Asymmetric Organocatalysis

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Manifestation of Felkin–Anh Control in Enantioselective Acyl Transfer Catalysis: Kinetic Resolution of Carboxylic Acids**

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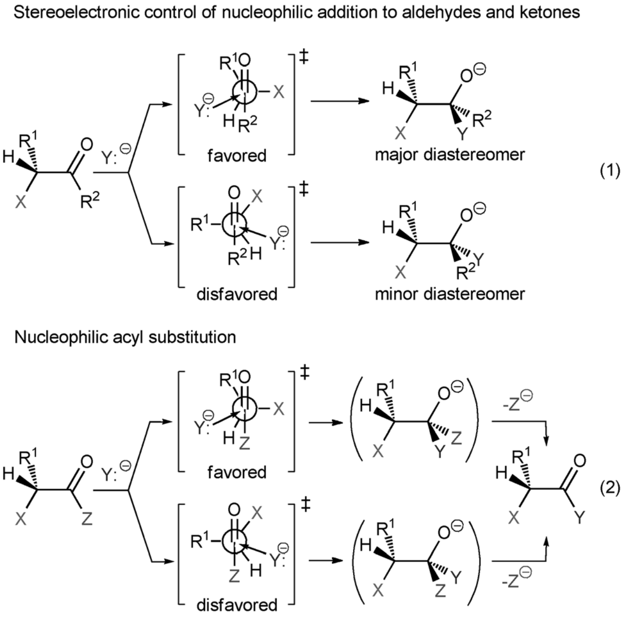
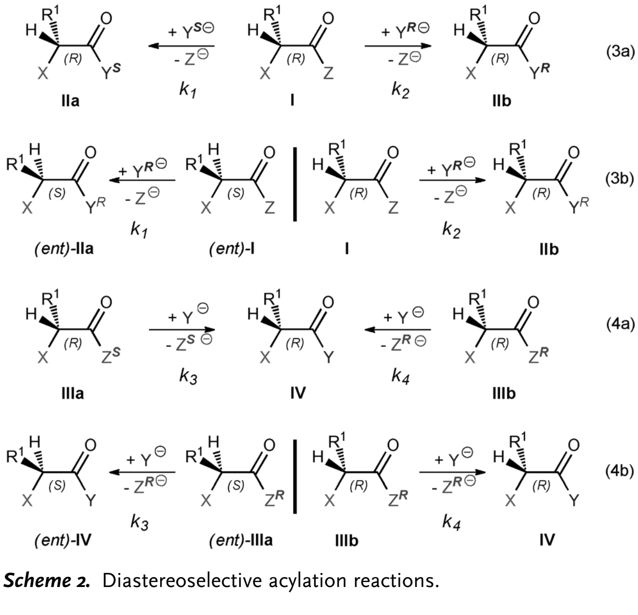
Polar α-substituents have long been known to control the diastereofacial selectivity of nucleophilic addition to a carbonyl group.[1] The transition-state model proposed by Felkin et al. and subsequently refined by Anh and Eisenstein[2] successfully explained the observed selectivity in terms of stereoelectronic control exerted by an electron-withdrawing group X at the α-position of the carbonyl (e.g., see Equation (1) in Scheme 1). For years, it has been used to predict which diastereomer will form predominantly in the addition of a Grignard reagent to a chiral aldehyde or in the hydride reduction of a chiral ketone, to name just the two most common examples.[3] Does stereoelectronic control manifest itself in nucleophilic acyl substitution reactions, and if so, how? At first glance, which face of an acyl carbonyl is attacked by a nucleophile may appear to be a moot question, because the subsequent (or concerted) elimination of the leaving group destroys the transient new stereogenic center [Eq. (2)]. However, if chirality is present in the nucleophile Y [Eqs. (3a) and (3b)] or the leaving group Z [Eqs. (4a) and (4b)], then the energy differences between the diastereomeric transition states may lead to alternative modes of diastereoselectivity, as illustrated in Scheme 2. Computational studies reported herein, combined with our recent experimental results,[4a,c,d] demonstrate that stereoelectronic effects indeed play a key role in controlling the enantioselectivity of catalytic, asymmetric alcoholysis of α-substituted acyclic anhydrides. Although the venerable Felkin–Anh model has been the subject of many theoretical investigations,[5] to the best of our knowledge, this is the first one extending its scope to stereochemical analysis of nucleophilic acyl substitution.



Scheme 1. Felkin–Anh model and nucleophilic acyl substitution. (R^1 = alkyl, aryl; R^2 = H, alkyl, aryl; X = electron-withdrawing group; Y = nucleophile; Z = leaving group).



Scheme 2. Diastereoselective acylation reactions.

In the context of developing amidine-based catalysts (ABCs, e.g., see **1** and **2** in Scheme 3) and exploring their applications in asymmetric acylation,[4,6,7] we have become interested in catalytic enantioselective alcoholysis of chiral acyl donors. In 2008, Shiina et al.[8] reported that benzote-

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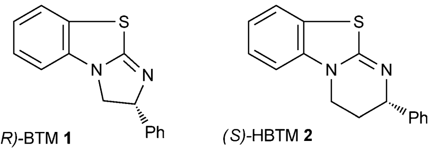


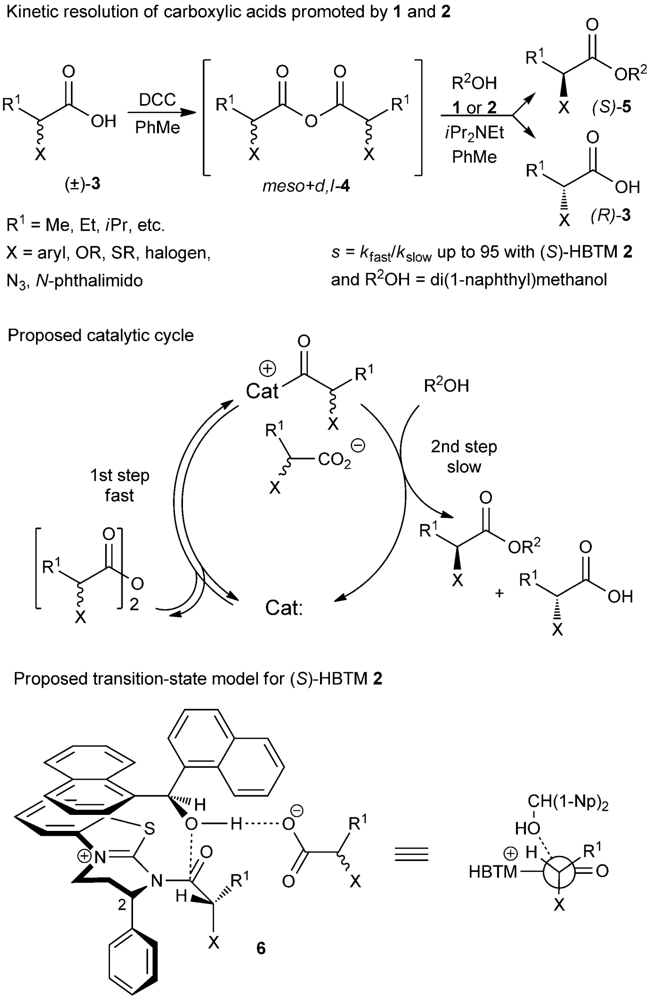
(R)-BTM **1** (S)-HBTM **2**

Scheme 3. Amidine-based catalysts used in this study.

tramisole (BTM) **1**[6d] is effective in promoting kinetic resolution (KR)[9] of α-arylpropionic acids. Subsequently, we demonstrated that a variety of heteroatom-substituted carboxylic acids can be resolved with homobenzotetramisole (HBTM) **2**[6h] using the protocol illustrated in Scheme 4.[4a,c,d] BTM **1** was also competent in most cases studied, albeit usually less active and enantioselective.[10]

Our long-standing interest in elucidating the origin of enantioselectivity in ABC-promoted acylations[4f,6i] prompted us to speculate on the mechanism of this new asymmetric transformation. In both Shiina's and our studies, the enantioselectivity was strongly dependent on the alcohol used, di(1-naphthyl)methanol being optimal and diphenylmethanol second best. This fact was in agreement with a) the importance of π-interactions in the transition state, analogous to the previously studied KR of secondary benzylic and other alcohols promoted by ABCs,[6i] b) the enantiodiscrimination occurring in the second step of the catalytic cycle following the diastereoselectivity mode indicated by Equation (4b) (Scheme 2) and c) the reaction being under Curtin–Hammett control,[11] that is, the enantioselectivity of the first step, if any, would be unimportant because of its reversible nature. These observations, although informative, were not by themselves sufficient to understand precisely how the enantiodiscrimination took place. Finally, we noted that in all cases illustrated in Scheme 4, the absolute sense of enantioselection remained the same regardless of the relative size of groups R^1 and X. This observation provided the key piece of the puzzle: it indicated that the enantiodiscrimination was governed by the electronic, rather than steric, properties of the α-substituents. Thus, we proposed transition state model **6**, wherein the alcohol nucleophile approached the acyl carbonyl from the face opposite to the electron-withdrawing substituent, in close analogy to the classical stereoelectronic Felkin–Anh model. To probe the validity of this hypothesis, we initiated the computational study described below.[12]

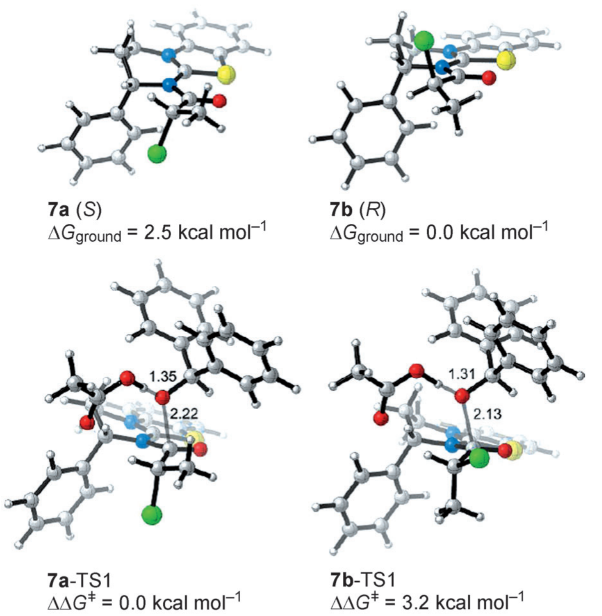
Kinetic resolution of carboxylic acids promoted by **1** and **2**



R^1 = Me, Et, *i*Pr, etc.
X = aryl, OR, SR, halogen, N_3, *N*-phthalimido

$s = k_{fast}/k_{slow}$ up to 95 with (S)-HBTM **2** and R^2OH = di(1-naphthyl)methanol

Scheme 4. Kinetic resolution of α-substituted alkanoic acids.



7a (S) ΔG_{ground} = 2.5 kcal mol^{-1}

7b (R) ΔG_{ground} = 0.0 kcal mol^{-1}

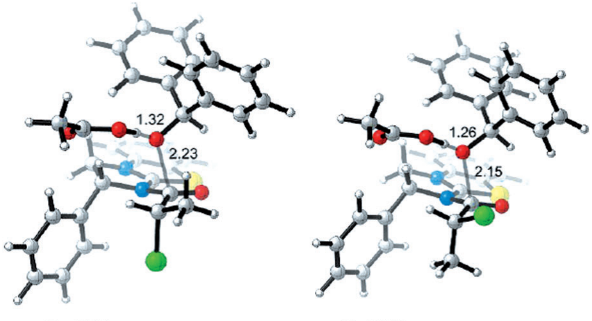
7a-TS1 $\Delta\Delta G^{\ddagger}$ = 0.0 kcal mol^{-1}

7b-TS1 $\Delta\Delta G^{\ddagger}$ = 3.2 kcal mol^{-1}

Figure 1. (S)- and (R)-2-chloropropionyl-(S)-HBTM cations (**7a** and **7b**, respectively) and the corresponding transition states with diphenylmethanol. Distances are in Å.

We began by comparing the two diastereomeric *N*-α-chloropropionyl-(*S*)-HBTM cations **7a** and **7b** (Figure 1).[13] Their geometries optimized at the B3LYP/6-31G(d) level of theory[14] using the SMD solvation model[15] in toluene demonstrate that the conformation of the acyl group in both cases is governed by stereoelectronic effects placing the carbon-chlorine bond almost perpendicularly to the carbonyl (about 98° dihedral angle). It is noteworthy that **7b**, corresponding to the slow-reacting enantiomer of the substrate, is thermodynamically favored over **7a** by 2.5 kcal mol^{-1}, which is consistent with the Curtin–Hammett control of enantioselectivity.

With these data in hand, we proceeded to analyze the transition states (TSs) corresponding to the two diastereomeric cations.[16] To minimize the calculation times, we replaced the chloropropionate counterion with acetate anion and di(1-naphthyl)methanol with diphenylmethanol. All accessible orientations of the three components were then subjected to geometry optimization. Structures **7a**-TS1 and **7b**-TS1 were finally identified as the most stable conformers for each respective diastereomer TS.[17] In both transition states, the hydrogen on the α-carbon atom points towards the bulky catalyst moiety so as to minimize steric repulsion. In transition state **7a**-TS1, the alcohol can be seen to approach the carbonyl from the unhindered β-face and at a 169° dihedral angle with respect to the C–Cl bond. In its diastereomer, however, the analogous Felkin–Anh geometry cannot be realized, because it would require the alcohol to approach from the α-face and overcome the severe repulsive interactions with the C2-phenyl group on the catalyst. Thus, in the latter case, the alcohol is forced to adopt the "anti-Felkin–Anh" trajectory and attack the carbonyl antiperiplanar to the methyl group (172° dihedral angle). M06-2X[18] single-point calculations indicated that **7a**-TS1 is favored over **7b**-TS1 by 3.2 kcal mol^{-1}, which is consistent with our experimental observation that the (*S*)-enantiomer of α-chloropropionic acid reacts faster than the (*R*)-enantiomer in the presence of (*S*)-HBTM. In a similar manner, we examined the two analogous diastereomeric transition states **8a**-TS1 and **8b**-TS1 derived from (*R*)-BTM (Figure 2) and obtained almost the same results, which is in accord with essentially the same enantioselectivities obtained with BTM and HBTM in the KR of α-chloropropionic acid (selectivity factors 23 and 21, respectively, were obtained using di(1-naphthyl)methanol).[4d,19]



8a-TS1
$\Delta\Delta G^{\ddagger} = 0.0$ kcal mol^{-1}

8b-TS1
$\Delta\Delta G^{\ddagger} = 3.4$ kcal mol^{-1}

Figure 2. Transition states derived from (*R*)- and (*S*)-2-chloropropionyl-(*R*)-BTM cations (**8a** and **8b**) with diphenylmethanol. Distances are in Å.

Not surprisingly, the transition states derived from HBTM (**7a**-TS1 and **7b**-TS1) and BTM (**8a**-TS1 and **8b**-TS1) look qualitatively similar. The C–Cl bond is somewhat elongated in the fast-reacting **7a**-TS1 and **8a**-TS1, compared to their respective diastereomers (1.86 Å for **7a**-TS1 vs. 1.82 Å for **7b**-TS1; 1.86 Å for **8a**-TS1 vs. 1.81 Å for **8b**-TS1), which is indicative of interactions between the σ* orbitals and the incoming nucleophile. Frequency analysis and intrinsic reaction coordinate (IRC) calculations indicate that the nucleophilic attack of the alcohol hydroxyl radical on the carbonyl group and the deprotonation of the former by the acetate proceed in a concerted fashion. In the transition state, the migrating proton is closer to the acetate (1.1 Å) than to the alcohol oxygen (1.3 Å). Other, less significant, interactions are suggested by the relatively short distances between the acetate anion and the hydrogen at C2 of both catalysts (2.1–2.2 Å), between the oxygen of the acyl carbonyl group and the α-hydrogen atom of diphenylmethanol (2.3–2.4 Å), and between the acetate and the α-proton of the acyl group (ca. 2.3 Å, observed only in **7a**-TS1 and **7b**-TS1). These interactions are similar in both diastereomeric transition states, and thus do not affect the energy differences between these TSs.

By analogy with our previous computational studies on the KR of benzylic alcohols,[6i] we expected to see evidence of significant cation–π interactions between the *N*-acylated catalysts and one of the phenyl groups of the alcohol. However, in each of the cases shown above, the benzothiazolium cation and the benzene ring are 4.1–4.2 Å apart (as measured between the closest atoms) and far from being parallel, which suggests weaker π-interactions in the present case, compared to the aforementioned study (3.74 Å distance, 8° dihedral angle between the analogous moieties).[6i]

It was also of interest to see whether our calculations would confirm the experimentally observed dependence of the enantioselectivity on the alcohol used. Replacing diphenylmethanol with benzyl alcohol in transition states **7a**-TS1 and **7b**-TS1 and re-optimization of the geometry resulted in a slightly decreased activation free energy difference ($\Delta\Delta G^{\ddagger}$; 3.0 vs. 3.2 kcal mol^{-1}), in accord with the lower enantioselectivities obtained using the less bulky alcohol. Analogous calculations using di(1-naphthyl)methanol produced a larger free energy difference (4.4 kcal mol^{-1}), which is consistent with its superior performance in kinetic resolution.[4d,20]

Having examined the simplest substrate in sufficient detail, we proceeded to investigate the effects of other electron-withdrawing and polarizable substituents (using diphenylmethanol to minimize the computational time). The differences of activation free energies ($\Delta\Delta G^{\ddagger}$) and the C–X bond lengths in both diastereomeric transition states are summarized in Table 1. As expected, considerable qualitative resemblance was observed in the geometries of all cases studied. Some correlation was noted between the calculated $\Delta\Delta G^{\ddagger}$ values and the experimentally observed structure–enantioselectivity trends: OMe > *N*-phthalimide ≈ Ph > SMe ≈ Cl ≈ N_3. Elongation of the C–X bond in the Felkin–Anh transition state by 0.01–0.04 Å was observed in every case.

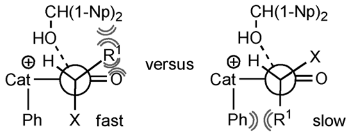
Finally, we examined the origin of an additional general trend we had observed in our KR experiments: increasing the size of the R^1 group on the α-carbon atom resulted in progressively lower enantioselectivities.[4d,21] It was difficult to predict a priori whether the fast- or the slow-reacting diastereomer of the transition state would suffer greater

Table 1: Comparison of stereoelectronic effects of different α-substituents in the transition state.

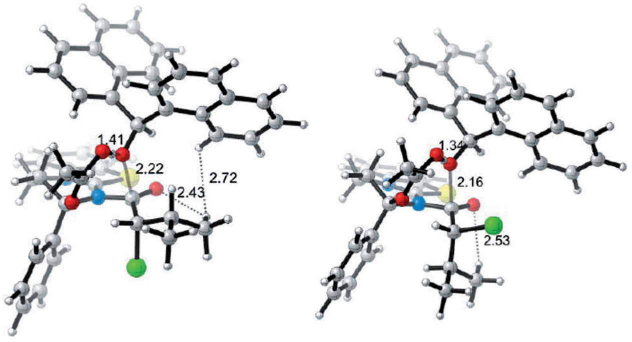
Entry	X	$\Delta\Delta G^{\ddagger}$ [kcal mol^{-1}]	*s*	C−X bond length [Å]	
				fast	slow
1	$-$OMe	5.3	96[a]	1.43	1.42
2	$-$NPht[c]	3.6	35[a]	1.48	1.46
3	$-$Ph	3.5	33[a]	1.53	1.52
4	$-$SMe	3.9	21[b]	1.87	1.85
5	$-$Cl	3.2	21[a]	1.86	1.82
6	$-N_3$	2.6	21[a]	1.50	1.48

[a] Selectivity factor *s*[19] obtained under standard KR conditions using di(1-naphthyl)methanol [b] Selectivity factor estimated from 91% *ee* obtained with the SPh analogue under similar KR conditions. [c] NPht = *N*-phthalimido.

destabilization by a bulkier R^1 group. On the one hand, in the former, there would be increased repulsion between the R^1 group and the carbonyl oxygen and/or the bulky alcohol. On the other hand, the phenyl group on the catalyst might also be repelled by the R^1 group (Scheme 5). Which of these two conflicting factors predominates? To answer this question, we replaced the methyl groups in the diastereomeric transition states **7a**-TS3 and **7b**-TS3 with isopropyl groups (Figure 3).



Scheme 5. Steric repulsions in the fast- and the slow-reacting diastereomeric transition states.



9a-TS3
$\Delta\Delta G^{\ddagger}$ = 0.0 kcal mol^{-1}

9b-TS3
$\Delta\Delta G^{\ddagger}$ = 2.5 kcal mol^{-1}

Figure 3. Transition states derived from (*S*)- and (*R*)-2-chloroisovaleryl-(*S*)-HBTM cations **9a** and **9b** with di(1-naphthyl)methanol. Distances are in Å.

The free energy difference decreased from 4.4 to 2.5 kcal mol^{-1}, which is in a qualitative agreement with the experimental data.[4d]

In summary, these calculations show that the stereoelectronic effects of α-substituents play a key role in determining the enantioselectivity of ABC-promoted alcoholysis of acyclic chiral acyl donors. This study provides theoretical support for our proposed transition-state model and, more generally, demonstrates that the Felkin–Anh line of reasoning is applicable to the analysis of diastereoselectivity in acyl substitution reactions. Although so far we have focused on only one type of such transformations [see Eq. (4b) in Scheme 2], we believe that our conclusions can be extrapolated to the other three types as well and thus will help elucidate their mechanisms of asymmetric induction.

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Keywords: asymmetric organocatalysis · enantioselective alcoholysis · Felkin–Anh Model · kinetic resolution · stereoelectronic control

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[12] Prior to our study, Shiina et al.[8b] performed calculations on the transition states derived from α-phenylpropionic acid and (*R*)-BTM. The results, however, were interpreted in terms of steric interactions, rather than stereoelectronic effects.

[13] All calculations in this study were performed with Gaussian 09 (Revision B.01, M. J. Frisch, et al., Gaussian, Inc., Wallingford CT, **2010**). The geometries of all intermediates and transition states were optimized with B3LYP/6-31G(d)[14] with the SMD solvation model[15] in toluene. Single-point energies were calculated with M06-2X/6-311++G(d,p)[18] in toluene. M06-2X is expected to perform better than B3LYP for the non-covalent dispersion interactions in the transition states. Our test calculations indicated that employing M06-2X/6-31G(d) instead of B3LYP for the geometry optimization of **7a**-TS1 and **7b**-TS1 gave similar selectivities. See the Supporting Information for details.

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[16] Intrinsic reaction coordinate (IRC) calculations performed on a simplified model (with *N*-acetyl-HBTM cation) indicate that the nucleophilic acyl substitution proceeds in a concerted fashion through an early transition state. See the Supporting Information for more details.

[17] The Cornforth–Evans[3e,5f] conformer of **7a**-TS1 was found to be 7.1 kcal mol^{-1} higher in energy than the one shown in Figure 1. See the Supporting Information for more details.

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[19] Selectivity factor is defined as the ratio of reaction rates of the fast- and the slow-reacting enantiomers of the substrate.[9a]

[20] Benzyl alcohol, diphenylmethanol, and di(1-naphthylmethanol) produced selectivity factors 5.2, 9.3, and 33, respectively, in the HBTM-catalyzed KR of 2-phenylpropionic acid.[4a,d] See the Supporting Information for the transition state structures with benzyl alcohol and di(1-naphthylmethanol).

[21] For example, HBTM-catalyzed KR of 2-chloropropionic, 2-chlorobutyric, and 2-bromoisovaleric acids were resolved with selectivity factors 21, 12, and 9.3, respectively.[4d]