



Catalyst–substrate helical character matching determines enantiomeric excess

David Zhigang Wang*

Department of Chemistry, Columbia University, 3000 Broadway, MC 3151, New York, NY 10027, USA

Received 13 December 2004; revised 5 May 2005; accepted 16 May 2005

Available online 15 June 2005

Abstract—In the framework of a helix theory recently developed for molecular chiralities and chiral interactions, it is further proposed that for an asymmetric reaction to be highly enantioselective, the helical characters, that is, the local energies of electrons on the helices, of the catalyst and the substrate complexed with it in the corresponding enantioselection-determining step must be matched. These helical characters can be analyzed on the basis of molecular polarizability and structure properties under a given reaction mechanism. This proposal highlights the importance of polarizability matching in three-dimension chiral space and in essence is a chiral version of the classical hard and soft acid–base theory. It also from an electronic effect angle sheds light on the nature of the conventional lock-and-key origin of high enantioselection and carries the message that, to design a good catalyst (the key), rather than focusing on the rigidity, bulkiness or C_2 -symmetry of the catalyst, one should focus more on the helical character of the substrate (the lock) with which the catalyst will interact. It is generally easier to discover a highly enantioselective catalyst for a substrate of a large helical character than for a substrate of a small helical character. The proposal is supported by theoretical modeling as well as numerous experiments and is used to understanding various aspects of current asymmetric catalysis.

© 2005 Elsevier Ltd. All rights reserved.

1. Introduction

In the preceding paper in this issue we described that an electronic effect, that is, homohelical interaction, controls the stereochemical courses of chiral recognition and induction processes.¹ Although the principle of the conservation of helical asymmetry allows for prediction on the sense of chiral induction in a catalytic asymmetric reaction, it does not yet address another important question, that is, along that sense, under what condition(s) can the magnitude of enantiomeric excess (ee) be ca. 100%; or for a given substrate, how chiral should a catalyst be to maximize asymmetric induction?

Using the well-established electron-on-a-helix theoretical model of Tinoco and Woody, we have shown that a homohelical electronic interaction is always lower in energy than its diastereomeric heterohelical interaction, and their energetic difference, that is, the difference between the free energy changes for homohelical and heterohelical interactions in an enantioselection-determining step, $\Delta\Delta G^\ddagger = E_{\text{homo}} - E_{\text{hetero}}$, is sufficient to bring about high ee and is

maximized when the local energies of electrons on the interacting helices are the same.² Because this energy is collectively determined by a molecular helix's parameters, which include radius, pitch, length, and mass of the electrons on the helix, the above conclusion equivalently shows that for a reaction to be highly enantioselective, these characteristics of the interacting helices must be similar. In short, they must be helically matched.

Since the origins of helical electronic structures in a chiral molecule are closely associated with its polarizability properties, as shown in the preceding paper, the conclusion highlights the importance of polarizability matching in a three-dimension chiral space and is essentially a chiral version of the classical hard and soft acid–base theory.³ It also incorporates itself into a larger theoretical framework concerning the general correlations between molecules' polarizabilities (softness, or its inverse, hardness) and their stabilities and reactivities.² Moreover, it in essence electronically reproduces the conventional lock-and-key wisdom on the origin of high ee, and carries the following important message: to design a good catalyst (the key), rather than focusing on the rigidity, bulkiness or C_2 -symmetry of the catalyst,⁴ one should focus more on the polarizability properties, thus the helical character, of the substrate (the lock) with which the catalyst will interact. For a given asymmetric reaction, it suggests a useful way to rank

Keywords: Asymmetric catalysis; Chirality; Helicity; Homohelical interaction; Polarizability.

* Tel.: +1 212 854 4964; fax: +1 212 932 1289;
e-mail: zw61@columbia.edu

a variety of chiral catalysts on the basis of their helical characters and then to investigate their matching with the helical character of the complexed substrate thus the ee resulted. Details of the theoretical treatment may be found in that paper,² we herein just quote two rules directly derived from it that are necessary for the ranking purposes in the following analysis. They are: a molecular helix's helical character (local electronic energy) increases as its length, which usually correlates to its ring size, decreases (Rule I); and, at a fixed helix length, increases as its radius, which correlates to the relevant groups' polarizability distinctions that result bonds' helical deformations, decreases (Rule II). These ranking rules are readily applicable to real molecules and will be closely followed throughout this paper. It should be noted that in the context of this helix theory, the terms, that is, the helical character and the local energy of electrons of a helix, are equivalent, but the former is more descriptive to helix parameters and molecular structures thus will be preferentially used. Although the method is qualitative at the present stage, it allows for, as shown in the following discussion, estimations of relative ee a catalyst or a substrate may achieve in a reaction without necessarily involving any numeric calculation, which is of considerable practical advantages to practicing chemists.

2. Results and discussion

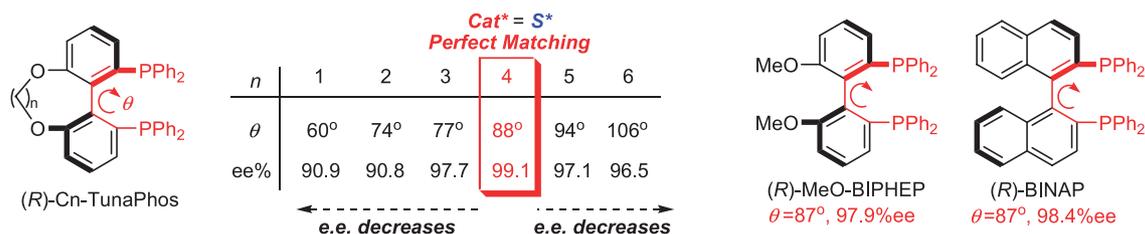
The catalyst–substrate helical character matching readily yields a catalyst structure–enantioselection correlation that a catalyst possessing a helical character (Cat*) that is either higher or lower than the substrate helical character (S*) should lead to energetic mismatching thus reduced $\Delta\Delta G^\ddagger$ thus diminished ee.⁵ Indeed, numerous experiments in literature independently carried out by various groups are in accord with this conclusion. To illustrate this point, we choose to focus on asymmetric hydrogenation since this is undoubtedly the most developed field in asymmetric catalysis and the availability of several series of structurally closely resemble chiral catalysts examined under identical

or comparable reaction conditions enables facile comparisons on helical characters and enantioselections.

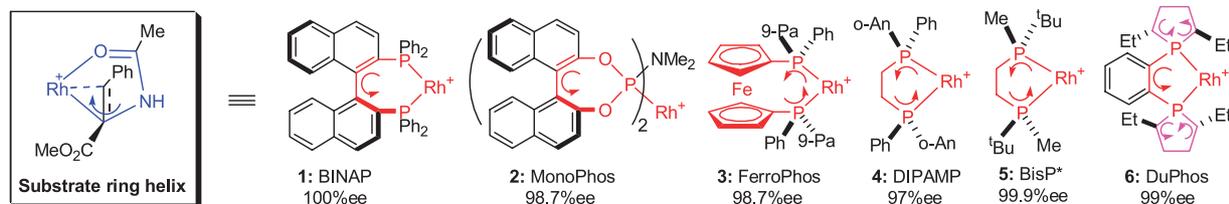
At the outset, a straightforward demonstration of the dependence of ee on the catalyst–substrate helical character matching comes from the well-designed C_n-TunePhos in Ru-catalyzed asymmetric hydrogenation of β -ketoesters, for example, methyl acetoacetate.⁶ Its biphenyl backbone helix character could be delicately modulated by systematically changing the linker length ($n=1-6$) thus changing the biphenyl bite angle θ from 60 to 106°, which in turn varies both the pitch and the radius of the ligand ring helix (shown in red, Scheme 1).

It has been previously shown that (*R*)-MeO-BIPHEP and (*R*)-BINAP, both having a bite angle of 87°, were excellent ligands for enantioselective reduction of methyl acetoacetate (97.9 and 98.4% ee, respectively). In other words, the catalyst ring helix characters of BIPHEP–Ru and BINAP–Ru should be close to that of methyl acetoacetate complexed with these Ru-catalysts. To best mimic that character, it is immediately expectable that a C_n-TunePhos with a bite angle close to 87° (herein 88° when $n=4$) would be most successful in the same reaction.⁷ Furthermore, other TunePhos with a helix character that is either lower or higher than that of C₄-TunePhos would be less effective in asymmetric induction. Indeed, these predictions are in accord with the experiments: as θ increases, ee increases first, reaches a maximum when $n=4$, and falls off as θ increases further. Plots of ee-versus- θ for hydrogenations of several other β -ketoesters visualize similar profiles (Scheme 1).^{6,8}

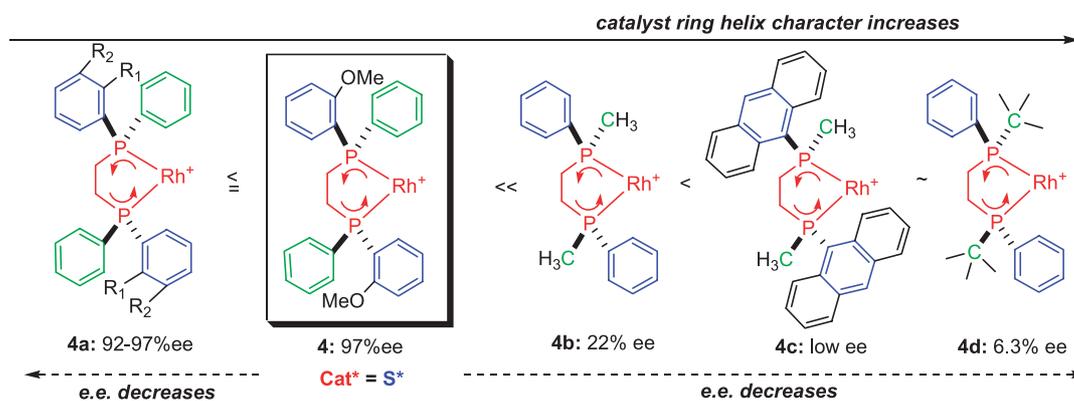
Summarized on the right part of Scheme 2 are some landmark chiral phosphorus–Rh catalysts, which differ considerably in sterics, in asymmetric hydrogenation of (*Z*)-methyl acetamidocinnamate. The extremely high ees achieved indicate a nearly perfect catalyst–substrate helical character matching, therefore catalyst ring helical characters of 1–6 (in red) should be all equal to that of the substrate



Scheme 1. Critical dependence of ee on the catalyst–substrate helical character matching in Ru-C_n-TunePhos-catalyzed asymmetric hydrogenation of methyl acetoacetate.



Scheme 2. Perfect catalyst–substrate helical character matching leads to extremely high ees in Rh-catalyzed asymmetric hydrogenation of (*Z*)-PhCH=C(CO₂Me)NHAc. The catalysts are all shown in enantiomers featuring right-handed ring helices (in red) thus all give (*R*)-phenyl alanine methyl ester.¹ 9-Pa, *o*-phenanthryl; *o*-An, 2-anisyl.



Scheme 5.

degree of catalyst–substrate helix character matching can be examined. As shown below, catalysts possessing a helix character that is either higher or lower than the perfect value suggested by **1–6** universally lead to lower ees.

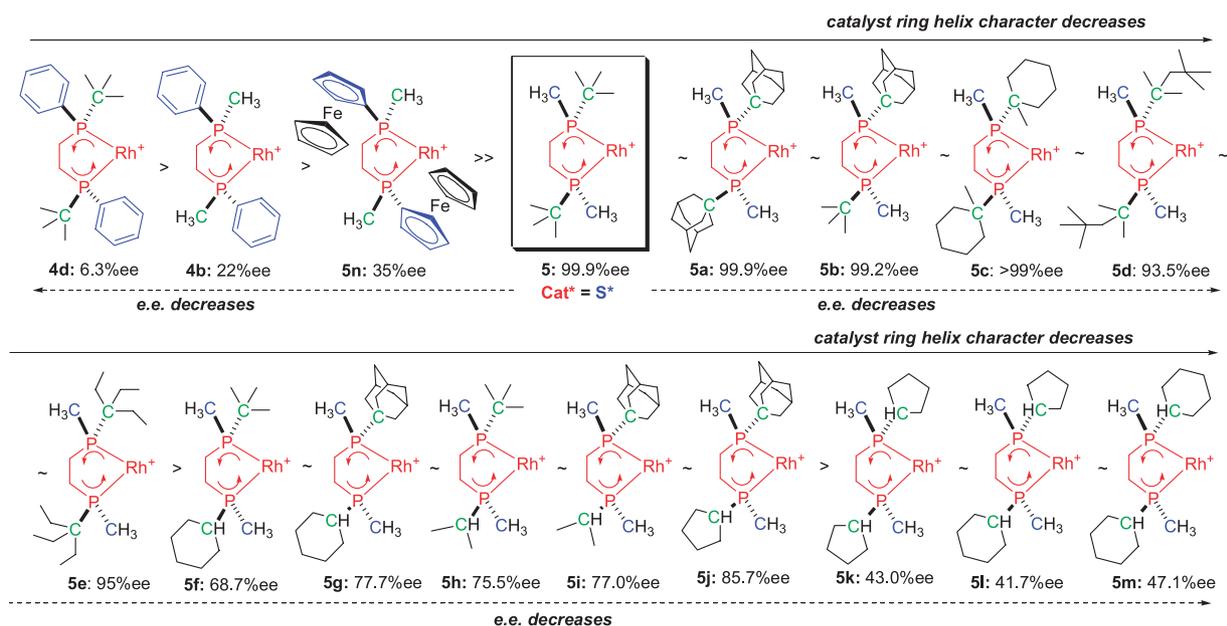
As shown in Scheme 3, catalyst ring helix character of **1** can be increased by replacing binaphthyl backbone with a highly twisted and polarizable π -helicene skeleton, or decreased by extending the ligand ring size, which increases the ring helix length (Rule I), with one or two CH_2 spacers. These produce analogs **1a**, **1b** and **1c**, respectively. Both **1a** and **1c** are found to be far less enantioselective catalysts.¹²

In Scheme 4, electron density at α -position of the naphthalene is more polarizable than that at its β -position which is as polarizable as a carbon center of the benzene.¹³ This makes the local Csp^2 carbon of the α -attached phenyl ring (in blue) of 9-phenanthryl in **3** or 1-naphthyl in **3a** is more polarizable than that of the phenyl ring itself (in green). Electron donating OMe-enhanced phenyl ring in **3b** is also more polarizable than the phenyl ring in their corresponding local Csp^2 carbons. These three catalysts mimic each other well in the catalyst ring helix characters

and consequently afford comparable ees (Rule II). In contrast, **3c** has an β -attached 2-naphthyl, and *ortho*-phenyl of 2-biphenyl in **3d** is atropisomeric to the phenyl ring to which it attaches thus poses little electronic influence on it. Therefore, P-substituents in **3c** and **3d**, although differ in sizes, do not differ in local polarizabilities thus do not define any appreciable helices in the corresponding catalyst ring structures. They lead to racemic products.⁹

In Scheme 5, **4** is slightly higher than **4a** ($\text{R}_1 = \text{Me}$, Et ; $\text{R}_2 = \text{H}$) in helical character because *ortho*-OMe is more electron-donating than *ortho*- R_1 , but it is much lower than **4b–d** because the aryl-versus-alkyl substituents polarizability distinctions are high (Rule II).¹ Accordingly, **4a** induces a lower ee and **4b–d** are essentially non-stereoselective catalysts.¹⁴ It may be noted that the coordinative ability of the methoxy group of **4** has been recognized to be unimportant for asymmetric induction.^{14a}

BisP*-Rh **5** and **5a–n** represent perhaps a class of catalysts most delicately examined to date on ligand structure–ee correlations in asymmetric enamides hydrogenations (Scheme 6).¹⁵ Rule II allows for facile helical character



Scheme 6.

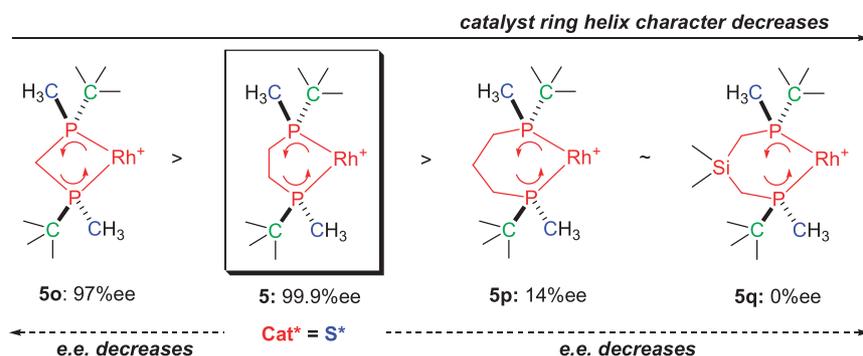
ranking of them. Replacing 3° CMe₃ carbon with another equally polarizable tertiary carbon, as in **5a–e**, does not change the resultant catalyst ring helical characters hence the ees. Systematically replacing one or both of the two 3° carbons with more polarizable 2° carbons, as in **5f–j** and **5k–m**, respectively, leads to catalysts of descending helical characters thus declining ees. They are all much lower in helical character than **4d**, **4b** or **5n** which has a large Ph-versus-3° CMe₃ (or 1° CH₃) or a ferrocene Cp ring-versus-1° CH₃ P-substituents local polarizability difference, respectively; therefore they are all far less enantioselective catalysts. Moreover, regardless of variations in P-substituents' sizes, catalysts of comparable helical characters give comparable ees whose values correlate to their deviations from **5**, which further highlights the critical helical electronic control in asymmetric induction.^{1,16,17}

By extending the ethane linker of **5** into a propane, or shortening it into a methylene, **5p–q** of lower helix characters or **5o** of a higher helix character can be made, respectively, (Rule I). They all lead to diminished ees (Scheme 7).¹⁵

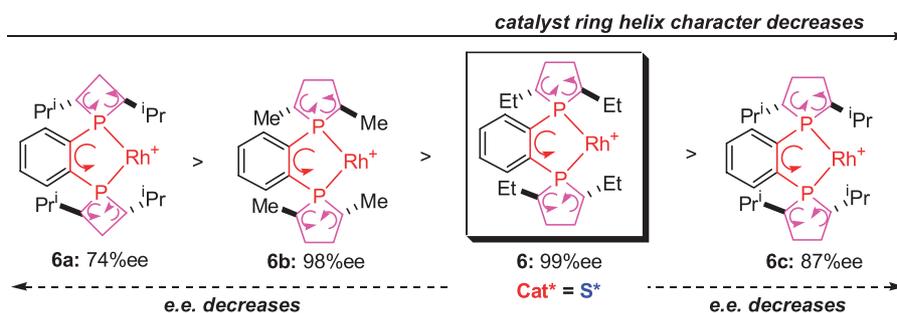
The helical character of **6** can be modulated by replacing CH₂ carbons in -Et with slightly more polarizable 1° CH₃ carbons or less polarizable 2° CHMe₂ carbons, the resultant higher helical character **6b** and lower helical character **6c** (Rule II) both yield lower ees (Scheme 8).¹⁸ However, ee changes here are less pronounced than those found in BisP*-Rh catalysts in Scheme 6 because helices variations at the remote C* centers are not sensitively sensed in catalysis. Compound **6a**, which has a smaller phospholane ring thus a smaller helix length, should possess a helix character that is higher than **6** and **6b–c** (Rule I). It indeed results in a much lower ee.

Although our analyses so far are focused on hydrogenations, there seems to be no reason to suppose that such critical dependence of ee on catalyst–substrate helix character matching is a privileged issue associated only with this type of asymmetric induction. Unfortunately, the lack of a variety of structurally comparable catalysts in many other asymmetric catalytic reactions hampers similar helix character-ee correlations. Nevertheless, scattered examples abound in literature. For example, in asymmetric epoxidations, chiral metal–Salen complexes have been established to be efficient catalysts,^{19a} implying good matching between their helix characters and those of the olefins in enantioselection-determining steps. Replacing the weakly helical chiral *trans*-1,2-diamino-cyclohexane in the Salen ligands with a large skewed [1,1'-binaphthalene]-2,2'-diamine apparently would significantly increase the helix characters of the resultant catalysts that should then be much higher than those of olefin substrates, therefore high ees can not be anticipated. By contrast, using a ring-extended, thus less helical, analog [1,1'-binaphthalene]-2,2'-diethanamine has achieved good ees in epoxidation.^{19b}

Since the invention of BINAP ligand, there have been, and still are, many intensive efforts of incorporating it and its various atropisomeric analogs into other asymmetric reactions with hopes of effecting high ees. It is clear now that, the helix characters of BINAP type ligands, although often match with those of enamides in hydrogenations, may not resemble those of other substrates in other processes. Therefore, their successes in hydrogenations may not be transferable. For a given reaction, without detailed information of the reaction mechanism and of the substrate helix character in that particular mechanistic framework, it is rather difficult, if not impossible, to predict beforehand whether such efforts are worthy of pursuing. At this point, it



Scheme 7.



Scheme 8.

may be also interesting to note that previous studies on electronic effects in asymmetric induction, primarily by means of electron-withdrawing or donating modulations on the corresponding catalyst or/and substrate structures, may be correlated to modulations on their electronic polarizabilities thus on their helical characters.²⁰

Clearly, the above results strongly support the notion that for a high ee to be realized, helical characters of the catalyst and of the substrate complexed with it must be matched. This principle might help account for several interesting observations in asymmetric synthesis, such as why autocatalysis²¹ tends to be highly enantioselective and why absolute asymmetric syntheses,²² despite years of efforts, unexceptionally met with failures. In the former a perfect catalyst–substrate helical character matching can be automatically satisfied because the catalyst and the product share the same structure;²³ and in the latter the chiral light is not even in the same structural domain as organic molecules, therefore there is barely any degree of matching between them. In general, it is easier, either by design or by serendipity, to discover a highly enantioselective catalyst for a substrate of a large helical character than for a substrate of a small helical character. Autocatalysis and absolute asymmetric syntheses represent two extreme situations in the global catalyst–substrate helical character matching–enantioselection correlation profiles for various asymmetric syntheses, and chances of success are evidently not evenly distributed between them. While asymmetric catalysis with substrates that are capable of defining relatively high helical characters in their corresponding enantioselection-determining steps has enjoyed enormous progresses in the past three decades, such as hydrogenations of enamides and functionalized ketones, hydrogenations and alkylations of simple aromatic or hetero-aromatic substituted C=X (X = C, O, N) bonds, and epoxidations, dihydroxylations and hydrogenations of *trans*-olefins, realizing highly enantioselective transformations for their counterpart substrates of low helical characters, such as unfunctionalized and/or purely alkyl substituted C=X bonds, particularly those of a *cis*-geometry, remains formidably challenging.^{1,2}

For a given asymmetric reaction, the catalyst–substrate helical character matching yields two practically useful implications. One, for a catalyst inducing a moderate ee, making a few analogs of it with finely tuned helical characters and examining their performances should help point out the promising direction for further endeavors, that is, whether a catalyst of a higher or lower helical character should be tried next;²⁴ two, for a catalyst inducing high ee, its helical character may serve as a ‘reference’ that guides further catalyst designs, that is, a new catalyst that mimics such a reference helical character should be also efficient. Studies fulfilling this strategy have indeed had many proven successes.⁴ For examples, mimicking the BINAP moiety of the Noyori transfer hydrogenation catalysts with a

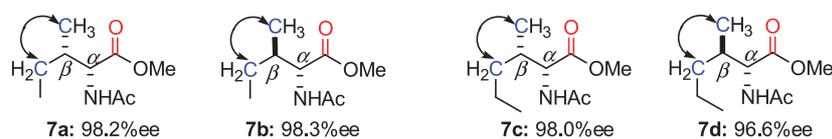
comparably helical spiro-Phos ligand leads to new catalysts that also achieved very high ees;²⁵ mimicking the BisP* ligands helix characters leads to the invention of new and robust TangPhos catalyst in enamides hydrogenations.²⁶ In fact, successes in the field of asymmetric hydrogenations owe much to the inspirational atropisomeric skew design criterion suggested by the BINAP type ligands.

The discussion developed so far has been largely confined to helical character matching issues between various catalysts and a fixed substrate. However, application of the principle in the opposite direction, that is, the helix character matching between various substrates and a fixed catalyst, is also profitable. Mimicking the helix character of a substrate that achieves high ee under the action of a certain catalyst in a reaction may lead to expanded scope of substrates that attain high ees with the same catalyst. This is often very desirable and, in fact, widely practiced in asymmetric catalysis.⁴

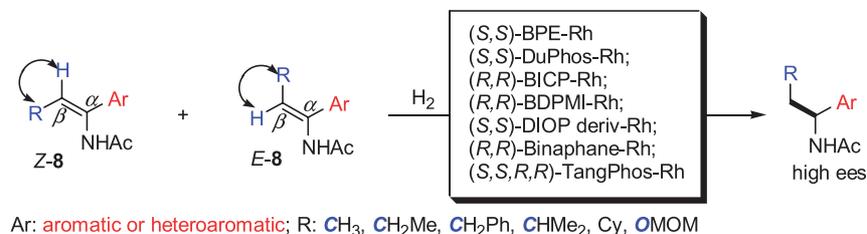
Still focusing on enamides hydrogenation, the directly relevant issues are so-called catalyst structural modularity and substrate *Z/E* geometry tolerance. Some eminent diphosphine–Rh catalysts, notably DuPhos, BPE and BICP, had been demonstrated to tolerate olefin *Z/E* geometry in highly enantioselective hydrogenations, which was previously attributed to their structural modularity or tunability. On the basis of the catalyst–substrate helix character matching principle, we, however, reasoned that these successes perhaps have more to do with the *Z/E* substrates’ helix character resemblance than with the catalysts’ modularity. As shown previously,¹ the enamide C_α substituent, often a very polarizable π-group, is the major contributor to the substrate ring twist and the C_β center tends to be placed outside the Rh’s square planar coordination plane. In hydrogenation of some β, β′-disubstituted enamides, when the C_α substituents (in red) are very polarizable and C_β substituents (in blue) are simple alkyls that display little local carbon polarizability difference, as in **7a–d** in Scheme 9, the C_α substituents overwhelmingly dominate the substrate ring twists thus both *Z/E* isomers have essentially the same helix character upon their complexations to the Rh centers. Therefore, they are hydrogenated not only in the same sense but also in virtually identical ees.²⁷

When C_α substituent in **8** is an aromatic ring that is even more polarizable than the ester carbonyl in **7** thus increasingly dominates the substrate ring helical characters, an even greater and broader level of *Z/E* tolerance is observed in various catalyst systems (Scheme 10).²⁸

However, when β-substituents polarizability differences get relatively larger, as phenyl-versus-alkyls in **9a–d**, and C=C-versus-alkyls in **9e–f**, *Z/E* isomers shall develop



Scheme 9.



Scheme 10.

different helix characters, thus variations of ee in hydrogenation of *Z*- and *E*-isomers appear (Scheme 11).²⁷

When β -substituents polarizability differences get very large, as phenyl-versus-H in **10**, the helices at C $_{\beta}$ centers may also contribute appreciably to substrate ring twists and *Z/E* isomers can have significantly different helix characters. In these cases, hydrogenations of *Z*- and *E*-isomers may not only proceed with sharply different ees, but even in opposite senses (Scheme 12).²⁹

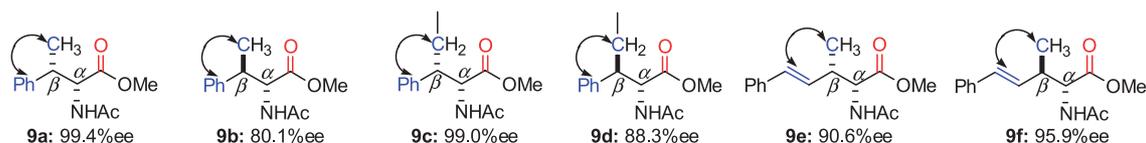
Dramatic responding of ees on *Z/E* geometry could also be anticipated in some other enamides in which the reversed substrate structure and polarizability characters are met, that is, small C $_{\alpha}$ substituent polarizability coupled with large C $_{\beta}$ substituents polarizability differences. In these cases, *Z*- and *E*-isomers differ much in substrate helix characters, and consequently can not be hydrogenated in comparable ees by the same catalyst, as exemplified in Scheme 13 with Duphos–Rh catalyzed hydrogenations. Similar *Z/E* effects on ee, albeit less pronounced, were also observed with the BICP–Rh catalyst.³⁰

The above analyses illustrate that a simple examination of substrate substituents' polarizabilities and their distribution characters can significantly help estimate the potential of *Z/E* geometry tolerance in asymmetric hydrogenations. In terms of substrate helical character, this *Z/E* issue in asymmetric induction is not special and has no difference

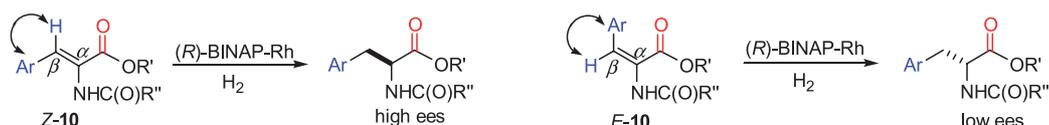
from the widely-seen small ee variations associated often with an aromatic-to-hetero-aromatic switch yet large ee variations associated with an aromatic-to-alkyl switch in substrate structures in many types of asymmetric catalysis.^{1,2,4} The essential underlying principle is that the degree of catalyst–substrate helix character matching determines the magnitude of ee.

3. Conclusion

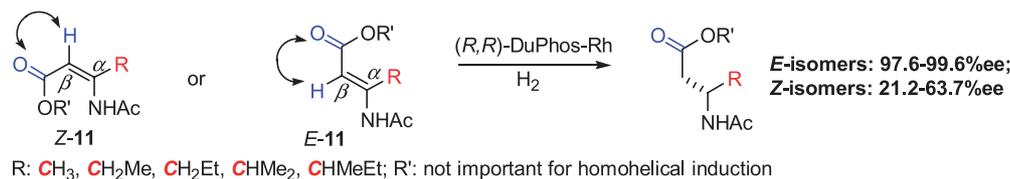
In summary, as a continuation of our efforts to understand chiral interactions from an electronic effect perspective, we proposed here that for an asymmetric reaction to be highly enantioselective, the corresponding helix characters of the catalyst (the key) and of the substrate complexed with it (the lock) in the enantioselection-determining step must be matched. This conclusion is new and useful. Although the focus of the present two papers¹ on this helix theory is placed on examinations of the conservation of helicity and helical character matching principles in asymmetric syntheses, their validities evidently do not depend on any individual reaction's own characteristics and they may be generally applicable to other types of chiral interactions as well. We believe that considering such local helical electronic effects and developing computational strategies that can quantitatively address them would help gain insights into efficient asymmetric induction that are beyond conventional geometry- or size-based scenarios, and are



Scheme 11.



Scheme 12.



Scheme 13.

meaningful for catalyst rational design. This goal seems to be achievable in light of the considerable maturity in current methods for polarizability calculations.³¹ Work towards this goal is now underway.

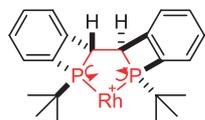
Acknowledgements

This material is based upon work supported by the US National Science Foundation under Grant No. 00-94723. Columbia University also provided partial support with a fellowship. I am sincerely grateful to Professor Manfred T. Reetz for kindly communicating his results on catalyst **1a** to me privately prior to publication and to the seven referees of this article for their valuable comments and suggestions.

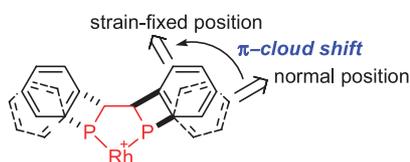
References and notes

- Wang, D. Z. *Tetrahedron*, **2005**, *61*, the preceding article in this issue: see doi: 10.1016/j.tet.2005.05.058.
- (a) Wang, D. Z. *Chirality* **2005**, *17*, S177. The paper also examines the relationships between helical electronic effects and steric and other effects in stereochemical controls in the general context of asymmetric catalysis. (b) Tinoco, I., Jr.; Woody, R. W. *J. Chem. Phys.* **1964**, *40*, 160.
- For classical treatments, see: (a) Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 581. (b) Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 643. (c) Pearson, R. G. *J. Chem. Ed.* **1987**, *64*, 561.
- (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
- An alternative statement of this principle would be that in a reaction a catalyst that effects a high ee towards a substrate would effect lower ees towards other substrates that have either higher or lower helical characters. Illustrations are given in the text. This principle helps guide the selection of more promising substrates for a catalyst. It is important to note that similarities in substrate helix characters often do not translate into similarities in their structural or steric characters. In asymmetric catalysis this gives a catalyst both specificity (highest ee towards one substrate) and versatility (comparable ees towards many other, helically resemble substrates). See Refs. 1,2,4 for many examples.
- Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223.
- Strictly speaking, the actual bite angles of their Ru complex, but not the free ligands, should be used for helix character comparisons. But it is reasonable to assume that these analogous ligands undergo very similar bite angle changes upon their complexations to the Ru centers.
- Remarkably, other investigations, although employing different methodologies, uniformly reveal the existence of an optimum point in the catalyst property-ee correlations, see: (a) Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S.; Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479. (b) Gao, D.; Schefzich, S.; Lipkowitz, K. B. *J. Am. Chem. Soc.* **1999**, *121*, 9481.
- For **1**: Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7930. ; the ee is for acetamidocinnamic acid. **2**: van den Berg, M.; Minnaard, A. J.; Schudde, E.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. **3**: Nettekoven, U.; Kamer, P. C. J.; van Leeuwen, P. W. N. W.; Widhalm, M.; Spek, A. L.; Lutz, M. *J. Org. Chem.* **1999**, *64*, 3996. **4**: Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Backman, G. L.; Weikauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. **5**: Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. **6**: Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.
- Asymmetric catalysis by monodentate ligands: Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315. In general, these reactions are relatively difficult to achieve high ees due to inefficient catalyst–substrate homohelical interactions. In the absence of appreciable helical electronic control, steric and other effects may therefore play decisive roles in realizing high enantioselections. For further discussion, see Ref. 2a.
- (a) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Williams, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308. (b) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348 and note 11 therein. Although bidentate catalysts are conventionally regarded to be more efficient than monodentate catalysts in asymmetric induction, the helix theory suggests what is important may be the efficiency of the corresponding catalyst–substrate stereochemical communication thus their helical character matching.
- For **1a**: Reetz, M. T.; Beuttenmuller, E. W.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 3211. ; ee of **1a**: private communication with Professor M. T. Reetz. **1b**: Takaya, H.; Ota, T.; Inagaki, K. *Eur. Pat. Appl.* (EP 96-301720 19960313), 1996. **1c**: Tamao, K.; Yamamoto, H.; Matsumoto, H.; Miyake, N.; Hayashi, T.; Kumada, M. *Tetrahedron. Lett.* **1977**, *16*, 1389.
- Millefiori, S.; Alparone, A. *J. Mol. Struct. (Theochem)* **1998**, *422*, 179.
- For **4a**: (a) Wada, Y.; Imamoto, T.; Tsuruta, H.; Yamaguchi, K.; Gridnev, I. D. *Adv. Synth. Catal.* **2004**, *346*, 777. (b) Imamoto, T.; Tsuruta, H.; Wada, Y.; Masuda, H.; Yamaguchi, H. *Tetrahedron. Lett.* **1995**, *36*, 8271. Experiments here also showed the ees induced by **4a** to be >99% when R₁ and R₂ are both electron-releasing alkyls or when R₁ is a more bulky alkyl. These situations bring minor modifications to ees. **4b**: Horner, L.; Simons, G. Z. *Naturforsch.* **1984**, *39b*, 512. ; the substrate is *N*-benzoyl- α -aminocinnamic acid. **4c**: Maienza, F.; Spindler, F.; Thommen, M.; Pugin, B.; Mezzetti, A. *Chimia* **2001**, *55*, 694. Maienza, F.; Spindler, F.; Thommen, M.; Pugin, B.; Malan, C.; Mezzetti, A. *J. Org. Chem.* **2002**, *67*, 5239.
- (a) Ref. 9 for **5**. (b) Ohashi, A.; Imamoto, T. *Org. Lett.* **2001**, *3*, 373. (c) Ohashi, A.; Kikuchi, S.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, 2535. (d) Imamoto, T. *Pure Appl. Chem.* **2001**, *73*, 373. (e) Sugiya, M.; Nohia, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 705. (f) Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79. (g) Oohara, N.; Katagiri, K.; Imamoto, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2171. (h) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988.
- In this light the high ee induced by catalyst **5n** of a P-stereogenic ligand having both an aromatic and an aliphatic substituents, but in a highly strained electronic environment, should not be

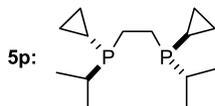
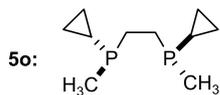
surprising. Its catalyst ring $-\text{Rh}-\text{P}^*-\text{C}^*-\text{C}^*-\text{P}^*-$ (in red) features right-handed helices arising largely from the two P^* centers (namely the helix $-\text{C}^*-\text{P}^*-\text{Rh}-$ at each P^* center; local polarizability sequences: $\text{Rh} > \text{C}^*\text{H}$; and $\text{Ph} > 3^\circ$ (CMe_3) therefore it induces (*R*)-phenyl alanine in excess. The 4-membered ring forces its phenyl ring π -electron cloud to move from the normal position to a strain-fixed position, weakening spatially its polarizability interactions with the Rh center that are directly responsible for formation of the ring helices; In addition, the rotations around the $\text{P}-\text{Csp}^2$ bonds are now restricted, rendering such phenyl–Rh interactions to be further weakened by the enhanced π -polarizability anisotropy. These effects lead to a net consequence that the effective polarizability of phenyl ring is substantially reduced thus the catalyst ring helical character of **5n** is much lower than those of other catalysts of similar aromatic-versus-alkyl P -substituents but in an unstrained electronic environment, such as **4b–d**, and may be close to that of the perfect catalyst **5**. This, in conjunction with steric effects posed by its rigid structure, might have made it a highly enantioselective catalyst. See: Imamoto, T.; Crépy, K. V. L.; Katagiri, K. *Tetrahedron: Asymmetry* **2004**, *15*, 2213.



5n: right-handed, 96% ee (*R*)



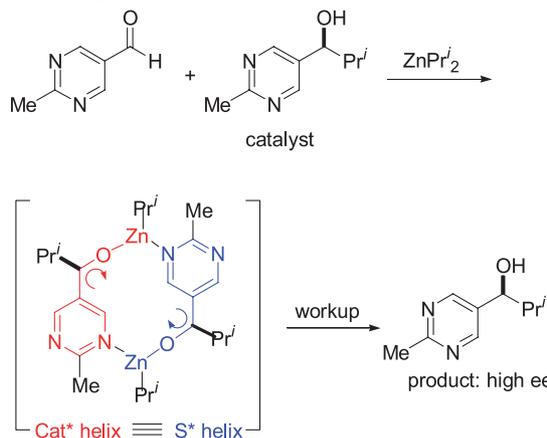
17. At this point qualitative predictions on some unknown P -stereogenic diphosphine ligands may be made. Enantiopure ligands **5o** and **5p** depicted below, when complexed to an Rh precursor, are expected to develop right-handed helicities ($-\text{CH}_2-\text{P}^*-\text{Rh}-$) of considerable helical characters in their $-\text{Rh}-\text{P}^*-\text{CH}_2-\text{CH}_2-\text{P}^*-$ catalyst rings (due to local polarizabilities: $\text{Rh} > \text{CH}_2$; and cyclopropyl $\text{CH} > \text{CH}_3$, CHMe_2) therefore to induce good-to-high ees of (*R*)-products in the hydrogenation of (*Z*)-methyl acetamidocinnamate and other α -(acylamino) acrylic derivatives. These predictions may be interesting in that the conventional steric theories, such as the quadrant rule, would predict opposite senses of asymmetric induction between them with a reasonable size sequence of isopropyl > cyclopropyl > methyl and low ees since steric distinctions in them much resemble those in mediocre catalysts **5k–m** and are significantly less than those in highly enantioselective catalysts **5** and **5a–e**. They invite experimental investigations.



18. (a) Marinetti, A.; Jus, S.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 8365. (b) See Ref. 9 for **6**. By contrast, 1,1'-bis(phosphetano)ferrocenes are highly enantioselective catalysts because P -ferrocene- P backbone in them is longer than P -phenyl- P in the Duphos–Rh catalysts. The concurrent presences of helix character-increasing 4-membered

phospholane rings and a helix character-decreasing longer backbone may thus make their catalyst ring helical characters still comparable to those of the Duphos–Rh catalysts. See: Marinetti, A.; Labrue, F.; Genêt, J.-P. *Synlett* **1999**, *12*, 1975.

19. (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (b) p 656 of Ref. 4a.
20. For representative works, see: (a) Rajanbabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101. (b) Jacobsen, E. N.; Zhang, W.; Guler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.
21. Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471.
22. Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418.
23. In this regard it should be emphasized here that asymmetric autocatalysis (and other self-replications) do not simply mean that the catalyst and the product share the same structure, but mean that their structural moieties actually involved in catalyst–substrate helical character matching should be the same. The Soai autocatalytic systems are outstanding examples, see: Soai, K.; Sato, I. *Chirality* **2002**, *14*, 548. In the proposed transition state model by Blackmond and Brown et al., as shown below, the catalyst ring helix is identical to the substrate ring helix in all aspects thus a perfect helix character matching between them is achieved, see: Blackmond, D. G.; McMillian, C. R.; Ramdeehul, S.; Schorm, A.; Brown, J. M. *J. Am. Chem. Soc.* **2001**, *103*, 10103. This, in conjunction with the operation of non-linear effect in these systems, not only furnishes product in extremely high ees, but also makes chirality amplifications extremely efficient. See: Singleton, D. A.; Vo, L. K. *J. Am. Chem. Soc.* **2002**, *124*, 10010. For non-linear effect in asymmetric catalysis, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923.



24. For examples, hydrogenation of (*Z*)- $\text{PhCH}=\text{C}(\text{CO}_2\text{Me})\text{NHAc}$ with $\text{Me}-\text{BPE}-\text{Rh}$ yields a 85% ee, with $\text{Et}-\text{BPE}-\text{Rh}$ yields a 93% ee. These results imply that, under comparable steric conditions, slightly decreasing the catalyst ring helix characters in this particular reaction would be electronically beneficial for higher ee, thus further optimizations may focus on $\text{R}-\text{BPE}-\text{Rh}$ catalysts with R of a less polarizable local carbon, such as that of a 2° -alkyls, but not with R of a more polarizable local carbon, such as that of a cyclopropyl or aromatic rings. Indeed, $^i\text{Pr}-\text{BPE}-\text{Rh}$ induces a 93% ee, see Ref. 9 for **6**. Variations on these ees may be arguably attributed to steric influences, but this seems to be disfavored by the facts that increasing substituent size from Me to Et and to ^iPr leads

- to increases of ee in BPE–Rh systems, but decreases of ee in structurally resemble DuPhos–Rh systems under otherwise identical conditions. Moreover, there were attempts to incorporate additional chiral centers in Me–BPE–Rh's ethane linker in the pursuit of higher ees. Since the above results suggest that the helix character of Me–BPE–Rh is actually higher than that of the complexed substrate, higher ee would be anticipated when the introduced ring helices brought about by the new chiral centers are opposite, but not same, in handedness to the original BPE phospholane ring helices. Indeed, the former case leads to a 98% ee while the latter leads to an even lower 77% ee. See: Fernandez, E.; Gillon, A.; Heslop, K.; Horwood, E.; Hyett, D. J.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 1663. In line with the above considerations, two other BPE–Rh-like catalysts in which the phospholane rings are replaced with largely skewed BINOL units, or with 4-membered rings, should both be significantly higher in helical character than the complexed substrate, therefore high ees cannot be anticipated. Indeed, a 19% ee was found with the former catalyst and a 15% ee with the latter. See: Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961. and Marinetti, A.; Labrue, F.; Pons, B.; Jus, S.; Ricard, L.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 2583.
25. Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. Because helical character of the 1,1'-spirobiindane backbone resembles that of the 1,1'-binaphthalene, it is not surprising that these spiro-ligands are also very effective for asymmetric enamides hydrogenations and conjugative additions in which the binaphthalene-derivatized catalysts were successful. See (a) Ref. 11b. (b) Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, *5*, 280. (c) Zhou, H.; Wang, W.-H.; Fu, Y.; Xie, J.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2003**, *68*, 1582.
26. Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612.
27. Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. The effect of *Z/E* double bond isomerization, which occurs in some systems but is not general, is ignored in our discussion. For a system involving *E/Z* isomerization, see Ref. 9 for **1**; for a system without *E/Z* isomerization, see: Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.
28. (a) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590. (b) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679. (c) Lee, S.; Zhang, Y.; Song, C.; Lee, J.; Choi, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 847. (d) Ref. 27. (e) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100. (f) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142. (g) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (h) Yan, Y. Y.; Rajanbabu, T. V. *Org. Lett.* **2000**, *2*, 4137. Another important class of substrates are itaconates which are helically closely resemble to enamides in hydrogenation transition states. For remarkable *Z/E* tolerances observed in various itaconates, see: (i) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931. In fact, from a very general perspective the similar stereochemical profiles for various classes of structurally diverse substrates could be understood on the basis of their comparable substrates ring helix characters which could be quickly examined by their substituents' polarizabilities, their distribution patterns around pro-chiral centers and the substrate-metal coordination modes. See: (j) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.
29. (a) Ref. 9 for **1**. (b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1247. The low ees of *E*-isomers suggest helix character-mismatched catalyst–substrate interactions.
30. Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907.
31. For some recent reviews, see: (a) Hasanein, A. A. *Adv. Chem. Phys.* **1993**, *85*, 415. (b) Maroulis, G. *Rev. Mod. Quantum Chem.* **2002**, *1*, 320. (c) Munn, R. W.; Papadopoulos, M. G.; Reis, H. *Pol. J. Chem.* **2002**, *76*, 155.