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# Electronic polarizability-based stereochemical model for Sharpless AD reactions

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ABSTRACT

Softness really is the hard force! Reported here was the critical yet long-overlooked role of electronic polarizability (i.e., softness) effect in controlling absolute stereochemical courses of general asymmetric induction events. Thus, a sensitive dependence of the sense of chiral induction on an alkene substrate's substituent electronic polarizability character was uncovered from a range of structurally highly comparable Sharpless asymmetric dihydroxylation (AD) systems, from which a new polarizability-based stereochemical model of predictive power was suggested.



## 1. Introduction

The Sharpless asymmetric dihydroxylation (AD) reactions serve as a cornerstone of enantioselective catalysis technologies in organic synthesis (Scheme 1).[1] Through extensive studies by Sharpless and others on both the reactivities and selectivities characteristic to this system, an empirical mnemonic device was established to rationalize and predict the stereochemical outcomes in these reactions. Central to the success of this steric device is the recognition that, when an alkene substrate was positioned as shown (Scheme 1) in a plane with each of the four substituents occupying a quadrant corner, the southwestern quadrant, which is believed to be an '*attractive*' substrate–catalyst interaction area critical for achieving high level of asymmetric induction, must be assumed by a substituent $R_L$ of the largest size, that is, preferably a '*flat and aromatic*' aryl group or, in its absence, a '*soft and large*' aliphatic moiety. Meanwhile, the substituent at the northwestern quadrant should ideally be a group $R_S$ of considerably small steric volume. The substituent $R_M$ at the northeastern corner constitutes another major '*attractive*' substrate–catalyst interaction site[2] thus functions synergistically with the $R_L$ group toward high enantiomeric excesses (ees), and can relatively flexibly accommodate medium steric sizes.

Although this steric mnemonic has proven to be very useful, a number of systems[2,3] in which the model made predictions opposite to experimental observations had been recorded. Consequently, considerable efforts had been made to rationalize some of these results with modified models.[2] These stereochemical abnormalities collectively invite conceptually new thinking on the general enantio-control scenarios in Sharpless AD processes.

With the recent development of a new helix electronic theory for molecular chirality and chiral interactions by one of us,[4] we have come to recognize the paramount importance of electronic polarizability effect in the general origin of enantioselection in asymmetric induction events. Indeed, it was remarkable that the widely appreciated adjectives '*flat-aromatic-soft-large*' describing an alkene substituent's structural prerequisites for its attaining high ees uniformly point to a single criterion of '*polarizable*', as both π-electron densities in a flat aromatic group and large σ-electron clouds in a soft and large aliphatic group possess high electronic polarizability (i.e., softness).[5,6] An analysis of an alkene's polarizability characteristics thus readily suggests a new paradigm for probing the origin of enantioselections in Sharpless AD reactions.

The implication of polarizability as a critical electronic effect in molecular interactions, as commented recently by Hansch, the originator of QSAR concept, has long been overlooked.[7] In the general context of asymmetric catalysis,[8] indeed, there are some widely observed yet intriguing experiments that cannot be easily rationalized

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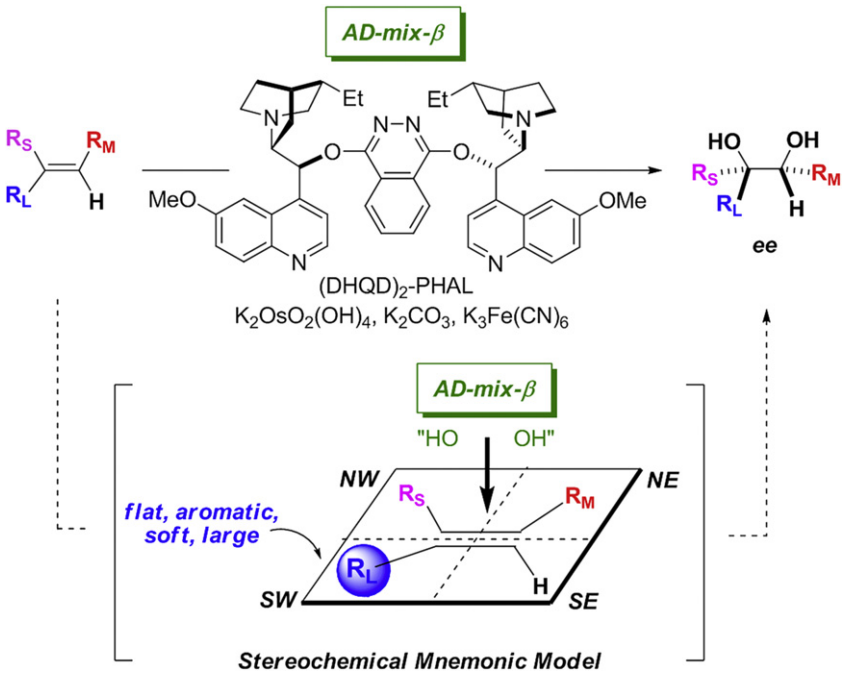
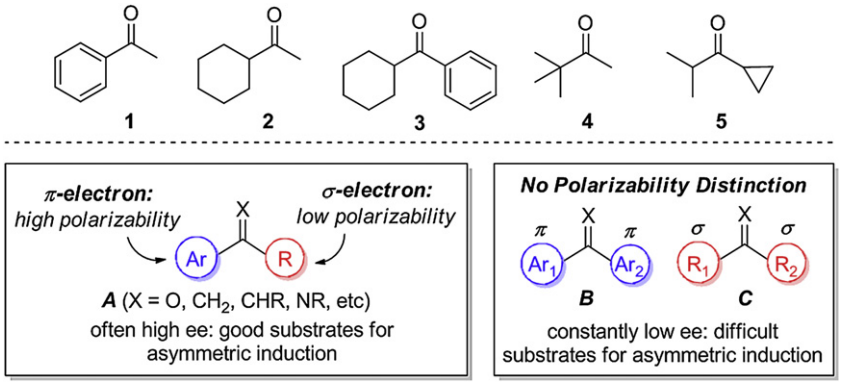



**Scheme 1.** Size-based mnemonic for Sharpless AD reactions.

by conventional steric theories, but are readily understandable with polarizability-based electronic effect considerations.[4] For examples, in the asymmetric reductions of simple ketone substrates (Scheme 2, X=O), regardless of the chiral catalysts and reaction mechanisms involved, it is *always* easier to achieve high ees with aryl ketone **1** than with aliphatic ketone **2**. The success with **1** is usually interpreted on the ground of the steric size of the phenyl substituent being considerably larger than that of the methyl group. But replacing the phenyl with an isosteric cyclohexyl group almost always leads to a dramatic decrease of ees in **2**, while comparable levels of ees are retained in **3** where substituent size difference is virtually absent. Replacing the phenyl with an even larger *tert*-butyl group, thereby enhancing the substituent steric volume distinction in **4**, often leads to even lower ees.[8] By contrast, in a substrate like **5** of significantly smaller substituent size difference, ees under otherwise similar conditions are surprisingly high, and the sense of asymmetric induction is opposite to those in **1** and **4**, and to sterically rationalize this, one has to resort to the counter-intuition proposal that a strained cyclopropyl ring is larger in size than an isopropyl group.[9] However, from a scenario going beyond steric theories, all these results can be rationalized with the substrate substituents' distinction in their electronic polarizabilities-but not their sizes-as the predominant force controlling the senses and magnitudes of asymmetric inductions.[4] It is the highly polarizable π-electronic clouds in the phenyl rings in **1** and **3**, and π-character orbitals in the strained cyclopropyl ring in **5**, respectively, that make high ees possible. An absence of such π-versus-σ polarizability distinction in **2** and **4** explains their failure.

This polarizability control scenario evidently operates very generally (Scheme 2).[8] Substrates structurally as ***A*** that possess a significant π-versus-σ polarizability distinction represent those capable of achieving high ees in asymmetric catalysis, while substrates structurally as ***B*** and ***C*** that lack such a polarizability distinction summarize those widely attempted but unsuccessful so far. Regardless of the substrate types (X=O, $CH_2$, CHR, NR, i.e., ketones, alkenes, amines, etc.) and the specific catalytic asymmetric processes in which they participate, these penetrating enantioselection trends have been consistently observed.[4,8]

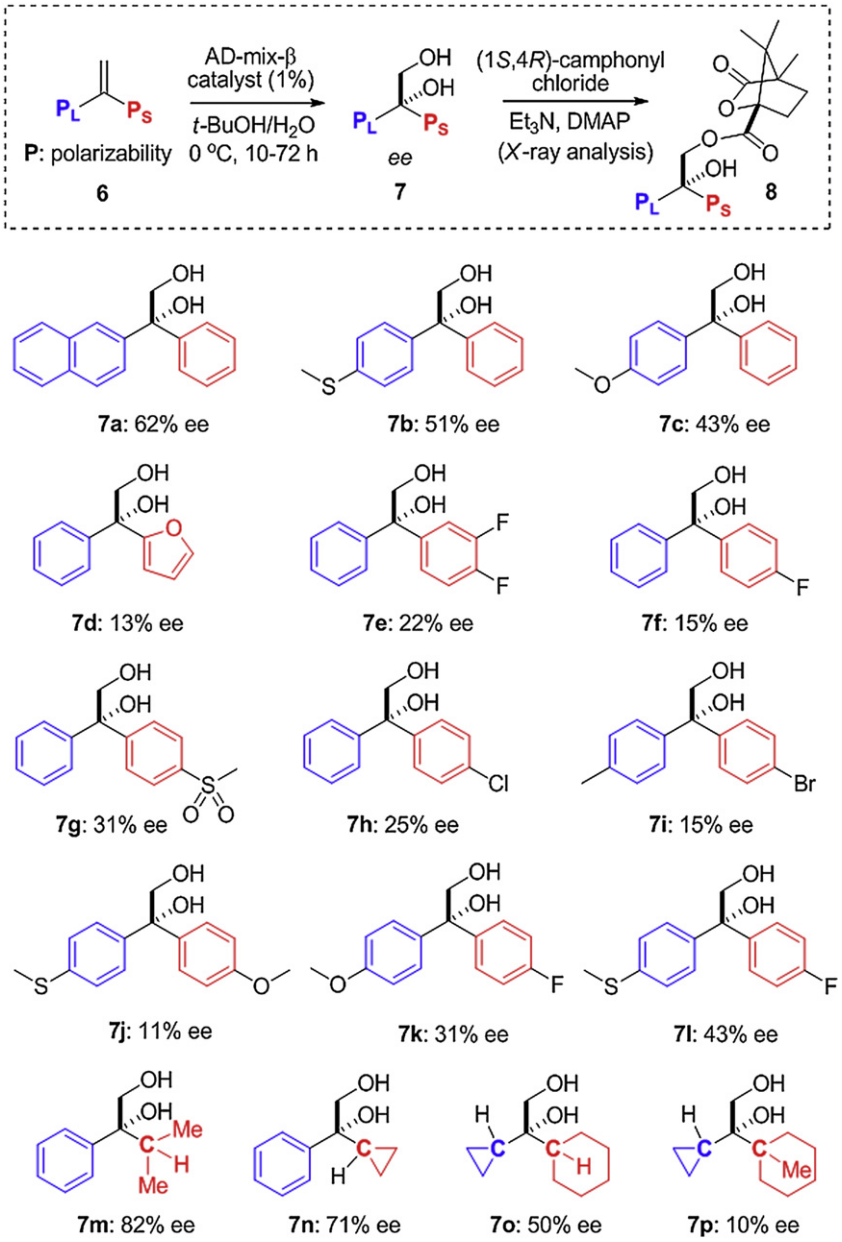



**Scheme 2.** A polarizability-based rationale: the π-versus-σ electronic effects widely observed in asymmetric inductions.

## 2. Results and discussion

In this work, we examined the issue of potential polarizability control in the stereochemical courses of Sharpless AD processes. Within this context the 1,1-disubstituted alkene substrates attract our particular interest because these two substituents situate at the closest vicinity and both are geometrically capable of competing for occupying the leading substrate–catalyst '*attractive*' interaction quadrant. Consequently, the enantio-facial selection on the substrate would be decisively determined by one of the two substituents that assumes the position at the SW quadrant. Moreover, since 1,1-disubstituted alkenes bearing both an aryl and an alkyl substituents had already been extensively studied in literature,[1] herein we decided to focus specifically on 1,1-diaryl- and 1,1-dialkyl-alkenes. As might well be anticipated, since the two aryl or alkyl substituents differ appreciably in neither electronic nor steric properties, the magnitudes of ees achievable on these substrates certainly cannot be high. Even so, should polarizability characters dictate the courses of asymmetric inductions in these systems, the senses of absolute stereochemical controls would be sensitively and directly correlated to the aryl or alkyl substituent possessing a higher polarizability.

Within this design framework, a series of 1,1-diaryl- and 1,1-dialkyl-alkene substrates **6** were synthesized, with particular emphasis on 1,1-diaryl substrates bearing electronically differentiated benzene rings, and 1,1-dialkyl ones containing a cyclopropyl substituent. These structures are expected to yield alkene substituents of relatively significant polarizability differences that would otherwise be virtually nonexistent (vide infra). These substrates were then subjected to the standard Sharpless asymmetric dihydroxylation conditions under the action of AD-mix-β reagent. The enantio-purities of the resulting diol products **7** were determined by chiral HPLC analysis. To ascertain the absolute stereochemistry of the predominant product enantiomer, the corresponding diols **7** were directly derivatized into its diastereomeric camphanoates **8** with the chiral auxillary (1*S*,4*R*)-camphanoyl chloride. The diol configurations of the major diastereomers of **8** were then analyzed by X-ray crystallography (Scheme 3).

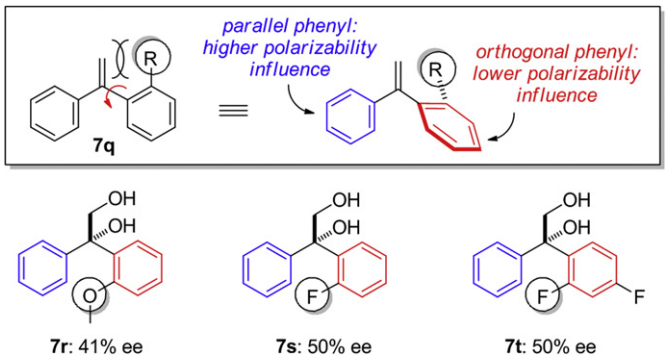



**Scheme 3.** Polarizability-controlled enantio-facial selections.

As summarized in Scheme 3, a variety of substrates **6** bearing a more polarizable substituent at the left side (in blue) and a less polarizable substituent at the right side (in red) were examined. The simple polarizability ranking principles employed here are exactly the same as those used more conventionally in inferring the softness of a group in the classical HSAB theories,[5] and conform to the *local* chemical environment in which the group under concern resides. The polarizability ranking for many common organic groups had been illustrated previously.[4] Relevant to this work are mainly the following two polarizability sequences: for benzenes electronically differentiated by substituents on their aromatic rings: benzene ring with electron-donating substituent>benzene ring itself>benzene ring with electron-withdrawing substituent; and for the central carbons in alkyl groups, strained alkyls (cyclopropyls) >unstrained alkyls.

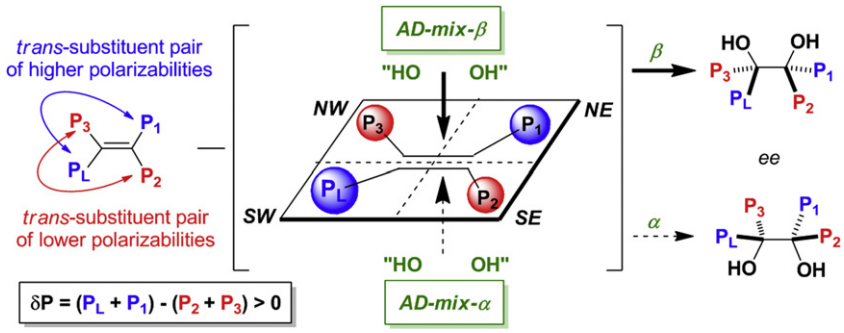
From the results listed in Scheme 3, it is experimentally evident that in each case the two substituents on **6** competed sensitively in responding to their relative local polarizabilities. For those 1,1-diaryl substituents bearing more π-conjugation (**7a**) or an electron-donating substituent (**7b** and **7c**), these substituents possess higher local benzene ring polarizabilities thus function as stereochemistry-controlling $P_L$ groups; for those 1,1-diaryl substituents bearing less π-conjugation (**7d**) or an electron-withdrawing substituent (**7e**, **7f**, **7g**, and **7h**), the corresponding local benzene rings here themselves behave as $P_L$ groups. In diols **7i**, **7k**, and **7l** flanked by both an electron-donating and -withdrawing group-substituted benzene rings, the benzenes of higher π-electron densities predominate in local ring polarizabilities. In diol **7j** where both benzene rings are substituted with electron-donating groups, the one with stronger electron-donating ability (SMe-vs-OMe) leads the stereochemical course.[10] At this point these comparisons on polarizabilities are qualitative in nature, there is certainly no basis for conducting quantitative analysis. But for structurally highly comparable systems, such as **7b**,**c**,**e**,**f**, and **7j**,**k**,**l**, in each series a clear trend of ees increasing with the increases of polarizability distinction between the two aryl substituent local benzene rings was observed. Cyclopropyl-containing diols **7n**–**p** represent a fascinating class of polarizability-tuned structures. Although the three-membered ring strain-induced bent carbon–carbon σ-bond electronic densities in a cyclopropyl group are less polarizable than those of an aromatic π-system, they are considerably more polarizable than those in unstrained cyclic or linear alkyls. Thus, from **7n** to **7o**,**p** a reversal of the role of the cyclopropyl substituent in directing asymmetric induction was observed in responding to its local polarizability ranking. Furthermore, as the polarizability difference between phenyl and cyclopropyl is smaller than that between phenyl and isopropyl, the ee in **7n** is lower than that in **7m**, despite the fact that steric size difference in **7m** is less conducive for achieving asymmetric induction than that in **7n**. These are important results exemplifying that, although there is no doubt that steric effects are important stereochemical factors, they can be overwritten by competing polarizability effects. Similarly, in **7o**,**p** polarizability controls also outweigh counter-acting steric effects: the local carbon (highlighted in bold) polarizability of cyclopropyl ring is higher than that of the bulkier cyclohexyl in **7o**, and methylcyclohexyl in **7p**, thus although the magnitudes of ees eroded with the increasingly developed unfavorable steric interferences from **7o** to **7p**, the sense of asymmetric induction remains unchanged.

Some 1,1-diaryl-alkenes with *ortho*-substituents were also examined (Scheme 4). This type of substrates merit particular attention because they stand out prominently among an extensive range of diaryl substrates (such as diaryl ketones) that generally perform very poorly in asymmetric catalysis when such *ortho*-substituents are absent. For examples, as already highlighted by some recent reports, a series of *ortho*-substituted diaryl ketones were capable of achieving high levels of ees in Cu-catalyzed hydrosilylation reactions.[11a] These results echoed earlier observations on highly enantioselective reductions of *ortho*-substituted diaryl ketones with Ru-catalyzed asymmetric transfer hydrogenations and chiral oxazaborolidines-catalyzed reductions, respectively.[9,11b–f] Furthermore, these magical '*ortho*-effects' on asymmetric inductions could not be easily accommodated by conventional steric rationales as in these systems, in order to stay in line with a self-consistent stereochemical model, the apparently bulkier *ortho*-substituted aryl rings must be assumed to be of smaller sizes when compared to unsubstituted aryl rings. However, these seemingly abnormal stereochemical behaviors were readily explained when polarizability electronic effects were considered. As illustrated through structure **7q**, the bond rotation incurred by minimizing the repulsion between *ortho*-substituent R and the alkene double bond π-cloud would inevitably interfere with the local benzene ring's parallel alignment with regard to the reacting double bond, thereby effectively reducing its ring polarizability influence on the reaction ee-determining state. Consequently, regardless of the electron-donating or -withdrawing nature of the R substituent, the aryl ring bearing an *ortho*-substituent exerts less stereochemical control than that of unsubstituted aryl ring. In accord with this polarizability effect, in each case of diols **7r**–**t**, the less bulkier benzene ring functions effectively as $P_L$ group leading to appreciable magnitudes of ees.




**Scheme 4.** Polarizability consequence of steric '*ortho*-effects'.

It should be emphasized again that, since the two aryl or aliphatic substituents in these examined 1,1-disubstituted alkenes have significantly smaller polarizability and steric size differences than those commonly observed in alkenes possessing both an aryl and an aliphatic groups, there is simply no basis for achieving high ees herein. But despite the moderate-to-low ees recorded with dihydroxylations compiled in Schemes 3 and 4, we believe that the uncovered sensitive dependence of the senses of asymmetric inductions on the aryl ring electronic polarizabilities is conceptually very significant and novel. Since the updated Sharpless AD stereochemical model[2] had already emphasized the synergistic effects in enantio-controls between the *trans*-alkene substituents at the SW and NE quadrants (Scheme 1), the revealed dependence readily suggests that mapping the polarizabilities of the SW-NE *trans*-substituents pair with those of the competing NW-SE *trans*-pair should be a productive and predictive means for rationalizing the general stereochemical outcomes in Sharpless AD processes. In other words, as summarized in Scheme 5, as long as the local polarizabilities of the SW-NE *trans*-substituents pair outweigh those of the NW-SE *trans*-substituent pair, the corresponding alkenes must be dihydroxylated with the same top-face trajectory with the AD-mix-β reagent, or conversely, the bottom-face selection with




**Scheme 5.** Polarizability-based new stereochemical model for Sharpless AD reactions: the *trans*-effect.

the AD-mix-α reagent. A comprehensive list of representative substrates extracted from a large body of literature on Sharpless AD reactions was compiled in online Supplementary data. It is remarkable that both the senses and magnitudes of ees seem to link more with the local polarizability distinctions between the two pairs of *trans*-substituents [$\delta P=(P_L+P_1)-(P_2+P_3)$] than with the alkenes' substitution patterns (i.e., mono-, *cis*/*trans*-di-, tri-, or tetra- etc.).

## 3. Conclusion

In summary, through investigations on a series of 1,1-diaryl- and 1,1-dialkyl alkene substrates of fine-tuned substituents electronic polarizabilities in Sharpless AD reactions, we have uncovered a direct and sensitive dependence of the enantio-facial selections on the alkene substituents bearing higher local polarizabilities. The senses and magnitudes of asymmetric induction seem to be generally and predominantly controlled by the local polarizability distinctions between the two competing *trans*-pairs of substituents. A polarizability-based stereochemical model of practical usefulness was proposed.

## 4. Experimental

### 4.1. General experimental

Reagents were purchased at the highest commercial quality from Acros and Aldrich and used without further purification unless otherwise noted. Silica gel (ZCX-II, 200–300 mesh) used for flash column chromatography was purchased from Qing Dao Ocean Chemical Industry Co. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III (300 MHz or 500 MHz) spectrometers and are internally referenced to residual solvent signals (note: $CDCl_3$ referenced at $\delta$ 7.26 ppm for $^1$H and $\delta$ 77.1 ppm for $^{13}$C). Data for $^1$H NMR are reported as follows: chemical shift ($\delta$ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, dd=doublet of doublets, ddd=doublet of doublet of doublets, and m=multiplet), integration, coupling constant (hertz) and assignment. Data for $^{13}$C NMR are reported in terms of chemical shift ($\delta$ ppm). High resolution mass spectrometric (HRMS) data were obtained using Bruker Apex IV RTMS. High pressure liquid chromatography (HPLC) was performed on an Agilent 1200 Series chromatograph using Daicel Chiralcell chiral columns (25 cm) and guard column (5 cm) as noted for each compound (OD-H columns). The room temperature (294±1 K) single crystal X-ray experiments were performed on a Bruker P4 diffractometer equipped with graphite monochromatized Mo Kα radiation. Unit cell was obtained and refined by 52 well centered reflections with $3.5^\circ<\theta<19.2^\circ$. Data collection was monitored by three standards every 100 reflections collected.

### 4.2. General experimental procedure for Sharpless AD reactions

A round bottom flask (25 mL) equipped with a magnetic stirrer was charged with *tert*-butyl alcohol (5 mL), water (5 mL), AD-mix-β (1.4 g), and $MeSO_2NH_2$ (95 mg, 1 equiv). The mixture is stirred at room temperature until both phases are clear, and then cooled to 0 °C, whereupon the inorganic salts partially precipitated. The olefin substrate (1 mmol) was added at once, and the heterogeneous slurry was stirred vigorously at 0 °C until TLC revealed the absence of the starting olefin (ca. 6–96 h). The reaction was quenched at 0 °C by addition of sodium sulfite (1.5 g) and then warmed to room temperature and stirred for 30–60 min. The reaction mixture was extracted three times with $CH_2Cl_2$, the combined organic layer was washed with 2 M KOH to remove most of the sulfonamide, dried over $MgSO_4$, and concentrated under vacuum. Purification by flash chromatography (silica gel, EtOAc/hexane) gave the corresponding pure diol product. Characterization data for a representative product 1-(naphthalen-2-yl)-1-phenylethane-1,2-diol (**7a**): $^1$H NMR (300 MHz, $CDCl_3$): $\delta$: 7.96 (s, 1H, CH), 7.84–7.77 (m, 3H, CH), 7.51–7.43 (m, 5H, CH), 7.36–7.24 (m, 3H, CH), 4.26 (d, $J$=11.4 Hz, 1H, $CH_2$), 4.19 (d, $J$=6.9 Hz, 1H, $CH_2$), 3.41 (br, 1H, OH), 2.24 (br, 1H, OH); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 143.7 141.1, 133, 132.5, 128.4, 128.3, 128.2, 127.5, 127.5, 126.5, 126.2, 126.2, 125, 124.8, 78.7, 69.2; HRMS ($m/z$) calcd for $C_{18}H_{16}O_2$ 264.1150, found 264.1038; The ee was determined by HPLC (Chiracel OD-H, *i*-PrOH/hexanes=92/8, flow rate 1.0 mL/min, $\lambda$=254 nm); $t_R$=25.4 (major) and 32.4 (minor) min, 62% ee. The absolute configuration of the major product enantiomer was determined by single crystal X-ray analysis.

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## Supplementary data

Detailed experimental procedures, single crystal X-ray structural analysis data, compound characterization data, and copies of $^1$H and $^{13}$C NMR spectra. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.09.073.

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