Significant Effects of Nonconjugated Remote Substituents in Catalytic Asymmetric Epoxidation

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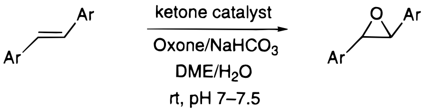
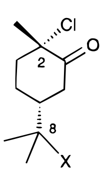
Since Jacobsen's report on electronic effects of remote substituents in asymmetric epoxidation catalyzed by chiral (salen)-Mn(III) complexes,[1] the electronic tuning has been recognized as an important tool in catalyst design. While the origin of electronic effects is poorly understood, a great deal of success in asymmetric catalysis has been achieved by changing conjugated remote substituents.[2,3] Here we report that electronic properties of nonconjugated remote substituents on the catalysts have significant effects in asymmetric epoxidation by chiral dioxiranes. We also propose an electrostatic model to account for the electronic effects of those substituents.

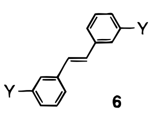
Chiral dioxiranes, generated *in situ* from chiral ketones and Oxone, are excellent reagents for asymmetric epoxidation of unfunctionalized *trans*-olefins and trisubstituted olefins.[4−7] As



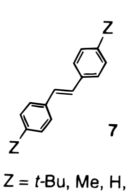
reactions between dioxiranes and olefins follow a concerted one-step process with a spiro transition state (TS),[5b,6a,8−10] chiral dioxirane epoxidation offers an ideal system for understanding the electronic effects of remote substituents on enantioselectivity. To probe the effect of nonconjugated remote substituents, a new series of chiral ketone catalysts **1**−**5**, prepared from (*R*)-carvone, was selected. Ketones **1**−**5** all have a quaternary carbon at C_2 position, but they differ in the remote substituent at C_8 position. Under our previously reported *in situ* conditions,[5,11] epoxidation of symmetrical, *meta*- or *para*-substituted *trans*-stilbenes **6** and **7** catalyzed by chiral (2*S*,5*R*)-ketones **1**−**5** all gave the (*S*,*S*)-epoxides as the major products. As suggested by the X-ray structure of ketone **2** (Figure 1), (2*S*,5*R*)-dioxiranes **1a**−**5a** adopt the most stable chair conformations with alkyl substituents at the equatorial positions and a 2-chloro atom at the axial position (Figure 2). Approach by bulky substrates **6** and **7** from the axial face is considered unlikely due to the steric hindrance of axial protons H-3 and H-5. For the equatorial approach, there are two possible spiro TS. The sterically favored one (TS$_\mathrm{f}$) has phenyl groups of *trans*-stilbenes positioned away from the 2-chloro atom of dioxiranes **1a**−**5a**, leading to (*S*,*S*)-epoxides. The disfavored one (TS$_\mathrm{d}$), giving rise to the (*R*,*R*)-epoxides, has steric clash between the 2-chloro atom and the phenyl groups. The free energy difference between TS$_\mathrm{f}$ and TS$_\mathrm{d}$ determines the enantioselectivity.[12]



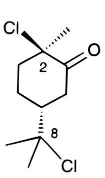
1 (X = F)
2 (X = Cl)
3 (X = OH)
4 (X = OEt)
5 (X = H)



6
Y = Me, H, OMe, F, Cl, OAc



7
Z = *t*-Bu, Me, H, F, Br, OAc



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Molecular models[13] suggested that the 2-chloro atom is very close to the dioxirane group in **1a**−**5a** and therefore is unlikely to have steric interactions with the remote *para*- or *meta*-substituents of *trans*-stilbenes **6** and **7** in either TS$_\mathrm{f}$ or TS$_\mathrm{d}$. This implies that the enantioselectivities of epoxidation are not sensitive to the steric sizes but possibly to the electronic properties of those remote substituents. Indeed, by using ketone **2** as the catalyst, higher ee's were obtained for the more electron-rich olefins, and the Hammett plot of log(er) against either σ_m or σ_p showed a linear relation (Figure 3: $\rho = -0.84$ and $r = 0.989$ for plot A; $\rho = -0.86$ and $r = 0.985$ for plot B).[14] The negative slope of plot A or plot B could be understood by considering the unfavorable n-π electronic repulsion, present in TS$_\mathrm{d}$ but not in TS$_\mathrm{f}$, between the 2-chloro atom of dioxiranes and the phenyl groups of *trans*-stilbenes (Figure 2). The evidence for the n-π electronic repulsion came from the observation that, despite of smaller steric size of Cl atom compared to the methyl group, ketone **2** gave much higher ee (85%) than its C_2 epimer ketone **8** (32% ee) for epoxidation of *trans*-stilbene under the same reaction conditions. For *trans*-stilbenes with stronger electron-donating substituents (smaller σ_m or σ_p values), the n-π electronic repulsion in TS$_\mathrm{d}$ becomes more severe, thereby giving higher ee's. Note that the slope of plot A or plot B (the apparent reaction constant ρ) is equal to $\rho_\mathrm{f} - \rho_\mathrm{d}$, where reaction constants ρ_f and ρ_d represent charge distributions of TS$_\mathrm{f}$ and TS$_\mathrm{d}$, respectively.[15] The negative value of ρ in plot A thus means that ρ_f is more negative or less positive than ρ_d, suggesting that more positive

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(12) Theoretical studies by Houk et al. showed that the spiro transition state of dioxirane epoxidation could be asynchronous (ref 10a). However, for epoxidation of *trans*-stilbenes **6** and **7** by dioxiranes **1a**−**5a**, the extent of asynchronicity is determined by the unsymmetrical structures of the dioxiranes but not by the remote substituents of symmetrical *trans*-stilbenes.

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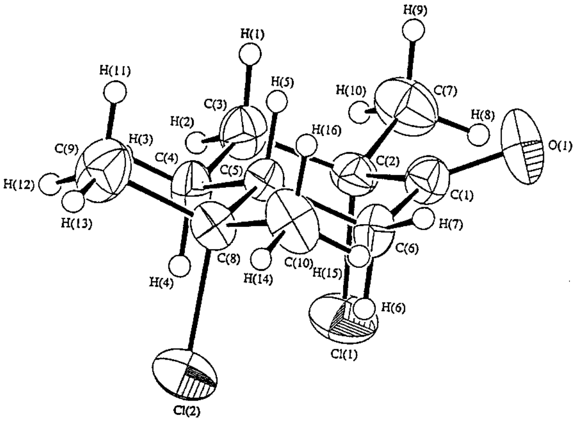

Figure 1. X-ray structure of ketone 2 (ORTEP view).

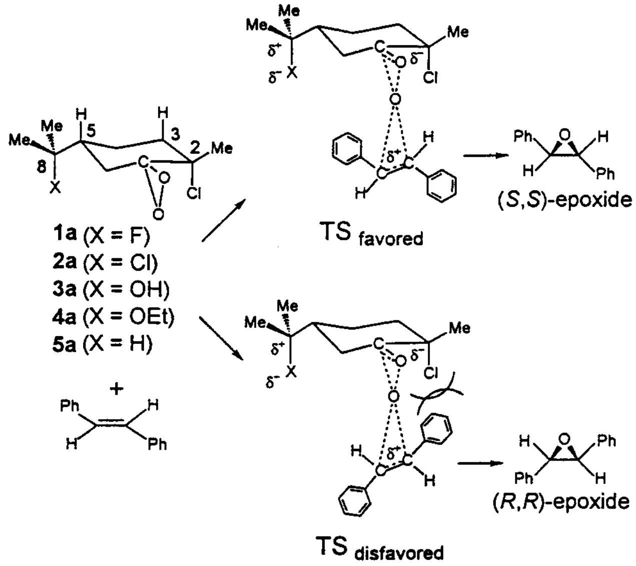

Figure 2. Spiro transition states for dioxirane epoxidation.

charges or less negative charges are developed on the olefin double bond of TS_f than that of TS_d.[16,17]

Molecular models also revealed that nonconjugated remote substituents at the C_8 position of dioxiranes **1a**−**5a** were too remote from the dioxirane group to have steric interactions with *trans*-stilbenes **6** and **7** in either TS_f or TS_d. However, given the different charge distributions in TS_f and TS_d, those substituents may affect the enantioselectivity of epoxidation by through-space electrostatic interactions, i.e., the field effects.[18,19] Indeed, a linear Hammett plot of log(er) against substituent field constant F[14] was observed for epoxidation of *trans*-stilbene[20] (Figure 3: $\rho = 1.72$ and $r = 0.999$ for plot C). As shown in Figure 2, small substituents F, Cl, OH, OEt, and H at C_8 position prefer the axial orientation, i.e., pointing to the α-face of dioxiranes **1a**−**5a**.[21] This implies that, in both TS_f and TS_d, the negative ends of polar C−X bonds are closer to the olefin double bond than their positive ends. By favorable field effects, more polar substituents (higher F values) should stabilize TS_f more than TS_d and thus give higher ee's, which explains the positive slope of plot C in Figure 3. Furthermore, the Hammett plot of log(er) against F was found to have a larger slope when a lower polarity solvent (e.g., 40% water in DME) was used (Figure 3: plot D).[22] The observed solvent effect on enantioselectivity lends additional support to the electrostatic model. The strong electrostatic effect in aqueous solutions[23] is not surprising because in water the transition state for dioxirane epoxidation is much more polarized than the reactants.[17,24]

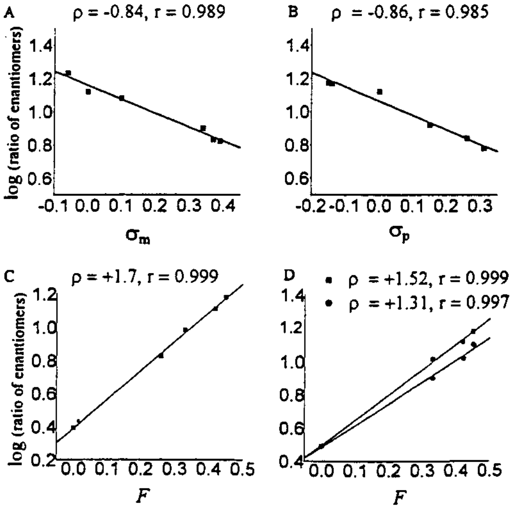

Figure 3. Hammett plots: A, asymmetric epoxidation of olefins **6** by catalyst **2** (ee range: 74−89%); B, asymmetric epoxidation of olefins **7** by catalyst **2** (ee range: 72−87%); C, asymmetric epoxidation of *trans*-stilbene by catalysts **1**−**5** for 22 h in DME−H_2O (3:2 v/v) (ee range: 42−87%); D, asymmetric epoxidation of *trans*-stilbene by catalysts **1**−**3** and **5** for 1 h in DME−H_2O (3:2 v/v; ■) and CH_3CN−H_2O (2:3 v/v; ●), respectively (ee range: 42−88%).

Our results represent the first report on electronic effects imparted by nonconjugated remote substituents in asymmetric catalysis. The significant effect of C_8 substituents of chiral ketones **1**−**5** on enantioselectivity (42−87% ee, $\Delta\Delta G^{\ddagger}$ ca. 1 kcal mol^{-1}) demonstrates the importance of this new type of electronic tuning. The proposed electrostatic model should provide a rational approach to catalyst design.

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Supporting Information Available: Hammett equations for enantioselective reactions; preparation and characterization data of ketones **1**−**5** and **8**; experimental details for catalytic asymmetric epoxidation reactions; determination of enantiomeric excess of epoxides, and X-ray structural analysis of ketones **2** and **8** containing tables of atomic coordinates, thermal parameters, bond lengths, and angles (57 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[16] Epoxidation reactions with ketones **1**−**5** were found to be faster for more electron-rich substrates, which implies that both ρ_f and ρ_d should be negative and the olefin double bond bears more positive charges in TS_f than in TS_d.

[17] For epoxidation of *para*-substituted styrenes by dimethyldioxirane, a ρ value of −0.90 was obtained, indicating the electrophilic nature of the oxygen transfer process. Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437.

[18] For a recent review of electronic field effects on chemical reactivity in organic reactions, see: Bowden, K.; Grubbs, E. J. *Chem. Soc. Rev.* **1996**, 171.

[19] Houk and co-workers reported that electrostatic effects influence the diastereoselectivities of hydride addition to cyclohexanones carrying remote polar groups. Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.

[20] C_8 substituted ketones **1**−**3** gave faster epoxidation reactions and higher ee's than unsubstituted ketone **5** (see Supporting Information for details). This result cannot be explained by Jacobsen's model (ref 1), which is built upon the Hammond Postulate argument.

[21] The axial orientation of C_8−Cl atom was also observed in the X-ray structure of ketone **8**.

[22] The *in situ* epoxidation reactions catalyzed by ketones **1**−**5** took place in only two solvent systems, i.e., CH_3CN−H_2O and DME-H_2O. The dielectric constants for DME, CH_3CN, and H_2O are 6, 36, and 78, respectively.

[23] For a recent report of the electrostatic effect in water, see: Conroy, J. L.; Sanders, T. C.; Seto, C. T. *J. Am. Chem. Soc.* **1997**, *119*, 4285.

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