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A Journal of
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Accepted Article

Title: Investigation of electrostatic interactions towards controlling silylation-based kinetic resolutions

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900754

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900754

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Investigation of electrostatic interactions towards controlling silylation-based kinetic resolutions

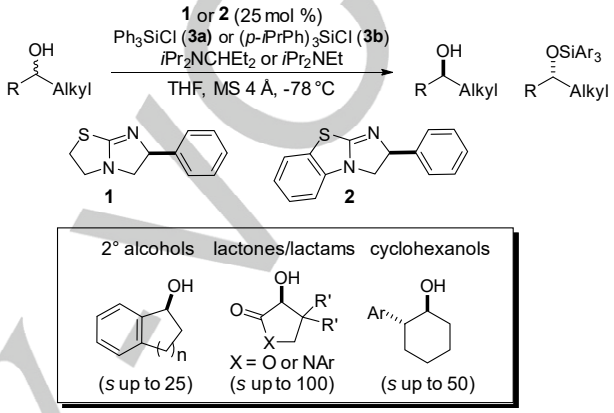
Tian Zhang,[a] Brandon Redden,[a] and Sheryl L. Wiskur*[a]

Abstract: Electrostatic interactions between a silylated isothiourea intermediate and an ester π system were explored by determining how variations in sterics and electronics affect the selectivity of a silylation-based kinetic resolution. Sterics on the π systems affect the selectivity factors of alkyl 2-hydroxycyclohexanecarboxylates, resulting in a strong correlation of selectivity factors to Charton values. Induction effects of electron withdrawing substituents on phenyl esters significantly enhance selectivity supporting an edge to face π-π interaction. The linear free energy relationships that were uncovered will aid in future incorporation of intermolecular electrostatic interactions towards controlling asymmetric reactions.

Introduction

Intermolecular interactions such as hydrogen bonding, π-π stacking, and ionic forces have been shown to play a large role in controlling the selectivity and reactivity of organocatalyzed reactions, in many cases working cooperatively to obtain a favorable outcome.[1] Electrostatic interactions such as π-π interactions and cation-π interactions[2] have been shown to aid in controlling the selectivity of asymmetric reactions through an electrostatic interaction between a substrate and a catalyst.[3] We have theorized that these type of electrostatic interactions are also controlling the selectivity of our silylation-based kinetic resolutions, given that our substrates need to have a π system within the structure to obtain any selectivity.[4] While exploring the kinetic resolution of trans 2-hydroxy cyclohexane carboxylate esters with isothiourea catalysts, linear free energy relationships were observed that correlates selectivity with both the size of the ester substituent and the electronics of the aryl group on the ester, indicating sterics and electronics affect the strength of this interaction. While we originally hypothesized that a cation- π interaction was the dominating factor, electronics suggest that a π-π type interaction is more likely the controlling factor. Herein, we highlight the selectivity observed with variations in this substrate class, and how sterics and electronics on the ester affect a potential electrostatic interaction with the π system.

Acylation-based kinetic resolutions have dominated the way secondary alcohols are resolved over the last 20 years,[5] but recently silylation-based kinetic resolutions have emerged as a competitive alternative with increasing diversity in the types of alcohols that can be resolved.[6] We have successfully resolved cyclic alcohols,[7] β-hydroxy lactones and lactams,[8] and 2-aryl cyclohexanols[4] with synthetically useful levels of selectivity (Scheme 1). Our method employs an isothiourea catalyst (**1** or **2**)[9] and a triarylsilyl chloride (**3a** or **3b**) to obtain efficient separation of the alcohol enantiomers.



Scheme 1. Previous silylation-based kinetic resolutions performed by our group.

In order to obtain selectivity in our silylation methodology, the substrates need to have a π system within the structure. For example, by changing the substituent on 2-substituted cyclohexanols from a phenyl ring into a cyclohexane ring, the selectivity factor drops from 10 to 2.[4] We hypothesize that an electrostatic cation-π or π-π interaction between the silylated cationic catalyst intermediate and the π-system of the substrate help to control the orientation of the two, which aids in controlling selectivity. These interactions are defined as electrostatic, non-covalent interactions between either a cation and a π system or two π systems, and the attractive force for the stronger cation- π interaction is comparable in strength to a hydrogen bond.[10] The attractive interaction forms between an electron deficient structure and the negatively charged surface of a π system, frequently an aromatic group. However, it can also be as simple as an alkene or acyl group. It has been suggested that this interaction aids in controlling selectivity in other asymmetric reactions,[3] including work by Birman using the same isothiourea catalysts for acylation-based kinetic resolutions.[11] In order to obtain a more thorough understanding how sterics and electronics of the π system affect this interaction, we began to explore trans 2-ester substituted cyclohexanols. The ester group provides the needed electronics, and it can be easily derivatized to alter the electronics and sterics of the π-system.

Results and Discussion

Optimized reaction conditions for the kinetic resolution were determined using trans-ethyl 2-hydroxycyclohexanecarboxylate (**(±)-4**) as the substrate. The results are shown in Table 1. Chiral

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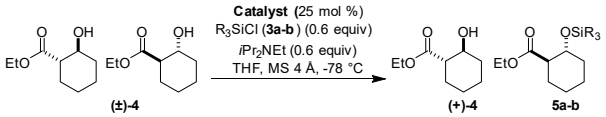
catalysts are employed to activate a silyl chloride to preferentially silylate one alcohol enantiomer over the other, generating silyl ethers **5a-b** and recovering enantiomerically enriched alcohol **(+)-4**. Similar to our previous work, the catalyst with the fused aromatic ring, benzotetramisole (**2**),[11] gave higher selectivity than the less conjugated version (tetramisole, **1**) (Table 1, Entry 1 vs 2, Entry 3 vs. 4). In a previous study, we noted that three phenyl groups on the silyl chloride is needed in order to obtain useful levels of selectivity,[7] and electron-donating isopropyl groups in the para position also resulted in improved selectivity.[13] These factors are also important in obtaining good selectivity with this substrate. When tris(4-isopropylphenyl)silyl chloride (**3b**) was utilized, selectivity increased versus employing the unsubstituted triphenylsilyl chloride (**3a**) (entry 2 versus 4). Electron donating groups on the silyl group are hypothesized to stabilize the reactive silicon/catalyst intermediate.[13]

Table 1. Optimization of reaction conditions for resolution of trans-ethyl 2-hydroxycyclohexanecarboxylate.

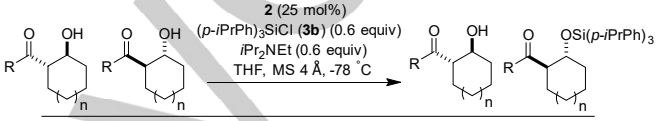


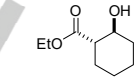
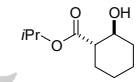
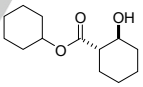
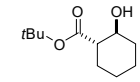
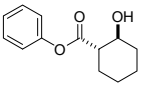
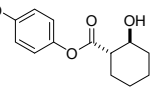
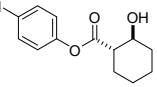
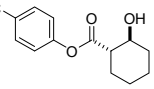
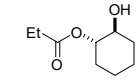
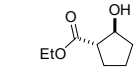
Entry[b]	catalyst	R	*t* (h)	conv (%)[a]	*s*[a]
1	**1**	Ph (**a**)	24	47	3
2	**2**	Ph (**a**)	24	44	11
3[c]	**1**	*p*-*i*Pr-Ph (**b**)	48	18	3
4	**2**	*p*-*i*Pr-Ph (**b**)	48	36	14

[a] Conversions and selectivity factors are based on the *ee* of the recovered starting materials and products. See ref [12]. [b] Selectivity factors are an average of two runs. Conversions are from a single run. [c] Conversion and selectivity factor is based on the *ee* of the recovered starting material and ^{1}H NMR conversion.

With the optimized reaction conditions obtained, the effect of altering the sterics on the ester group was explored (Table 2). When the ethyl group of trans ethyl 2-hydroxycyclohexanecarboxylate (**4**) was changed to an isopropyl group, a decrease in the selectivity factor was observed (from *s* = 14 to 10) presumably from an increase in steric hindrance of the ester (Table 2, entry 2). In order to provide evidence that sterics on the ester correlate to the selectivity factor, two more 2-ester cyclohexanol derivatives were synthesized through the esterification of 2-hydroxycyclohexanecarboxylate and tested under the optimized conditions. As predicted, substrates with cyclohexyl and *t*-butyl groups also followed the same trend of decreasing selectivity as the alkyl group on the ester increased in size (Table 2, entry 3 and 4). The sensitivity of these selectivity factors (Table 2, entries 1-4) to steric hindrance was then investigated using Charton (υ) values in a linear free energy relationship[14] to establish if there is a correlation between the steric effect and selectivity. Charton values are substituent parameters that use the van der Waals radius of the substituent to study sterics.[15] The log of the selectivity factors for the different substrates were plotted against the Charton values associated with each alkyl group (Figure 1). Indeed, there is a strong linear correlation between the steric effect near the π-system and the selectivity factors (Ψ = -0.7), showing that as sterics increase selectivity decreases. The sterics obviously have a negative impact regarding how the substrate and the reactive intermediate organize in the transition state to obtain selectivity. The sterics also play a negative effect on reactivity, with the conversion of the reaction decreasing as sterics increase. In fact, the *t*-butyl substrate has very little conversion over a 24-hour period (Table 2, entry 4).

Table 2. Substrate scope of the silylation-based kinetic resolution of trans-alkyl-2-hydroxycyclohexanecarboxylate.



entry[b]	recovered alcohol	er of recovered alcohol	conv (%)[a]	*s*[a]
1		72:28	36	14
2		55:45	35	10
3		66:34	30	8.4
4[c]		52:48	6	4.7
5[c]		64:36	41	3
6[c]		58:42	20	4.4
7[c]		82.5:17.5	43	27
8[c]		69:31	29	34
9		60:40	38	3
10		61:39	45	2.7

[a] Conversions and selectivity factors are based on the *ee* of the recovered starting materials and products. See ref [12]. Selectivity factors are an average of two runs. Conversions are from a single run. [b] Reactions were run for 48 h at a concentration of 0.42 M with respect to alcohol on a 0.4 mmol

scale. [c] Conversion and selectivity factor is based on the *ee* of the recovered starting material and ^{1}H NMR conversion.

In order to modulate the electronics of the ester with the intention of altering the strength of the electrostatic interaction controlling selectivity, phenyl esters were synthesized with either a hydrogen or an electron withdrawing group in the para position on the phenyl ring (Table 2, Entries 5-8). It is known that the phenyl group on a phenyl ester is not in resonance with the ester group, but is rotated such that the plane of the phenyl group is perpendicular to the plane of the *s*-trans ester.[16] Since Neuvonen and coworkers have shown that electron donating and withdrawing substitutents on these phenyl groups affect the polarity of the carbonyl,[17] we hypothesized that the selectivity of the kinetic resolution would be affected also with different substituents. When just a phenyl group was employed, the selectivity was pretty low (Table 2, Entry 5). By adding a methoxy group, which is electron donating in Neuvonen's work, the selectivity slightly increased to *s* = 4.4 (Table 2, Entry 6), therefore weakly enhancing the electrostatic interaction. When the para position was substituted with strong electron withdrawing groups such as a chloro or a trifluoromethyl group, the selectivity significantly increased to *s* = 27 and 34 respectively (Table 2, Entries 7 and 8). While stronger electron withdrawing groups increase the electron density on the carbonyl carbon which would help promote a cation- π interaction, electron donating groups decrease the electron density on the carbonyl which would ultimately decrease the strength of the interaction with the cationic catalyst which does not support the methoxy data.

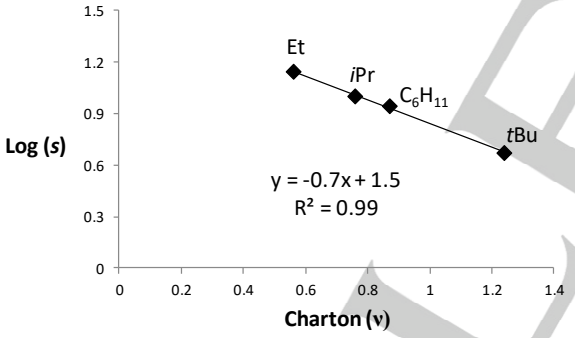


Figure 1. Linear free energy relationship employing Charton values versus selectivity for the sterics of the ester substituent.

A linear free energy relationship (LFER) was found for the four substrates when sigma meta (σ^m) substituent parameters[18] were plotted against the log of the selectivity factor showing that as electron withdrawing groups become stronger selectivity increased, resulting in a significant sensitivity constant (ρ) of 2.6 (Figure 2). Methoxy is an electron withdrawing group when employing sigma meta, which is consistent with the increase in selectivity over just phenyl. Edge to face π-π interactions are enhanced when one π system is electron deficient,[19] suggesting that the selectivity defining interaction for the phenyl esters is a π interaction with one of the aryl groups on the catalyst or silicon.

In order to provide more evidence that the substituents are contributing to the interaction through induction, not resonance the Swain-Lupton dual parameter approach was used to determine the percent contribution of each effect, by using substituent constants for both field effects and resonance.[20] The log of the selectivity factor is set equal to the sum of the substituent constants for field effects (F) and resonance (R), with sensitivity factors for each (*f* and *r* respectively) (Eq. 1). Using a least-squares regression analysis, the experimental data is plotted against the predicted data and the sensitivity factors are solved for, ultimately looking for a slope of one. As expected, the sensitivity factor for field effects was about 2.5 times higher than the sensitivity constant for resonance, indicating that the field effects contribute more significantly towards controlling selectivity (Figure 3).

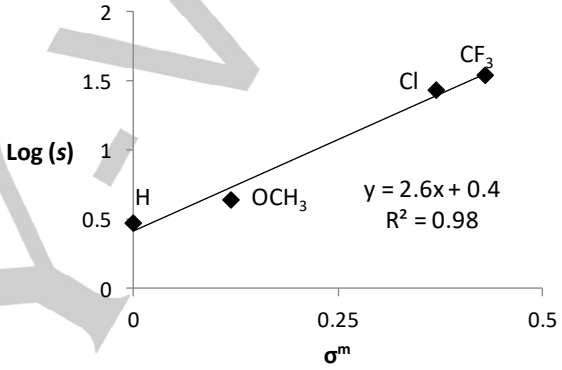


Figure 2. Linear free energy relationship employing σ^m versus selectivity for the induction of the ester substituent.

$$\log(s) = fF + rR \qquad \text{Eq. 1}$$

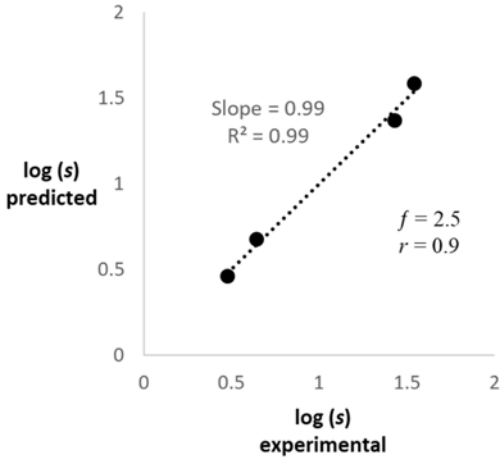


Figure 3. Comparison of the experimental log(s) using the selectivity factors from Table 1 (entries 5-7) versus predicted log(s) calculated from Eq. 1.

The last two entries in table 2 highlight the importance of ring size and positioning of the π system. A six membered ring is needed in order to obtain selectivity, as seen in entry 10 (vs. entry 1) where the selectivity factor dropped to 2 when a cyclopentanol substrate was employed. When the orientation of the ester on the cyclohexanol was reversed, the selectivity of the reaction was very low (entry 9, *s* = 3). We hypothesize that the intramolecular hydrogen bonding between the ester carbonyl and hydroxyl group of **4** forms a stable six-membered ring which aids in controlling selectivity, by favoring a chair conformation with both the hydroxyl and ester group in an equatorial position and prevents free rotation of the ester. When the orientation of the ester is switched in entry 9, the intramolecular hydrogen bond forms a less energetically favorable seven membered ring, weakening that interaction (Figure 4). Ultimately, the π system is moved further from the reacting alcohol, and the ester is more likely to be freely rotating. This prevents optimal electrostatic interactions, reducing the selectivity of the kinetic resolution.

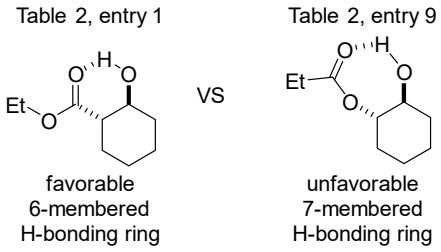


Figure 4. Comparison between 6- and 7-membered rings formed from intramolecular hydrogen bonding.

Conclusions

In conclusion, we have investigated potential electrostatic interactions between the proposed, reactive catalytic species and trans 2-ester substituted cyclohexanols by varying sterics and electronics on the ester π system. The electrostatic attraction helps align the substrate to the catalyst in an orientation that allows for increased selectivity. An increase in sterics adjacent to the π-system affects the ability to orient favorably, resulting in a decrease in selectivity which correlates well with Charton substituent constants. Substituting the ester with aryl groups affects the selectivity, mainly through field effects deduced from a Swain-Lupton analysis. The data suggests that an edge to face π-π interaction is dominating given that electron withdrawing groups dramatically increase the selectivity of the reaction. Finally, the ability of the hydroxyl group to form a favorable hydrogen bond to the carbonyl of the ester (6- vs 7-membered rings) is an aspect that promotes an increase in selectivity. Future work will focus on computational modeling of these and similar systems, and looking at other systems to see if similar trends are followed.

Experimental Section

General procedure for the kinetic resolution of trans-alkyl-2-hydroxycyclohexanecarboxylate To an oven dried 1-dram vial with an oven dried Teflon coated stir bar and activated 4Å molecular sieves, the racemic alcohol substrate (0.4 mmol) and catalyst (0.1 mmol) were added. The vial was then purged with argon and sealed with a septa. The N, N-diisopropylethylamine (0.24 mmol) was added via syringe and the resulting mixture was dissolved in THF (0.55 mL) to make a 0.72 M concentration solution with respect to the alcohol. The vial was then cooled to -78 ºC for 30 mins. The cooled mixture was then treated with a 0.65 M solution of silyl chloride in THF (0.4 ml, 0.26 mmol) and was left to react for 48 h at -78 ºC. The resulting solution was 0.42 M with respect to the alcohol. After 48 hours, the reaction was quenched with 0.3 ml of methanol. The solution was allowed to warm to room temperature and the crude contents were diluted with diethyl ether and transferred to a 4-dram vial. Solvent was removed by rotary evaporator and the crude mixture was purified via silica gel chromatography (5% EtOAc in hexanes increasing to 10% and 25% EtOAc in hexanes). The silylated alcohol was concentrated and saved for analysis and the unreacted alcohol could either be analyzed directly by HPLC or be converted to the benzoate ester for HPLC analysis.

Acknowledgments

Support from the University of South Carolina and the Office of the Vice President for Research Aspire Awards is gratefully acknowledged.

Keywords: kinetic resolutions • linear free energy relationship • noncovalent interactions • cation-pi interactions

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[12] Conversions and selectivity factors are based on the *ee* of the recovered starting materials and products. Percent conversion = $ee_s/(ee_s + ee_p) \times 100\%$ and $s = \ln[(1 - C)(1 - ee_s)]/\ln[(1 - C)(1 + ee_s)]$, where ee_s = *ee* of recovered starting material and ee_p = *ee* of product. See ref H. B. Kagan, J. C. Fiaud In *Topics in Stereochemistry* (Ed.: L. Ernest, S. H. Wilen), John Wiley and Sons: New York, 1988; Vol. 18, p 249.

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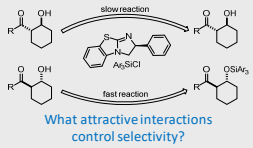
COMMUNICATION



The intermolecular interactions that aid in controlling asymmetric reactions are investigated. Alterations in the electronics and sterics of a π system are studied to understand the effect on selectivity that results from electrostatic interactions between the catalyst and the substrate.

*physical organic interactions

Electrostatic Control*

*Tian Zhang, Brandon Redden, Sheryl L. Wiskur**

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Investigation of electrostatic interactions towards controlling silylation-based kinetic resolutions