Electrostatic repulsion as an additional selectivity factor in asymmetric proline catalysis†

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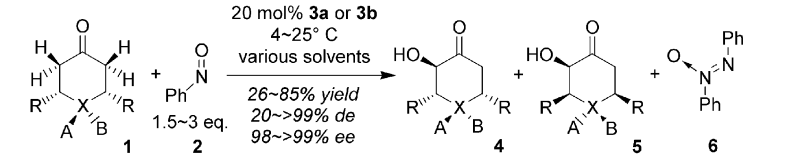
The metal free, single amino acid-catalyzed asymmetric desymmetrization (ADS) of *meso*-compounds 1 with nitrosobenzene 2 has been investigated using DFT. In this communication, we describe the role of electrostatic and dipole–dipole interactions in amino acid-catalyzed reactions, which has not previously been invoked in discussions of these important reactions.

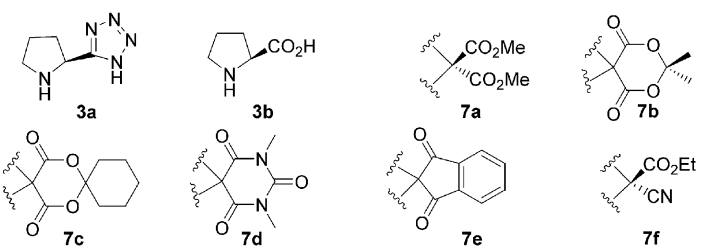
The ability of L-proline and similar chiral organocatalysts to catalyze asymmetric conversions involving carbonyl compounds has been explored recently for classical organic reactions such as: aldol, Mannich, amination and α-aminoxylation.[1] The origin of catalytic activity here is two-fold. The increased nucleophilicity of the α-carbon due to enamine formation with proline is a major contributor. The other source of catalysis and selectivity comes from the increased electrophilicity of the substrate because of the hydrogen bond and eventual proton transfer from the carboxylic acid H of proline.[2] Let us consider asymmetric α-aminoxylation reactions by which α-hydroxycarbonyl compounds can be directly prepared from aldehydes and ketones.[3] Here the observed excellent enantioselectivity arises from the hydrogen bond that exists favorably only in one transition state due to the chirality of the proline. It was shown for the major product that, in the transition state corresponding to the rate determining step, the enamine double bond is *anti* to the carboxyl group. This allows the proton transfer to N of Ph–N=O without deviating from the favorable planar enamine geometry.[4]

For substrate **1** (Scheme 1), the asymmetric desymmetrization[5,6] (ADS) *via* α-aminoxylation is expected to yield both diastereomers **4** and **5** but with excellent ee as *anti*-enamine-carboxyl arrangement is possible in both the diasteromeric transition states, and is indeed found (**1a,b**).[7,8] However, Ramachary and Barbas recently demonstrated that excellent diastereoselectivity can be achieved by suitable substituents at the 4th position of substrate **1** (Scheme 1).[8] Reaction of *meso*-cyclohexanones **1c–g** with nitrosobenzene **2** under L-proline-catalysis furnished the tandem α-aminoxylation/O–N bond heterolysis products **4** as a single diastereomer with very good *ee.* However, **1a** and **1b**, where the substituent at the 4th-position is either **7a** or methylene, generated ADS products in poor de but with very good *ee.* Here



a: R = CH_3 **A-X-B = CH_2** **de = 40% (5a) and ee = >99% (4a) & ee = >99% (5a)**
b: R = C_6H_5 **A-X-B = 7a** **de = 20% (4b) and ee = >99% (4b) & ee = >99% (5b)**

c: R = 3,4-(OCH_2O)C_6H_3 **A-X-B = 7b** **de = >99% (4c) and ee = 99%**
d: R = C_6H_5 **A-X-B = 7b** **de = >99% (4d) and ee = >99%**
e: R = C_6H_5 **A-X-B = 7c** **de = >99% (4e) and ee = >99%**
f : R = C_6H_5 **A-X-B = 7d** **de = >99% (4f) and ee = >99%**
g: R = C_6H_5 **A-X-B = 7e** **de = >99% (4g) and ee = 99%**
h: R = C_6H_5 **A-X-B = 7f** **de = 99% (4h) and ee = 98%**



Scheme 1 Experimentally known selectivity trends for L-pyrrolidine-2-yl-1*H*-tetrazole **3a** and L-proline **3b** catalyzed ADS reactions.[7,8] α-Hydroxyketones are formed by tandem α-aminoxylation/O–N bond heterolysis under the same reaction conditions.

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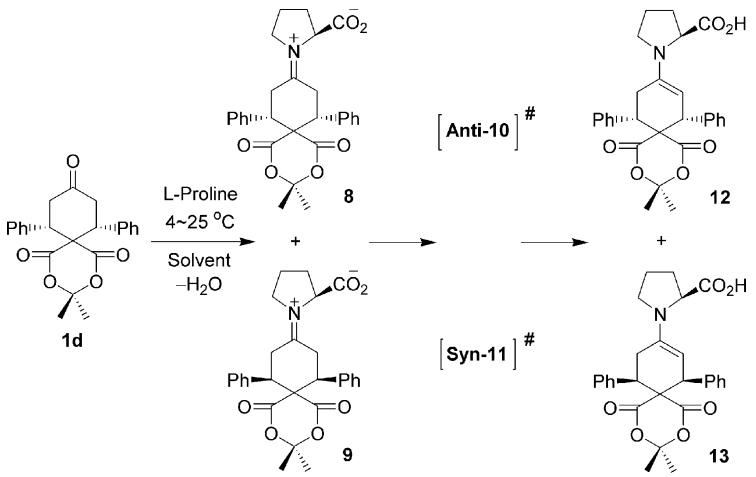
† Electronic supplementary information (ESI) available: Figs. S1–S3: lowest energy TS structures for **1a**, **1h** and **26**; molecular energies and geometries. See DOI: 10.1039/b606996g

we show with density functional theory calculations[9] that the additional selectivity in the ADS reactions of substrates **1c–h** is due to electrostatic interaction.[10] This can be used profitably as an additional selectivity factor in asymmetric organocatalysis.

Since the observed diastereoselectivity could be explained by hypothesizing that one of the enamines fails to form in the reaction, we first checked whether this is true. The reaction centres (Scheme 2) for substrates **1c–g** are virtually the same and hence the results of any one of them are representative. Therefore **1d** was selected for this study. The two proline enamines, **12** and **13**, of substrate **1d** originate from the imines **8** and **9** *via* the transition states (TSs) *anti*-**10** and *syn*-**11** respectively (Scheme 2). Both the lowest energy TSs (Fig. 1) were located at the B3LYP/6-31G* level[11] and confirmed by frequency analysis. The energy (E + zero point energy) difference between the transition states is only 0.23 kcal mol^{-1}, which rules out the hypothesis that the observed diastereoselectivity arises at the stage of enamine formation. So the diastereoselectivity in the above reactions must come from the next step, *viz*, the α-aminoxylation stage which is known to control the enantioselectivity for simple aldehydes and ketones.[4]

Transition states for α-aminoxylation were calculated after Houk's and Cordova's models[4] involving (*E*)-*anti* enamine attack on the oxygen of nitrosobenzene **2**, in which the phenyl group adopts the axial position, *anti* to the carboxylic acid group, similar to the proline-catalyzed Barbas–List–Mannich reactions.[12] The conformation with the enamine double bond *syn* to the carboxylic acid is unfavourable for α-aminoxylation, due to the energetic cost of distorting the molecular geometry to place proton transfer at a more proximal nitrogen, and is the reason for excellent enantioselectivity for simple aldehydes and ketones.[4] For all the substrates in the present study, the *syn* conformation lead to the minor enantiomer for both the major and minor diastereomers and since the enantioselectivity was excellent in all cases we did not explore the TSs in the *syn* conformation. In view of the relatively large size of the experimental systems, it was necessary to adopt a model that retains the significant aspects of the actual molecules but is small enough to do optimization and frequency calculations during conformational searching. Scheme 1 suggests that aryl groups at the 3rd position do not have a major role in the selectivity, as exemplified by the reactions of substrates **1b** and **1d**, which show a large difference in selectivity and, consequently, the computationally demanding aryl groups were replaced by methyl groups (Scheme 3). Reaction of **1a** revealed that the Me substituent also does not play much of a role in stereoselectivity and will not bring in any bias. Nevertheless, the effects of Ph and Me were explored separately without any substituents at the 4th position. In Scheme 3, **14** models the substrates **1c–g** and **17** models **1b**. The reasons for the formation of the sole product **15** with substrate **14** and the absence of such a selectivity with model **17** were sought specifically. Further, to make the computations simpler, all the lowest energy transition states were initially identified at the B3LYP/6-31G level. A re-optimization and frequency analysis



Scheme 2 The reaction mechanism for the formation of enamines **12** and **13** from substrate **1d** with L-proline.

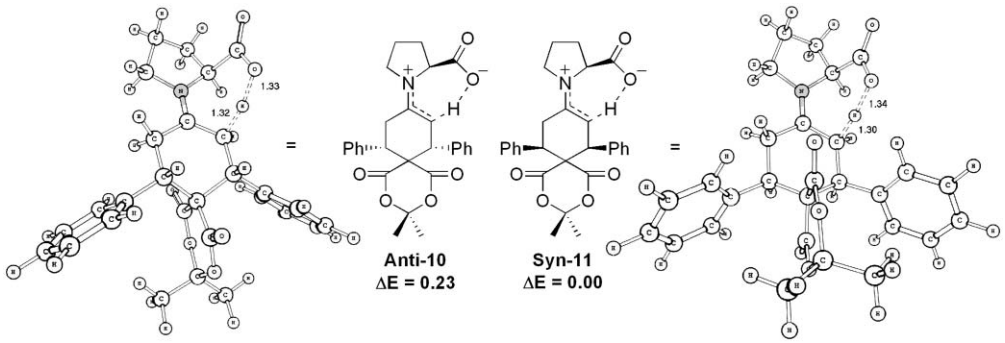
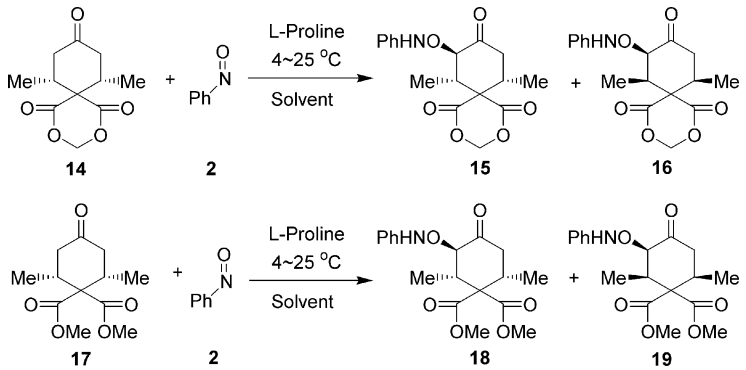


Fig. 1 The lowest energy TS structures leading to enamines **12** and **13** from substrate **1d** (interatomic distances in Å, energies in kcal mol^{-1}).



Scheme 3 Model ADS reactions studied computationally in this work. Compound **14** models *meso*-cyclohexanones **1c–g** of Scheme 1 and **17** models **1b**.

were carried out for the identified lowest energy TSs at the B3LYP/6-31G* level. The following discussion uses the results at this level.

Fig. 2 shows the lowest-energy transition structures for the ADS reaction of *meso*-compound **14** with **2**. The transition structure, *syn*-**21**, that leads to the minor diastereomer is 6.20 kcal mol^{-1} higher in energy. It predicts a de of >99% of the product favoured experimentally in agreement with the experimentally reported de of >99%. On the contrary, the energy difference between the corresponding TSs for substrate **1a** is only 0.36 kcal mol^{-1} in favour of the *anti* TS,[13] which suggests little selectivity in accordance with the experimental result **a** in Scheme 1. The high de for the reaction of **14**, therefore, arises from the spiroketo moiety present in **14**. This alone causes a difference of ~6 kcal mol^{-1} between TSs *anti*-**20** and *syn*-**21**. A careful analysis of the structural parameters of *anti*-**20** and *syn*-**21** reveals that the *syn*-**21** transition state is higher in energy due to the strong electrostatic repulsion between the two oxygens of nitrosobenzene and the ester carbonyl. This is supported by the distances (4.38 *vs* 2.89 Å; *anti*-**20** and *syn*-**21** respectively) observed in the TSs. Besides, the dipole of C=O of the ester group in *syn*-**21** faces the dipole of N=O of Ph–N=O while it is almost perpendicular in *anti*-**20**. The rigid nature of the spiroketo group does not allow the C=O to tilt so as to avoid the repulsion from Ph–N=O in TS *syn*-**21**.

One way of decreasing these repulsive interactions is to enable the C=O group to twist away from Ph–N=O. Substrate **17** meets this criterion. The corresponding TSs are shown in Fig. 3. Here the difference in energy is lowered to 2.61 kcal mol^{-1} from 6.20 kcal mol^{-1} and the related experiment (**b**, Scheme 1) shows poor diastereoselectivity.[14] Due to the greater twist of the carbonyls in

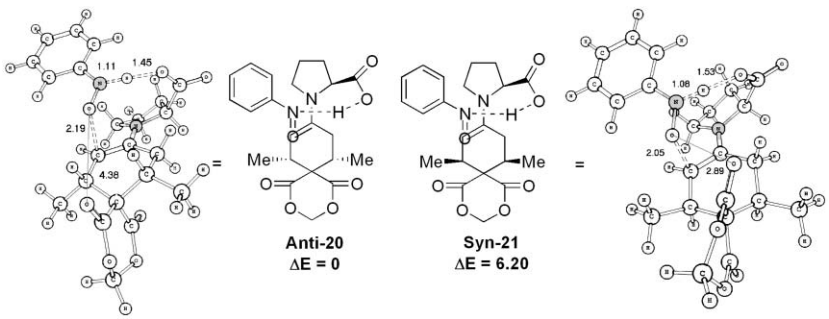


Fig. 2 The lowest energy TS structures leading to **15** and **16** for α-aminoxylation of substrate **14**.

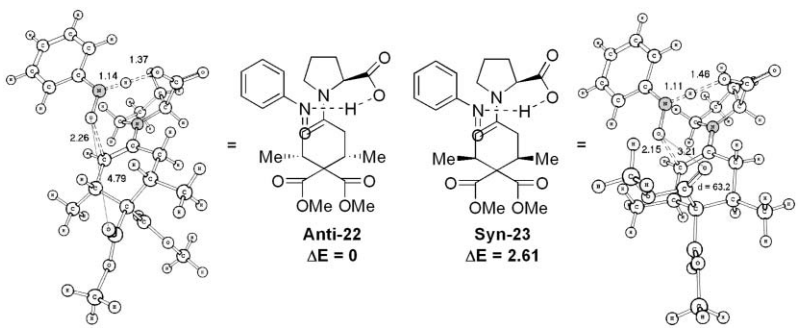


Fig. 3 The lowest energy TS structures leading to **18** and **19** for α-aminoxylation of substrate **17**.

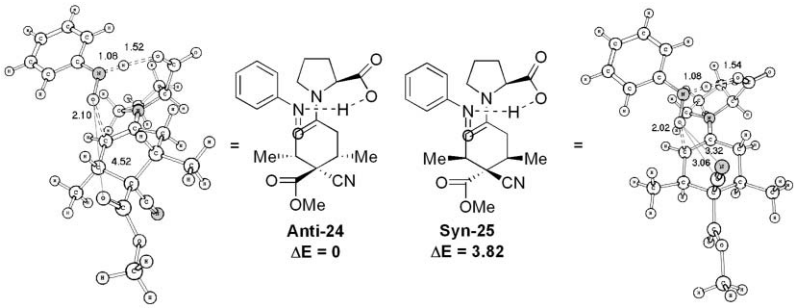


Fig. 4 The lowest energy TS structures leading to **18a** and **19a** for α-aminoxylation of substrate **17a**.

the non-spiro system, the O…O distance in *syn*-**23** is increased to 3.21 Å from 2.89 Å present in *syn*-**21**. Besides, the dipoles are no longer parallel; the near zero dihedral angle of the O(CO)–C–C…C(CN) in *syn*-**21** increases to 63.2° in *syn*-**23**. These help to decrease the repulsive contribution by 3.59 kcal mol^{-1}.

The yet to be accounted for reaction of substrate **1h** also shows high de despite the substituent at 4th position not being tied back. Calculations on the real system support the experimental de: the TS leading to minor diastereomer, **5h**, is 4.85 kcal mol^{-1} higher in energy than the TS leading to major diastereomer **4h**.[13] To relate this to the results in Figs. 2 and 3, a comparable system, where the axial ester group of **17** is replaced by CN group (**17a**), was also studied and the results are shown in Fig. 4. The energy difference of 3.82 kcal mol^{-1} suggests a high de and is caused by the axial CN group. What is the origin of this larger energy difference between TSs *anti*-**24** and *syn*-**25** with respect to that in Fig. 3? It may be attributed to the electrostatic repulsion between the O of Ph–N=O and the π electron density of CN in *syn*-**25**. The greater π electron density on CN than on C=O, and the position of O directly facing CN in *syn*-**25**, account for the surprising result of greater diastereoselectivity in Fig. 4 than in Fig. 3. Based on the results in Figs. 3 and 4 it becomes apparent that the diastereoselectivity will decrease if the CN and the ester group exchange their positions.

Finally, to show that electrostatic repulsion alone can explain the excellent diastereoselectivity of the reactions **c–h** in Scheme 1 we calculated the TSs for α-aminoxylation using the substrate *cis*-3,5-diphenylcyclohexanone (**26**).[13] The energy difference of 1.21 kcal mol^{-1} in favour of the *anti* TS (0.36 kcal mol^{-1} for **1a**) confirms that neither a Ph or Me group at the 3rd position in substrate **1** can stop the products **5c–h** from forming in the reaction, although there may be a preference for product **4** as with electron rich substituents at 4th position and the effects can be additive as is revealed in the case of **1h** above.

In summary, we have shown that transition state structures and diastereoselectivity in proline-catalyzed ADS reactions of different highly substituted *meso*-cyclohexanones **1** with **2** are largely controlled by electrostatic/dipole–dipole interactions. Computational evidence shows that the observed diastereoselectivity is due to the polar groups at the 4th-position of cyclohexanone and due to differences in the conformations. These selectivities are the best demonstration that electrostatic interaction can be used as an additional selectivity factor in amino acid catalysis.

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13 See supporting information for the structures.

14 Unlike all other substrates studied here, for **1b** there might be a favourable interaction with the ester group and Ph at the 3rd position in the *syn* TS, because of the proximity of OMe and Ph caused by the twist of the ester group to avoid electrostatic repulsion from Ph–N=O. The energy for the *syn* TS may be brought further down by this, causing a poorer de than the results on **17** suggest.