- in dimeric DHQDs, must be the ligand ring helices (highlighted in red) in the DHQD family that actually execute the homohelical transmission of chirality to the substrate ring* (Scheme 1). Ring helices around the C^{10} and $C^{10'}$ centers, i.e., -N-C^{10}-C^9- and -$C^{9'}$-$C^{10'}$-N-, are weak as the polarizability distinctions between N and C^9 or $C^{9'}$, and between $\boldsymbol{C}H_2$ and H, are all small. In contrast, ring helices around the C^9 and $C^{9'}$ centers, i.e., -C^{10}-C^9-O-and -O-$C^{9'}$-$C^{10'}$, are significant, and are right-handed due to polarizabilities: $\boldsymbol{C}_{sp2}$ in methoxyquinoline >> H, and C^{10}, $C^{10'}$ > O. More importantly, these C^9- and $C^{9'}$-ring helices are close to the π-moiety whose π-π stacking with the substrate double bond helps

establish the enantiofacial control (see the following discussion for this point). Consequently, the ligand rings in DHQDs are dominated by the C^9 and $C^{9'}$ right-handed helical twisting. On the basis of these considerations, DHQD ligands could be electronically simplified into an N/π representation that features a right-handed helix twisting (Scheme 1).

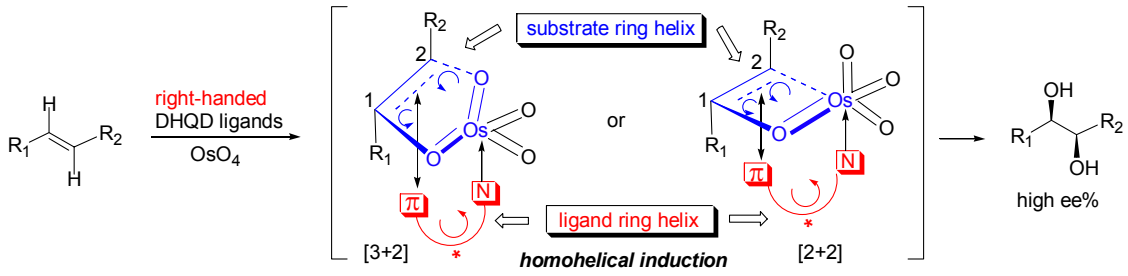


Scheme 1. A simple helical electronic representation of the DHQD ligands.

Despite intensive investigation, the mechanism of dihydroxylation remains a subject of controversy. The complications arise from not only the concerted [3+2] *versus* stepwise [2+2] addition of ligated-OsO_4 to an alkene at an achiral platform, but also the origin of high enantiofacial selection on a pro-chiral alkene plane.[2] In the most influential stereochemical model a stacking stabilization effect between the 9-OR group and one of the alkene substituents is proposed as the key factor that controls the enantioselection.[1] For an aromatic substituent such a stacking of some π-π attraction character is readily conceivable. But for an alkyl substituent, such a stacking should be substantially weak; however, *trans*-dialkyl substituted alkenes are often found to work in comparable efficiency as *trans*-diaryl substituted alkenes. Moreover, some substrates of two isosteric *cis*-substituents, a class of substrates having generally poor efficiency in asymmetric dihydroxylations, are also capable of achieving considerable ees (for instances, some *cis*-allylic and homoallylic alcohols have been dihydroxylated by $(DHQD)_2$-PHAL with 54-74%ee).[3] These cases seem to pose challenges to the alkyl substituent/9-OR stacking mechanism since stereochemically differentiating the two *cis*-isosteric alkyls should be very difficult. In some other substrates, most notably a series of 1,1-disubstituted alkenes displaying favorable substituent steric characters that are required by that stacking model, the experimentally observed senses of dihydroxylations are surprisingly opposite to those predicted by the model.[4]

Considerations on these issues, in conjunction with the basic fact that high enantioselections must rely on interactions between the 9-OR group and a structural fragment of the alkene, lead us to propose that *it is more likely to be the double bond itself, but not its substituents, that is generally involved in stacking with the ligand 9-OR group*. For all suitable substrates such an alkene double bond/9-OR stacking in the enantioselection-determining step may be generally characterized by a π-π attraction nature, which should considerably help locate the relative orientation of the double bond to the incoming OsO_4 attack and facilitate efficient homohelical enantiofacial control. It should be noted that, this proposal is not new and it has been previously suggested by Lohray et. al. with supports from some designed experiments, which, unfortunately, has been overlooked.[5] The validity of this proposal will be further enhanced by its power in rationalizing experimental observations in various AD-based asymmetric induction and kinetic resolution systems. Herein we wish to emphasize that the combination of N-Os coordination and alkene double bond/9-OR π-π attraction provides a pair of judicious bonding/non-bonding interactions that are capable of coupling the right-handed DHQD

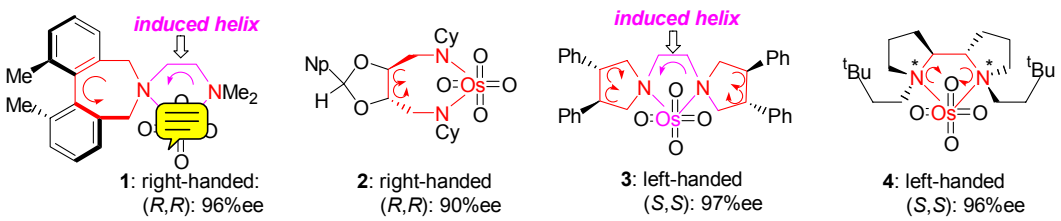
ligand ring helix with the corresponding alkene substrate ring helix to allow for efficient homohelical chirality transmission. The facial selection on a double bond is thus electronically controlled by the homohelical induction, which in turns sets a critical polarizability requirement on the double bond substituents. The double bond must add to the OsO_4 in such a way that in the transition state the substrate ring also defines a right-handed helicity.



Scheme 2. Homohelical induction in Sharpless asymmetric dihydroxylations using DHQDs ligands.

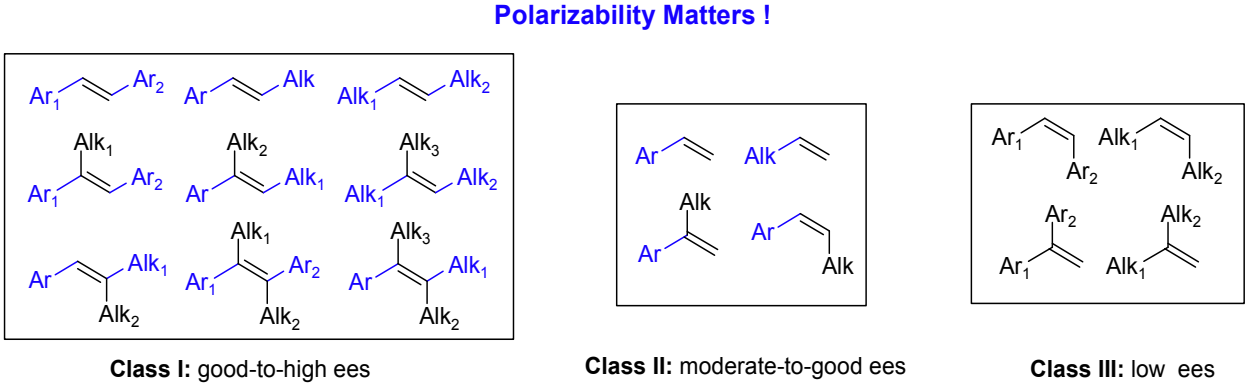
Such a homohelical induction course is shown in Scheme 2 using a *trans*-disubstituted alkene substrate. The exact pathway of cycloaddition, either a [3+2] or a [2+2] type, has not been unambiguously established. However, in this particular case this mechanistic obscurity doesn't complicate the homohelical induction analysis simply because in the enantioselection-determining transition state the two partially breaking O=Os bonds in the [3+2] mode and the one O=Os bond and the Os atom in the [2+2] mode are all more polarizable than the alkyl termini (Scheme 2). Specifically, in the [3+2] mode, the polarizability sequences under concern at the C^1 center are: $R_1 > H$; and O=Os $> C^2$; at the C^2 center are: $R_2 > H$; and O=Os $> C^1$. In the [2+2] mode, the polarizability sequences under concern at the C^1 center are: $R_1 > H$; and O=Os $> C^2$; at the C^2 center are: $R_2 > H$; and Os $> C^1$. In both modes the shown facial selection establishes the right-handed substrate ring helices through the homohelical induction mechanism and consequently determines the product absolute stereochemistry in a highly enantioselective fashion.

This catalyst handedness-product configuration correlation in Sharpless AD systems is in accord with those in other asymmetric dihydroxylations effected by structurally simpler tertiary diamine-OsO_4 complexes (Scheme 3). Although these complexes function only in a stoichiometric fashion and do not employ a π-π attraction in enantiocontrol, they share the similar homohelical induction mechanism with the DHQD catalysts. These correlations are summarized in Scheme 3. When *trans*-stilbene is used as a standard substrate, all right-handed catalysts give (*R*,*R*)-diol and left-handed catalysts give (*S*,*S*)-diol. **1** has an atropisomeric right-handed helix (in red) which transmits its twisting to the substrate ring (not shown) via an induced intermediate helix in the diamine-Os chelate ring (i.e., tandem homohelical induction); In **2**-**4** the substituents polarizability sequences around each chiral center used to deduce the catalyst ring handedness (in red) are: for **2**: $\boldsymbol{C}H_2 > \boldsymbol{C}^*H$, and O > H; for **3**: $\boldsymbol{C}H_2 > \boldsymbol{C}^*H$, and Ph > H; for **4**: Os > $\boldsymbol{C}^*H$ and $\boldsymbol{C}H_2$ in a strained 5-membered ring > $\boldsymbol{C}H_2$ in a linear chain (note that in this case the N* helices dominate the catalyst ring twisting due to their proximity to the reaction site and their involvement of highly polarizable Os electrons, see also earlier discussion under footnote 14 in section 19).[6]



Scheme 3. Catalyst handedness-product configuration correlation in chiral tertiary diamine-OsO_4 complexes-catalyzed asymmetric dihydroxylation of *trans*-stilbene.

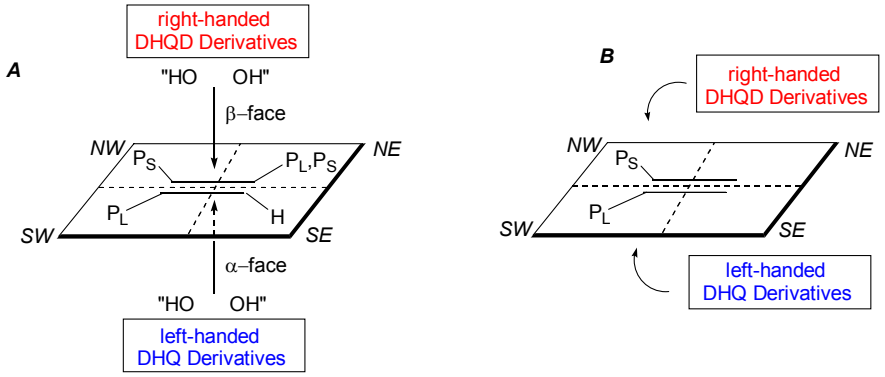
As exemplified in Scheme 2 and also discussed previously,[7] it is very important to note that the "*trans*-effect" of R_1 and R_2 enables that the helices at both forming chiral carbon centers in dihydroxylations have the same handedness therefore contribute to the substrate ring twisting synergistically. Considerations on such "*trans*-effect" and an alkene substrate's substituents polarizabilities readily lead to the classifications shown in Scheme 4. Class **I** alkenes, regardless of their di-, tri-, or tetra-substitution patters, are capable of defining significant substrates helical twistings when interacting with the Os-catalysts which constantly lead to products of good-to-high ees and very predictable stereochemistries. Class **II** alkenes generally yield lower substrates helicities, therefore the ees of their products are usually moderate-to-good and sometimes are of considerable fluctuations. The substituents of higher polarizabilities in these two classes of alkenes are highlighted below in blue. They dominate the corresponding substrates ring helicities therefore control the enantiofacial selections on the double bonds. Class **III** alkenes, because the helices at the forming chiral centers in dihydroxylations would be effectively cancelled out by the substituents' nearly identical polarizabilities, have barely any net substrate twisting, and with the lack of helical electronic control, the reactions ees are often very low.



Scheme 4. Critical dependence of the reaction enantioselections on the alkene substituents polarizabilities in asymmetric dihydroxylations. Ar: aromatic, hetero-aromatic, or other π groups (triple bonds, double bonds); Alk: alkyls.

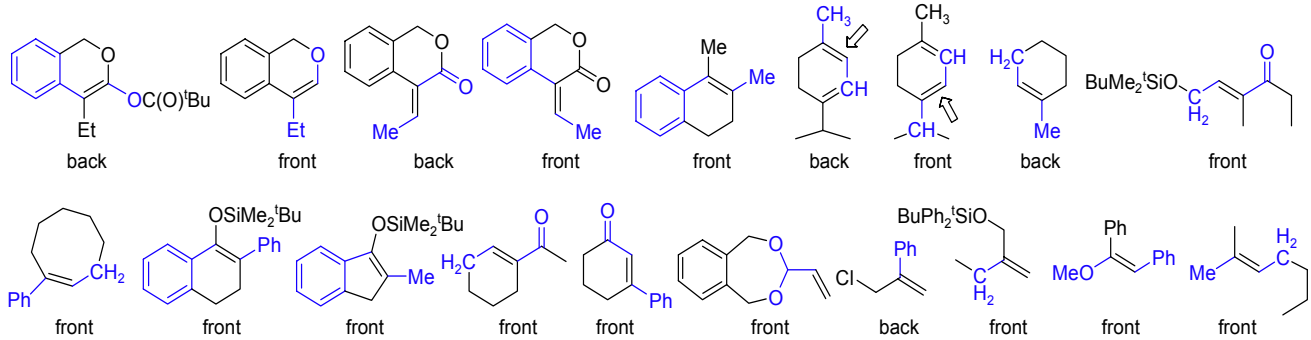
Prior to this polarizability-based rationale on substrate structures, there has been a very influential mnemonic device that empirically predicts enantiofacial selectivity in the dihydroxylation reactions.[1] The device roots in related molecular mechanics model for explaining the enantioselectivity and places an alkene substrate's substituents into four quadrants. The most profound appreciation of that device is that the southwest quadrant, believed as an *attractive* area, is special in that it is well-suited to

accommodate *flat*, *aromatic* substituents or, in their absence, *soft* and *large* aliphatic groups. An alkene fitting this device will be dihydroxylated from the top face (i.e., the β-face) by DHQD-derived catalysts, or from the bottom face (i.e., the α-face) by DHQ-derived catalysts. Notably, the wordings of "flat, aromatic, soft and large" may be readily replaced by a single adjective "polarizable". With these insights gained from the homohelical induction theory, a new, polarizability-based model ***A*** is suggested below. In ***A*** the *trans*-substituents in the southwest and northeast quadrants dominate the substrate ring helix twisting thus define the attacking trajectory of a catalyst. When the catalyst is a right-handed DHQD derivative, attacking electronically preferentially occurs from the β-face; and when the catalyst is a left-handed DHQ derivative, it occurs at α-face (Scheme 5).



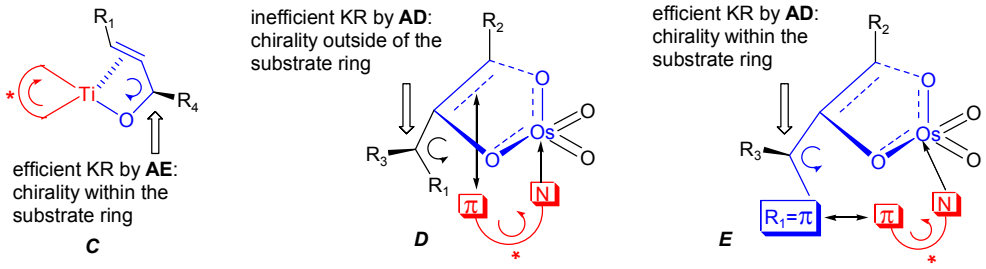
Scheme 5. A new, substituent polarizability-based stereochemical model that allows for general and reliable predictions of enantiofacial selections in asymmetric dihydroxylations. P_L: substituent of larger polarizability, such as aryls, alkenyls, or alkynyls; P_S: substituent of smaller polarizability, such as alkyls.

This model ***A*** is non-empirical because the relevant double bond substituents polarizability sequences can be easily assigned. ***A*** allows for unambiguous stereochemical predictions in highly enantioselective dihydroxylations. Applying it to an extensive range of alkenes[1] achieving >70%ee shows that it is generally held.[8] For 1,1-disubstituted alkenes, ***A*** can be reduced to a simpler model ***B*** (Scheme 5). The promising 1,1-disubstituted substrates are 1,1-aryl alkyl-alkenes (class **II**, Scheme 4) in which relatively large substituents polarizability distinctions are achieved by a pair of aryls (P_L)-*versus*-alkyls (P_S).[1] It is recommended here that the reader check these new models ***A*** and ***B*** in new experiements. Listed below are some alkenes illustrating their applications.[8] The preferred dihydroxylation trajectory with a DHQD ligand-derived catalyst is shown under each structure.



(b) AD-*versus*-AE: a paradox of efficiency on asymmetric catalysis and kinetic resolution

A long-standing puzzle in Sharpless AD and AE has been their inversed pictures of efficiency in asymmetric catalysis and kinetic resolution. Despite the generally high enantioselections AD enjoys over a wide range of alkenes, it has not achieved the same level of success in kinetic resolution and in fact, to date efficient kinetic resolution systems based on AD have been quite limited; In sharp contrast, in asymmetric catalysis the AE only works on allylic alcohols, but it has been proven to be remarkably superior in chiral discriminations in various kinetic resolution processes.[9]



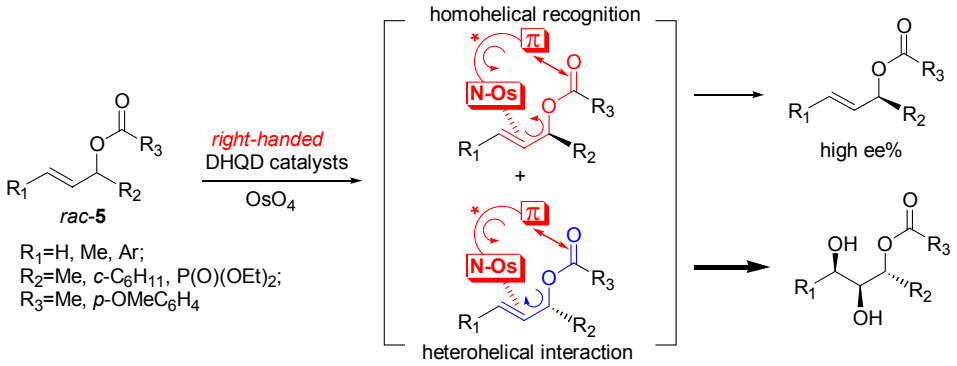
Scheme 6. Substrate structural requirements for efficient kinetic resolution in AE and AD.

The helix theory, remarkably, may help explain why this is the case. As shown in ***C*** of Scheme 6, in AE-based kinetic resolutions, the Ti center interacts with the double bond of a chiral alkene via a dioxirane intermediate, and, simultaneously, with the hydroxyl group by coordination. This coordination mode mimics well that of an achiral alkene and locates the substrate chirality *within* the substrate ring, an ideal situation in which the homo- and hetero-helical interactions between the ligand ring helix and the helix from that substrate chirality are efficient thus allows for facile discrimination of the substrate enantiomers in kinetic resolutions. In AD-based kinetic resolutions, however, it is clear from the above homohelical induction analysis (see Scheme 2) that both N-OsO_4 and π-component of the ligand helix target on the substrate double bond. While this "dual-interaction control" mechanism leads to remarkably high enantiofacial selections on a wide variety of alkenes, it also precludes the possibility of incorporating the chiral center of a racemic alkene within the corresponding substrate ring, and consequently, electronically it exerts essentially no influence on the substrate/ligand ring helical interactions. This situation is illustrated by ***D*** and it might generally account for much failure met in AD-based kinetic resolutions. However, this also suggests that choosing some substrates that are capable of incorporating their original chiralities inside the corresponding substrate/ligand ring structures of helical interactions may lead to kinetic resolutions. Since in the ligand ring N-OsO_4 must attack the alkene double bond, the only approach to potentially achieve the above goal is to place another π-moiety R_1 in a substrate that can compete effectively with the double bond to participate in the π-π attraction with the ligand 9-OR moiety. This rational kinetic resolution strategy is illustrated in ***E***. Indeed, so far chiral alkenes succeeded in AD-based kinetic resolutions, without exception, are all featured by a general structure -C=C-chirality-π moiety- in which the π moiety is often chosen to be a C=O (ester, amides, etc) or an aryl. It should be pointed out that, while this kinetic resolution strategy may allow for the recovery of one substrate enatiomer (the one featuring homohelical recognition with the ligand, see below) in high ee, the ee in the kinetically active heterohelical pathway may be severely jeopardized simply because the desired π-π attraction in the "dual-interaction control" mechanism for high enantiofacial selection, i.e., that between the alkene double bond and the ligand 9-OR moiety, may be disrupted by the competing π-π interaction between the substrate π-R_1 substituent and the

ligand 9-OR group. Consequently, the dihydroxylation products should be produced much less enantioselectively than those obtained from normal achiral alkenes lacking such a π moiety. This is indeed again in line with AD-based kinetic resolutions reported so far, in fact, as will be detailed below, literature works concerned mostly the ees of the recovered substrate enantiomers, the ees of the dihydroxylation products were either not reported or disappointedly low.

(c) Kinetic resolution of allyl alcohol derivatives

Allyl alcohol derivatives **5** feature both a double bond and a carbonyl π moiety in the substrate ring helix -C=C-C*-O-C(O)-. Upon complexation to the right-handed DHQD catalysts through the above discussed ligand/substrate interactions, i.e., -N-Os/C=C attacking and 9-OR/C=O π-π attraction, enantiomers of **5** yield both homohelical and heterohelical intermediates (polarizabilities: C=C > O; and R_2 > H). As expected, the homohelical complexation leads to the recovery of the substrate enantiomer, and the heterohelical complexation undergoes dihydroxylation (Scheme 7)[10]. To appreciate more about the origin of chiral recognition in these systems, two additional characteristics of these substrates merit attention: (1). Free alcohols (i.e., when $C(O)R_3$ is replaced by H) don't yield kinetic resolution; (2). While allylic acetates achieve moderate kinetic resolution efficiency (k_{rel} < 25, mostly around 10), k_{rel} reaches a record number 79 when R_3 = *p*-$OMeC_6H_4$, which could be attributed to additional π-π stacking with the DHQD 9-OR group contributed from the phenyl ring (in addition to that contributed from C=O). In fact, phenyl ring itself alone can function as an efficient π-component in AD-based kinetic resolution; [11] (3). Although alkenylphosphonates [R_2= $P(O)(OEt)_2$] formally contain a P=O double bond, this π moiety can't interact with the ligand 9-OR group simply because the tetrahedral phosphorus effectively prevents it from participating in a π-π stacking which requires a planar geometry. These observations highlight the role of -$C(O)R_3$ type π groups in kinetic resolutions.

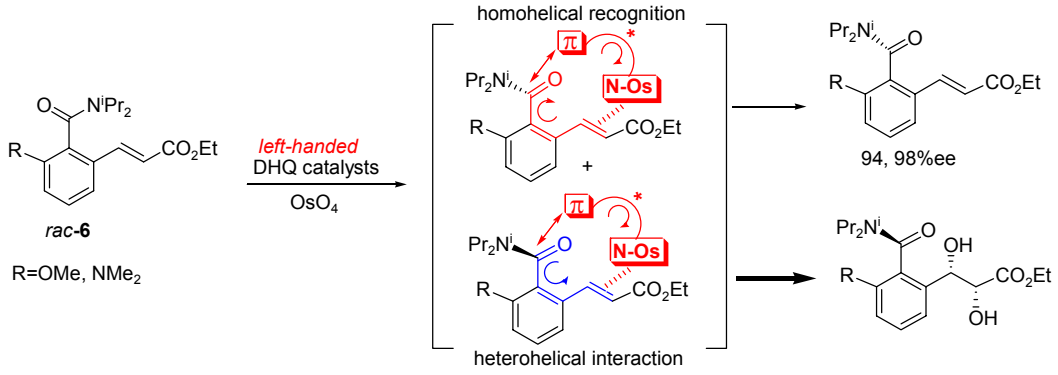


Scheme 7. Homohelical recognition control in kinetic resolution of allyl alcohol derivatives.

(d) Kinetic resolution of atropisomeric amides

The left-handed DHQ catalyst, AD-mix-α, has been used to effect kinetic resolution of atropisomeric amides **6** in which the amide carbonyl may participate in the substrate/ligand π-π attraction. The double bond is inherently framed into the substrate ring helix induced by the atropisomerism. When such a substrate ring helix is left-handed, homohelical substrate/ligand recognition is expected and this

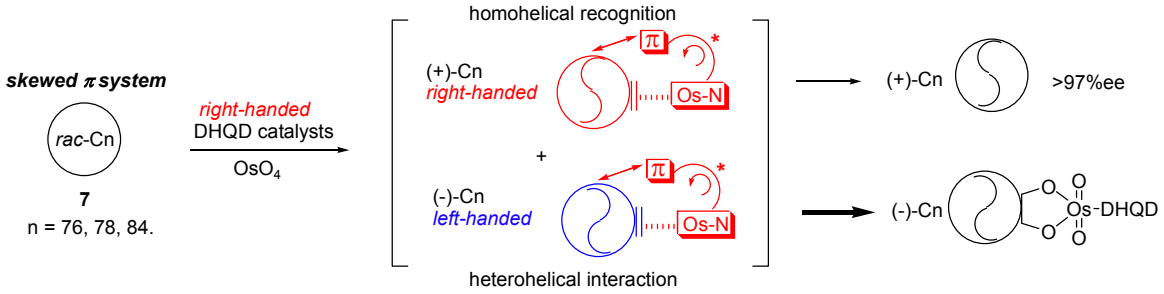
returns the substrate enantiomer. When the ring helix is right-handed, the heterohelical intermediate readily undergoes dihydroxylation (Scheme 8).[12,13]



Scheme 8. Homohelical recognition control in kinetic resolution of atropisomeric amides.

(e) Kinetic resolution of chiral fullerenes

Discrimination of enantiomers of fullerenes Cn **7** (n = 76, 78, 84) represents to date the most interesting applications of AD in kinetic resolution.[14] Cn is structurally unique in that the skeleton is featured by a large, skewed π electron system. From the helix theory point of view, the possible stereochemical complications that may arise from enantiomeric discriminations of 30 (for C_{76}) different double bonds on the fullerene skeleton seem not to be troublesome since all these double bonds are connected by highly fluxional skeleton π electron densities thus are uniformly chiral in one handedness. Therefore, the π-π interaction between any of these 30 double bonds with the right-handed DHQD catalyst should tell the same stereochemical story. Experimentally, the dihydroxylation selectively occurs at one of the two more pyramidalized double bonds, with another vicinity C=C functioning as a π moiety. As expected from the homohelical recognition control, when **7**'s skewed π system is right-handed, the enantiomer is left untouched; when it is left-handed, the enantiomer undergoes fast osmylation (Scheme 9).[15,16]



Scheme 9. Homohelical recognition control in kinetic resolution of fullerenes.

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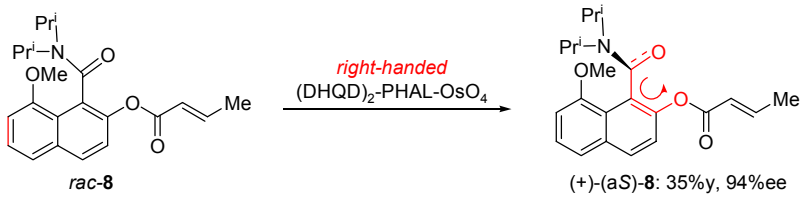
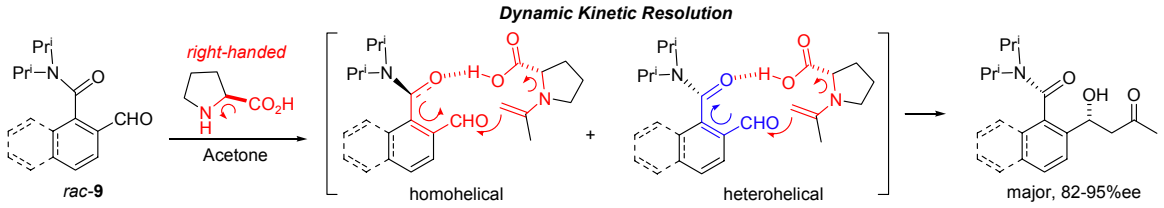
6. A complete list of these diamine ligands can be found in Fig.1 on page 717 of Ref. 2. To eliminate the uncertainties in the catalyst handedness-product configuration analysis, secondary diamines **10** and **13** (numbers are those used in the original Figure) are not included here because their catalytic intermediates may be structurally different from those of tertiary diamines systems. Studies have shown that the osmate esters formed in the reactions with some secondary amines readily lose one molecule of H_2O at ambient conditions, indicating the addition of N-H bond to Os=O bond. See: (a) Hanessian, S., Meffre, P., Girard, M., Beaudoin, S., Sanceau, J-Y., Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991-1993; (b) Corey, E. J., Jardine, P. D., Virgil, S., Yuen, P-W., Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243-9244. Tertiary diamines **6** (Footnote 9 of the above Hanessian paper; see also: Tokles, M., Snyder, J. K. *Tetrahedron. Lett.* **1986**, *27*, 3951-3954.), **11** (Fuji, K., Tanaka, K., Miyamoto, H. *Tetrahedron. Lett.* **1992**, *33*, 4021-4024.) and **14** (Tanner, D., Andersson, P. G., Harden, A., Somfai, P., *Tetrahedron. Lett*. **1994**, *35*, 4631-4634.) are also not included because of conflicting literature reports, uncertainties in coordination modes arising from the multiple N centers, and very limited catalysis evaluation, respectively.
7. See previous analysis on this issue in section 2h.
8. The survey is based on data in the Refs. 1 and 2.
9. Katsuki, T. in chapter 18.1 of *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, **1999**.
10. (a) Corey, E. J.; Noe, M. C.; Guzman-Perez, A. *J. Am. Chem. Soc.* **1995**, *117*, 10817-10824; (b) Lohray, B. B.; Bhushan, V. *Tetrahedron. Lett.* **1993**, *34*, 3911-3914; (c) Yokomatsu, T.; Yamagishi, T.; Sada, T.; Suemune, K.; Shibuya, S. *Tetrahedron*, **1998**, *54*, 781-790; (d) Crispino, G. A.; Makita, A.; Wang, Z-M.; Sharpless, B. M. *Tetrahedron Lett.* **1994**, *35*, 543-546.
11. Yamaguchi, S., Muro, S., Kobayashi, M., Miyazawa, M., Hirai, Y. *J. Org. Chem.* **2003**, *68*, 6274-6278.
12. Rios, R.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10272-10273.
13. A Sharpless AD-based kinetic resolution of atroisomeric *N*, *N*-diisopropyl-1-naphthamides was also reported, see: Dai, W-M.; Zhang, Y.; Zhang, Y. *Tetrahedron: Asymmetry*, **2004**, *15*, 525-535. An example, *rac*-**8**, is shown below. Note that the (a*S*)-configuration of the recovered enantiomer suggests that it is released from a homohelical catalyst/substrate association. The double bonds in these substrates are relatively remotely disposed from the amide axial helicity, therefore their kinetic resolutions are generally less efficient than those discussed in Scheme 8.



Likewise, as illustrated below, a remarkable dynamic kinetic resolution of various atropisomeric amides **9** catalyzed by the right-handed *L*-proline (ring helix: -HN-C*-CO_2H-; Polarizabilities: ***C***H_2 > H; C(O) > N) proceeds favorably through a heterohelical pathway, see: Chan, V.; Kim, J. G.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2004**, *6*, 2051-2053.



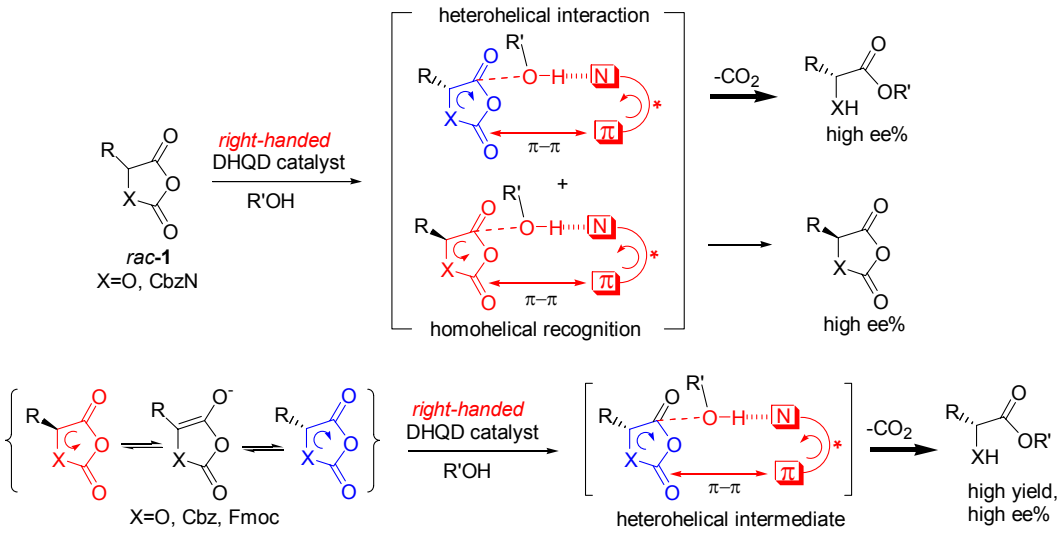
14. Hawkins, J. M. *Science*, **1993**, *260*, 1918-1921.
15. Kinetic resolution of some sterically-demanding olefins was also reported, see: VanNieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7864-7865. These substrates do not possess a π-component around the C=C bond, therefore can not interact with the AD-mix catalysts through the mechanism depicted in structure ***E*** in Scheme 6.
16. A very interesting observation (see both page 2503 and footnote 108 in Ref. 1a) in kinetic resolution of some 3-substituted cyclohexenol derivatives by using right-handed $(DHQD)_2$-PHAL-OsO_4 is that the structurally similar **10** and **11**, as shown below, behave quite differently in terms of the selectivity factor and enantioselection (note that, however, in both cases the (*R*)-substrate enantiomer featuring a double bond framed in a right-handed cyclohexene ring helix is selectively recovered. Polarizabilities: O > H.; C=C > ***C***H_2). This notable difference may be rationalized by the chiral catalyst's stronger tendency to attack to the double bond in **11** than to that in **10** simply because phenyl is more polarizable than methyl thus the former attack would gain the sysestem a more electronically favorable catalyst/substrate homohelical interaction.

21. Kinetic resolution and desymmetrization of carbonyl derivatives by DHQD-catalyzed asymmetric alcoholysis and related processes.

(a) Kinetic resolution, parallel kinetic resolution and dynamic kinetic resolution of anhydrides

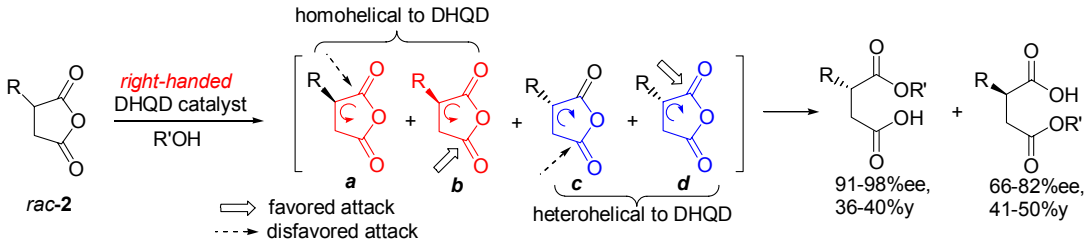
Kinetic resolution of anhydrides by DHQDs-catalyzed asymmetric alcoholysis and Sharpless AD-based processes, although obviously different in reactions, may share a similar chiral recognition mechanism. Ring opening of anhydrides by DHQDs (tertiary amines) in the presence of an alcohol nucleophile follows the general base-catalysis mechanism.[1] The helical structures in the substrate and the catalyst may be connected by two means: (1) the coordination of the incipient alcohol nucleophile to the nitrogen center and subsequent attack to one of the two carbonyls (the one of higher electrophilic nature); and (2) the π-π stacking between the other substrate carbonyl and the DHQD 9-OR π group (see section 20). In this light, it may be noted that the two carbonyls in the substrates are

the necessary structural features allowing for efficient chiral descrimination thus kinetic resolution. As shown in Scheme 1, these two interactions bring the substrate **1**'s ring helix and the right-handed DHQD catalyst ring helix into homohelical and heterohelical communications (polarizabilities: C=O > X; and R > H). The stereochemical outcomes in these kinetic resolutions are completely predictable from the homohelical recognition control principle.[2] Furthermore, when **1** undergoes DHQD-catalyzed dynamic kinetic resolution, the kinetically active heterohelical channel leads to the product of expected configuration in both high yield and ee[3]



Scheme 1. Homohelical recognition control in kinetic resolution and dynamic kinetic resolution of anhydrides catalyzed by the DHQD catalyst.

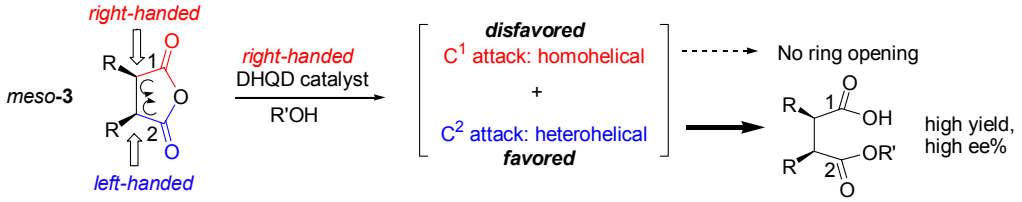
Interestingly, for parallel kinetic resolution of 2-alkyl succinic anhydrides **2** of a structure similar to **1** but X = CH_2, the substrate/catalyst helical interactions yield intriguing stereochemical information. In these substrates the ring helix twisting is less significant than that in **1** simply because ***C***H_2 is more polarizable than O or N, therefore the substituents polarizability difference [C=O-*versus*-***C***H_2] is smaller than [C=O-*versus*-O (or N)]. Presumably due to both this less significant substrate ring helix twisting and the comparably electrophilic nature of the two carbonyls, both enantiomers of **2** undergo DHDQ-catalyzed alcoholysis to give ring opening products. The stereochemistries are readily deducible from the corresponding homohelical and heterohelical substrate/catalyst associations. Notably, because in this system both carbonyls are potential sites for nucleophilic attacks, totally four substrate/catalyst complexations are expectable: of them two (***a*** and ***b***) are homohelical and two (***c*** and ***d***) are heterohelical. Homohelical recognition control should lead to preferential attack to the carbonyl that has less homohelical interaction characters, or more heterohelical interaction characters, with the catalyst, respectively. This in turn defines ***b*** and ***d*** as favored trajectories since the attacked carbonyl in the former is remote from the right-handed twisting at the chiral center, and that in the latter is in the close vicinity of the left-handed twisting of the chiral center. Experimental observations in a series of **2** are in full agreement with this rationale (Scheme 2).[4]



Scheme 2. Homohelical recognition control in parallel kinetic resolution of 2-alkyl succinic anhydrides.

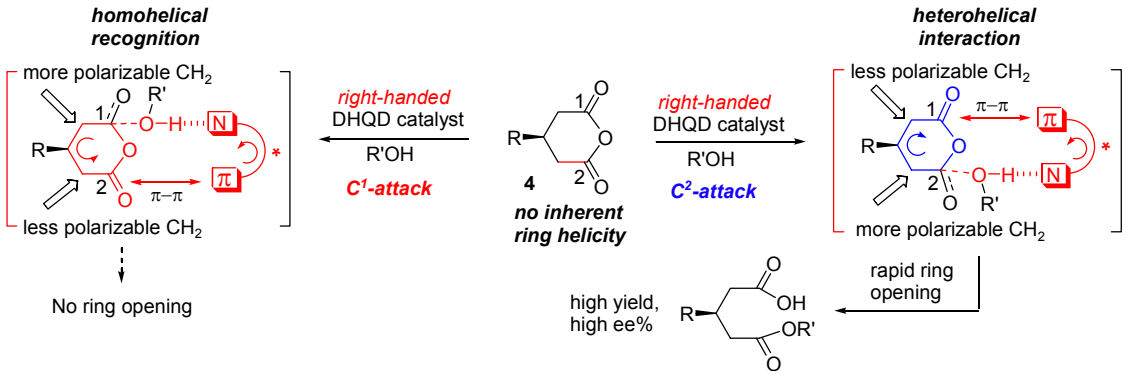
(b) Desymmetrization of *meso*-cyclic anhydrides

Meso-**3** is characterized by two equally twisted but oppositely handed helices in the substrate ring. As shown in Scheme 3, attack to C^1=O and C^2=O will lead to homohelical and heterohelical substrate/catalyst complexation, respectively (polarizabilities at each chiral center: C=O > C*; and R > H). As expected, the heterohelical attack at C^2=O yields the ring opening product in both high ee and high yield.[5]



Scheme 3. Homohelical recognition control in desymmetrization of *meso*-cyclic anhydrides.

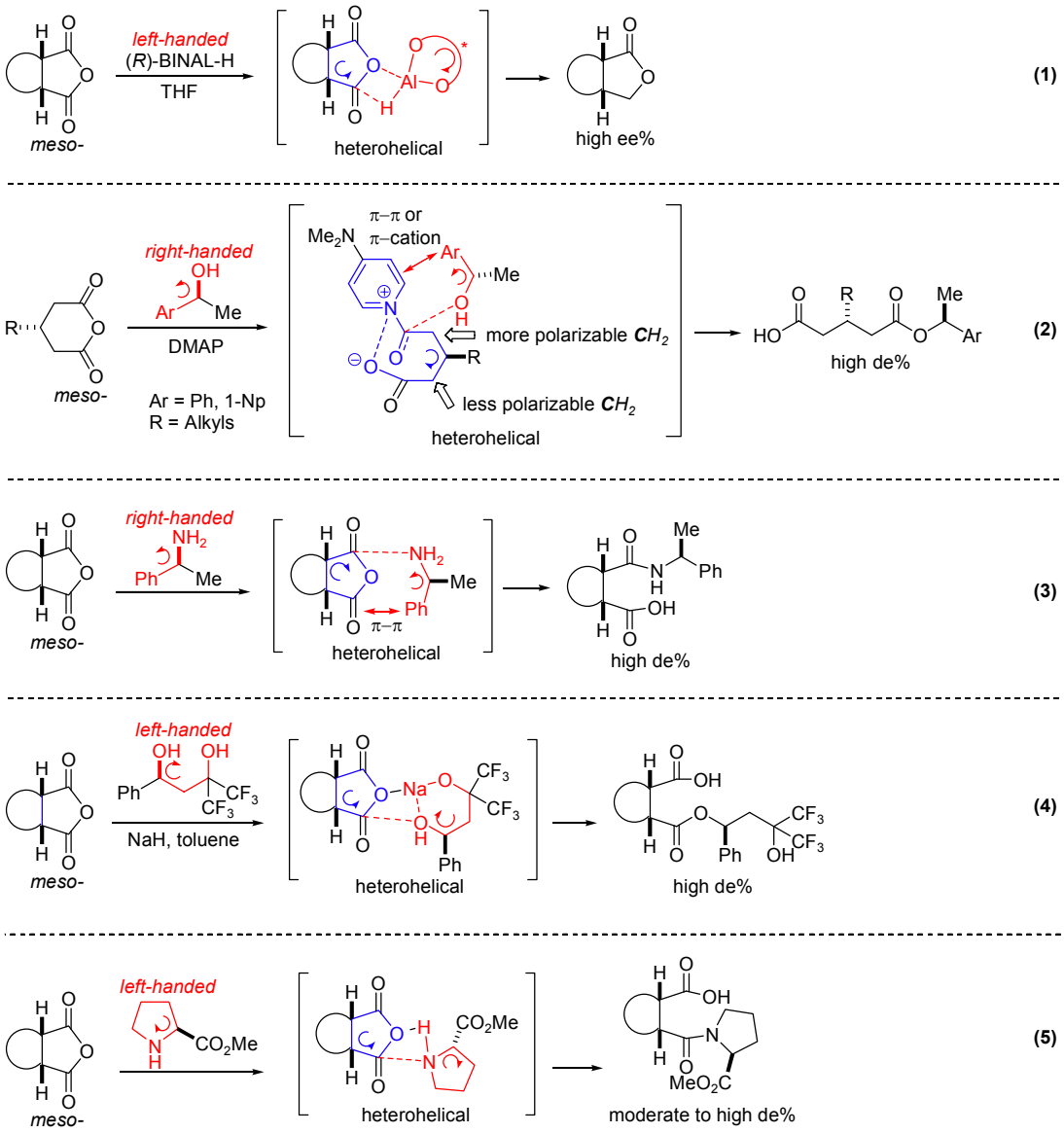
Desymmetrization of **4** is even more stereochemically intriguing because the two ***C*H$_2$** groups around the pro-chiral center are equally polarizable thus the substrate ring originally has no inherent helical twisting. In this case the efficient substrate/catalyst chiral discrimination must occur at a later stage in the reaction in which the two ***C*H$_2$**s are electronically differentiated. Upon alcohol's attack to one of the two carbonyls, it transforms that electron-withdrawing carbonyl into a hemiacetyl which makes its α-***C*H$_2$** more polarizable. When the attack is on the C^1=O, the resultant substrate ring helix is right-handed (polarizabilities: ***C*H$_2$** α to C^1=O > ***C*H$_2$** α to C^2=O; and R > H), which constitutes a homohelical resting substrate/catalyst association. When the attack is on the C^2=O, the resultant substrate ring helix is left-handed, and it generates a kinetically active heterohelical intermediate with the catalyst that leads rapidly to ring opening product in high ee (Scheme 4).[5] From the above analysis, it becomes obvious that this simple homohelical recognition control principle brings a unified rationale for all the empirical stereochemical rules that were previously formulized for these systems.[6]



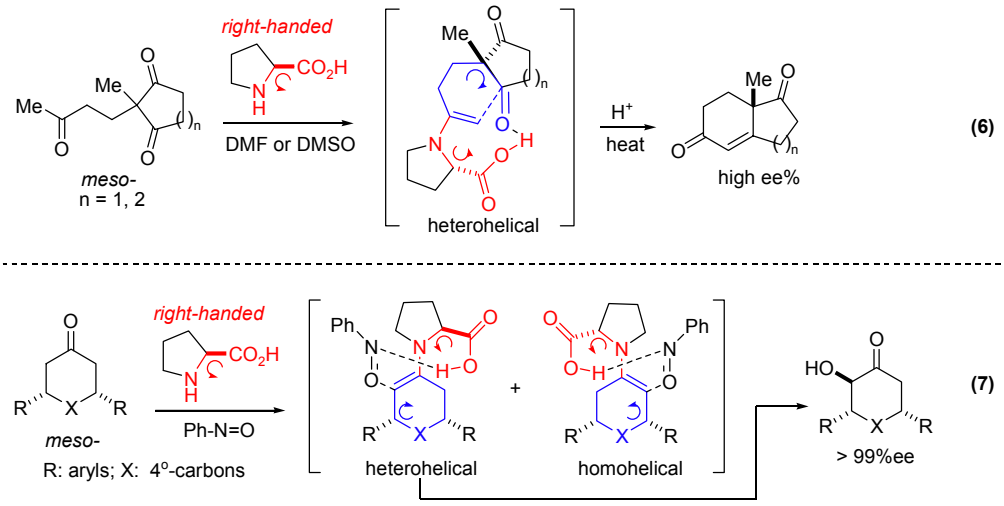
Scheme 4. Homohelical recognition control in desymmetrization of achiral cyclic anhydrides.

(c) Some related processes

Some notable processes for desymmetrization of *meso*-anhydrides are graphically summarized below.[7] In each case the corresponding kinetically active heterohelical reagent/substrate association is constructed on the basis of the mechanistic model presented in the original reference,[7] and the relevant helices are highlighted in colors. Note that in (**5**) the *L*-proline methyl ester, unlike *L*-proline itself (see footnote 13 in section 20), functions as a left-handed reagent (ring helix -HN-C*-CH_2-CH_2-CH_2-; polarizabilities: ***C***H_2 > NH, and C=O > H) because the carboxylic acid is protected and the helix -HN-C*-C(O)- does not play a role in chiral recognition.



Some *meso*-ketones are catalytically desymmetrized by *L*-Proline (right-handed) in extremely high ees, as shown below in (**6**) and (**7**).[8] The stereochemical courses in them can be again deduced from the heterohelical catalyst/substrate associations. Polarizabilities used to assign the substrate ring helix are the following: in (**6**), C=O > ***C***H_3, and C=O > ***C***H_2; in (**7**), C=C > X, and R > H.

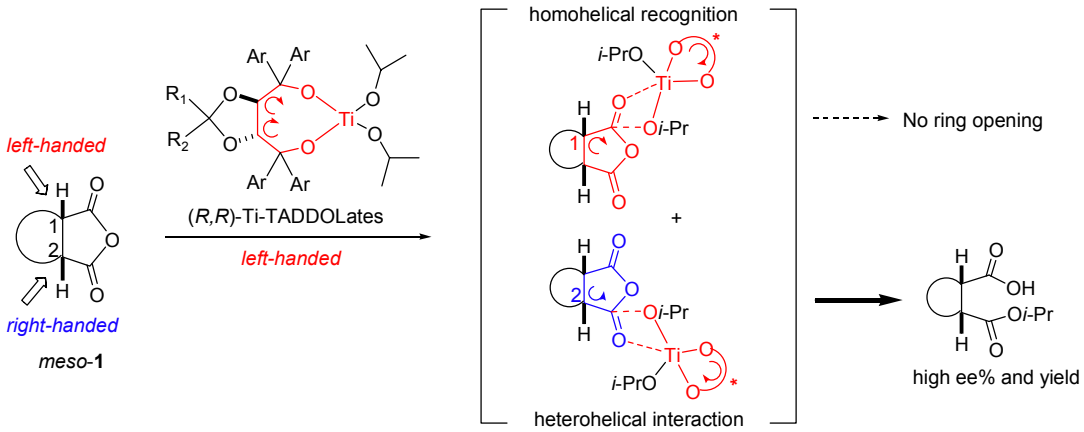


References:

1. Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965-2984.
2. (a) Hang, J.; Tian, S. K.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 12696-12697; (b) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870-2871.
3. Hang, J.; Li, H.; Deng, L. *Org. Lett.* **2002**, *4*, 3321-3324.
4. Chen, Y.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302-11303.
5. Chen, Y.; Tian, S. K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542-9543.
6. See specifically Figure **7** of page 2973 and Figure **8** of page 2976 in ref. 1.
7. For **1**: Matsuki, K.; Inoue, H.; Takeda, M. *Tetrahedron Lett* **1993**, *34*, 1167-1170; for **2**: Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142-146; for **3**: Ward, R. S.; Pelter, A.; Edwards, M. I.; Gilmore, J. *Tetrahedron: Asymmetry*, **1995**, *6*, 843-844; for **4**: Suda, Y.; Yago, S.; Shiro, M.; Taguchi, T. *Chem. Lett.* **1992**, 389-392; for **5**: Albers, T.; Biagini, S. C. G.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A.; North, M.; Uriarte, E.; Zagotto, G. *Synthesis*, **1996**, 393-398.
8. For **6**: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1627; (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497; (c) Allemann, C.; Gordillo, G.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558-569. For **7**: Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1577-1580.

22. Asymmetric ring opening of *meso*-cyclic anhydrides with Ti-TADDOLates

The Ti-TADDOLates promote efficient desymmetrizations of *meso*-cyclic anhydrides of a general structure **1**. The catalyst ring is left-handed (polarizabilities at each C*: O > H; and 3° ***C****H > quaternary ***C***). The substrate ring has a left-handed helix at C^1 center (polarizabilities: R > H; and C=O > C^2) and a right-handed helix at C^2 center (polarizabilities: R > H; and C=O > C^1). Therefore the catalyst's attack to C^1=O defines a homohelical complexation and the attack to C^2=O gives a heterohelical complexation. In a variety of substrates the corresponding heterohelical pathways lead to ring opening products in high yields and ees (Scheme 1).[1]

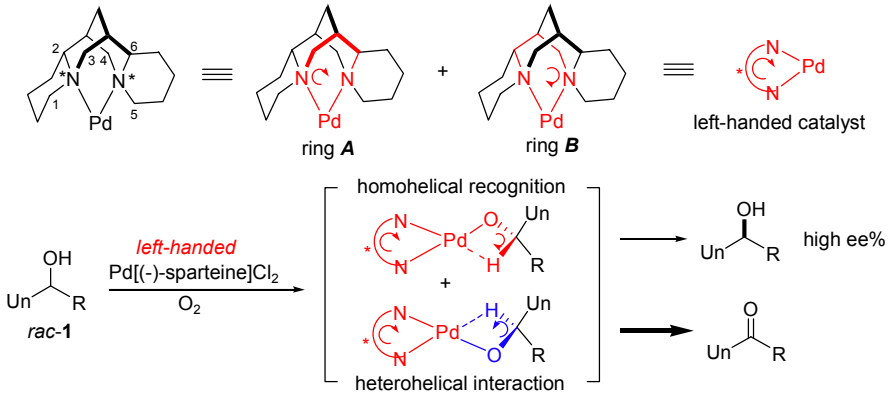


Scheme 1. Homohelical recognition control in asymmetric ring opening of *meso*-cyclic anhydrides.

References:
1. (a) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 2395-2396; (b) Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190-1197.

23. Pd-catalyzed aerobic oxidative kinetic resolution of alcohols:

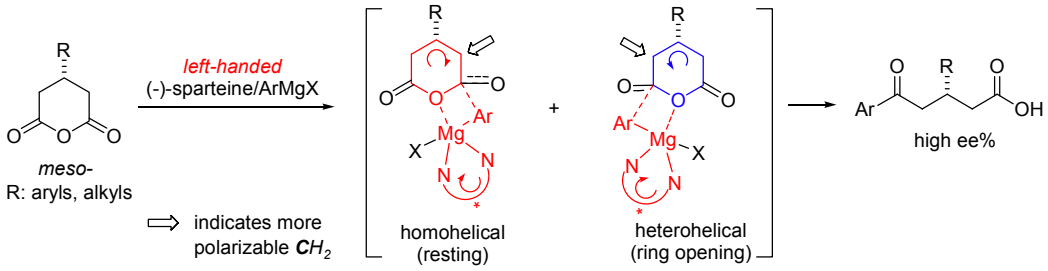
The most successful system developed so far utilizes the Pd-[(-)sparteine] catalysts.[1] Recent mechanistic works showed that intramolecular deprotonation in the Pd-bound alcohol generates a readily accessible coordination site for β-hydrogen.[2] It therefore may be expected that the Pd-O and Pd-H coordinations should couple the catalyst and substrate ring helices together in their associations. The substrate ring helix -O-C*-H- of **1** is right-handed in (*R*)-enantiomers (assuming OH > Un > R > H in CIP priority) and left-handed in (*S*)-enantiomers (polarizabilities: Un > R; and O > H). The catalyst features left-handed helices in both of its ring structures [polarizabilities in ring ***A***: at the left N* center, Pd > C^3, and C^1 (2^o carbon) > C^2 (3^o carbon); the right N* center doesn't contribute because of nearly identical polarizability of C^4 and C^5, both of which are 2^o carbons in a 6-membered ring; in ring ***B***: the left N* center doesn't contribute for the same reason; at the right N* center, Pd > C^4, and C^5 > C^6]. Both kinetic resolution of *rac*-**1** and desymmetrization of *meso*-diols by such left-handed catalysts follow stereochemical courses defined by homohelical recognition control (Scheme 1).[3]



Scheme 1. Homohelical recognition control in Pd-[(-)sparteine]-catalyzed aerobic kinetic resolution of alcohols. Un: Un: unsaturated substituents, R: simple alkyls.

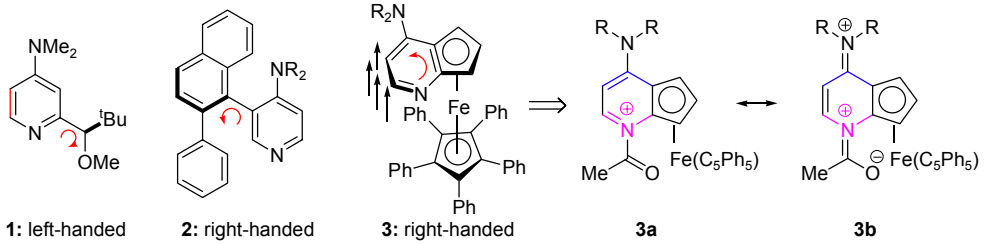
References:

1. (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475-7476; (b) Jensen, D. R.; Sigman, M. D.; *Org. Lett.* **2003**, *5*, 63-65; (c) Mandal, S. K.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 7535-7537; (d) Ferreira, E. M.; Stoltz, B.; *J. Am. Chem. Soc.* **2001**, *123*, 7725-7726; (e) Bagdanoff, J. T.; Ferreira, E. M. Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835-837; (f) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 353-357.
2. (a) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2003**, *42*, 3810-3813; (b) Mueller, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 7005-7013; (c) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202-8203.
3. A left-handed [(-)-sparteine/Mg] complex was successfully used to desymmetrize various *meso*-anhydrides in high ees, see: Shintani, R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1057-1059. As shown below, productive ring opening occurs selectively through the heterohelical pathway.



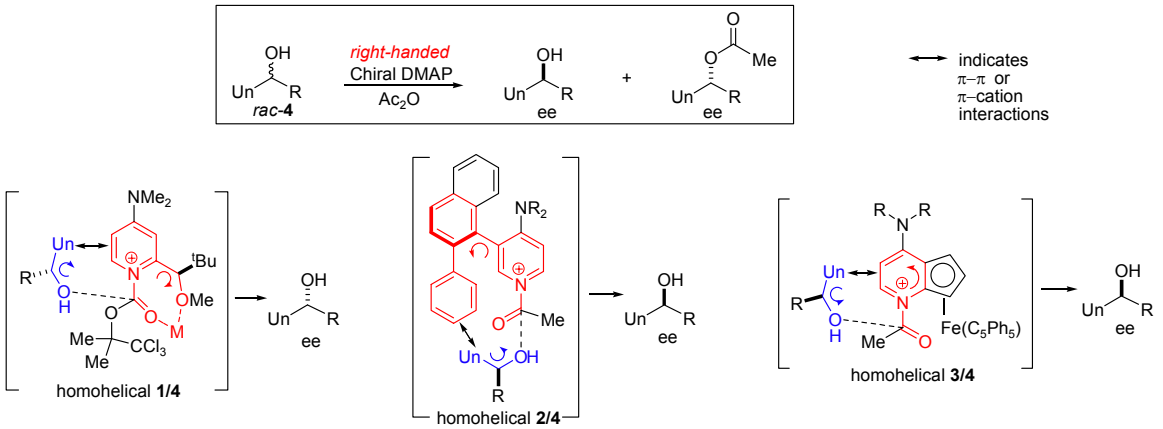
25. Kinetic acylation resolution of alcohols by chirally modified DMAPs:

Structurally tailored molecules **1-3** are notable examples of chirally modified DMAPs that effect asymmetric acylation of *sec*-alcohols in generally high selectivity factors and ees.[1] The relevant helix in each of them is marked in red in Scheme 1. Polarizabilities in **1** are: $\boldsymbol{C}_{sp2}$ > O, and $\boldsymbol{C}Me_3$ > H. The helix of **2** is from atropisomeric skew. For **3**, its *N*-acetylated species has two important resonance forms: **3a** and **3b**, in which the *C*-terminal region of the pyridine ring is more polarizable than the *N*-terminal region due to the electronegativity of the nitrogen atom and the positive charges partially localized in the region. Therefore, the pyridine ring should develop right-handed helicity, that is, it becomes inherently helical, when twisted by the repulsions from the bottom $Fe(C_5Ph_5)$ moiety (note that replacement of C_5Ph_5 with much less bulkier C_5Me_5 should significantly decrease the strengths of these repulsions, which leads to reduced helical twisting in the pyridine ring thus experimentally less selective catalyst).[1d]



Scheme 1. Helices in some chirally modified DMAPs. R: alkyls. The straight arrows in **3** indicate the respulsions the bottom Fe(C_5Ph_5) imposes on the pyridine ring. In **3a** and **3b** the more polarizable *C*-terminal of the pyridine ring is painted blue, and the less polarizable *N*-terminal is in purple.

Scheme 2 summarizes the homohelical associations between **1-3** and one enantiomer of an alcohol substrate of a generic structure of **4**. They lead to recovery of these enantiomers.[2] Note also that the presence of the π-electronic group Un in **4** is necessary for an efficient kinetic resolution, which may be attributed to its π-π or π-cation interactions[3] with a moiety of **1-3** as indicated below. The corresponding heterohelical associations are not drawn, which yiled active acylation of the opposite substrate enantiomers.[4]



Scheme 2. Homohelical reagent/substrate associations in kinetic resolution of *sec*-alcohols **4**. Un: a group of π-electronic characters, such as aryls, alkenyls, or alkynyls; R: alkyls; M: a Lewis acidic metal, such as Zn, Mg. Note that in the **1/4** association the acylation reagent is a chloroformate.

References:

1. For **1**, see: (a) Vedejs, E.; Chen, X.; *J. Am. Chem. Soc.* **1996**, *118*, 1809; for **2**: (b) Spivey, A. C.; Leese, D. P.; Zhu, F.; Davey, S. G.; Jarvest, R. L. *Tetrahedron*, **2004**, *60*, 4513-4525; (c) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154-3159; for **3**: (d) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412-420; (e) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542-547.
2. The *N*-acetylated species **3a/b** can also kinetically resolve some racemic *sec*-amines bearing an aryl group in good stereoselections and in the same stereochemical senses, see: Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119-120. However, with an *O*-acylated azlactone as the acylating agent, these senses are inversed, see: Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 234-236. It may be tentatively suggested that the latter agent could modify the electronic characters of the pyridine ring and induce a polarizability reversal between the *C*- and *N*-terminals thus a reversal of helicity in the resultant catalyst.
3. For general treatments on π-π and π-cation interactions, see: (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303-1324; (b) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans*, *2*, **2001**, 651-669.
4. Most recently, a new chirally modified DMAP featuring a cation-π interaction-induced conformational switch was reported to catalytically resolve racemic *sec*-alcohols. The catalyst is right-handed thus the reaction stereochemical courses are similar to those of **2** and **3**. See: Yamada, S.; Misono, T.; Iwai, Y. *Tetrahedron Lett*. **2005**, *46*, 2239-2242.