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Kinetic Analysis of the HBTM-Catalyzed Esterification of an Enantiopure Secondary Alcohol

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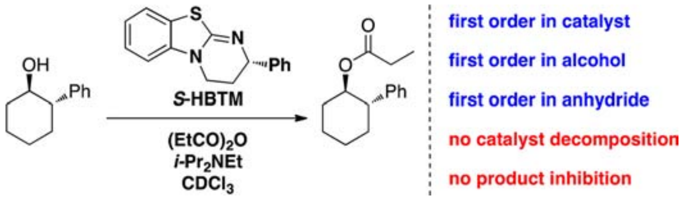
ABSTRACT



A detailed kinetic analysis of the homobenzotetramisole-mediated esterification of the enantiopure secondary alcohol (1*R*,2*S*)-2-phenylcyclohexanol is presented. The results of this analysis show that the reaction is first order in the homobenzotetramisole catalyst, first order in (1*R*,2*S*)-2-phenylcyclohexanol, and first order in propionic anhydride. Initial rates, the turnover frequency of the catalyst, and "different excess" plots were utilized in this evaluation. Additionally, a "same excess" plot revealed no noticeable catalyst decomposition or product inhibition during the course of the reaction.

Kinetic resolutions have become an important part of the synthetic chemist's toolbox for preparing enantiopure compounds. Chiral acylation catalysts, in particular, are attractive because of their high enantioselectivity and the simple conditions used for the resolution of chiral building blocks.[1] Homobenzotetramisole (HBTM) is a chiral amidine-based catalyst utilized for enantioselective acyl transfer that was first reported by Birman.[2,3] Since the initial report, this catalyst and subsequent analogues have been used for a variety of kinetic resolutions of different functional groups by multiple research laboratories.[4] The wide interest in these catalysts and questions about their broader application stimulated our interest in their reactivity. Herein we report the first full kinetic analysis of an enantiopure acylation catalyst, (*S*)-HBTM, with an enantiopure alcohol.

We recently reported the Competing Enantioselective Conversion (CEC) method for the determination of the absolute configuration of stereogenic centers using the HBTM catalyst.[5,6] The CEC method utilizes each enantiomer of a kinetic resolution reagent (catalytic or stoichiometric) in parallel reactions. The absolute configuration is assigned according to a mnemonic based on the higher conversion between the two reactions. The CEC method has been applied to secondary alcohols,[5] oxazolidinones,[6] lactams,[6] and primary amines.[7] The conversion data are used as a surrogate for the reaction rates for

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[1] France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

[2] Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115.

[3] For a review of amidines, isothioureas, and guanidines as nucleophilic catalysts, see: Taylor, J. E.; Bull, S. D.; Williams, J. M. *J. Chem. Soc. Rev.* **2012**, *41*, 2109.

[4] (a) Zhang, Y.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2525–2529. (b) Yang, X.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2301. (c) Yang, X.; Birman, V. B. *Chem.—Eur. J.* **2011**, *17*, 11296. (d) Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722. (e) Joannesse, C.; Simal, C.; Concellon, C.; Thomson, J. E.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 2900. (f) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 9479. (g) Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914. (h) Belmessieri, D.; Joannesse, C.; Woods, P. A.; MacGregor, C.; Jones, C.; Campbell, C. D.; Johnston, C. P.; Duguet, N.; Concellon, C.; Bragg, R. A.; Smith, A. D. *Org. Biomol. Chem.* **2011**, *9*, 559. (i) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714. (j) Morrill, L. C.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088.

[5] Secondary alcohols: (a) Wagner, A. J.; David, J. G.; Rychnovsky, S. D. *Org. Lett.* **2011**, *13*, 4470. (b) Wagner, A. J.; Rychnovsky, S. D. *J. Org. Chem.* **2013**, *78*, 4594. (c) Wagner, A. J.; Miller, S. M.; Nguyen, S.; Lee, G. Y.; Rychnovsky, S. D.; Link, R. D. *J. Chem. Educ.* **2013** submitted.

[6] Oxazolidinones, lactams, and thiolactams, see: Perry, M. A.; Trinidad, J. V.; Rychnovsky, S. D. *Org. Lett.* **2013**, *15*, 472.

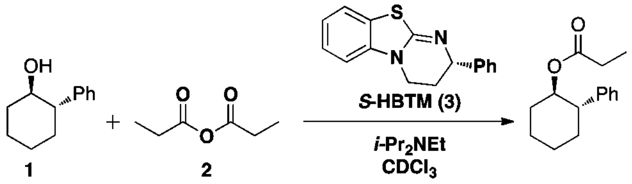
[7] Primary amines: Miller, S. M.; Samame, R. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2012**, *134*, 20318.

10.1021/ol402643n

each catalyst and the optically pure substrate. When the reaction is first order in substrate, the relative rates will match the selectivities (s-values) determined in a kinetic resolution experiment. A clear understanding of the rate law in reactions with these catalysts would validate the assumptions underlying the CEC method.

The archetypical nucleophilic acylation catalyst is 4-dimethylaminopyridine (DMAP).[8] A complete kinetic analysis of an alcohol acylation catalyzed by DMAP was reported in 2005,[9] and a partial kinetic analysis of 4-pyrrolidinopyridine was recently described.[10] Kinetics studies using related catalysts, phosphines[11] and bicyclic guanidines,[12] have also been studied, as well as a preliminary analysis of the parent achiral HBTM system.[13] The goal of the current work was to define the order of the reaction and possible roles of product inhibition and preequilibrium in the HBTM-catalyzed acylation reaction. The (*S*)-HBTM catalyst was studied with the matched enantiopure secondary alcohol (1*R*,2*S*)-2-phenylcyclohexanol (**1**) (Scheme 1).[14]

Scheme 1. *S*-HBTM-Catalyzed Esterification of Alcohol **1**



The initial set of experiments examined the change in reaction rate of alcohol **1** over time with respect to the concentration of *S*-HBTM (**3**) present in the reaction (Figure 1). The reactions were run at 25.0 °C in an NMR tube, and conversion was monitored by ^{1}H NMR spectroscopy. The experiments in Figure 1 show an increase in the rate of the loss of **1** corresponding to an increase in the concentration of catalyst **3** over the four experiments.[15]

A plot of the initial rate of reaction versus the concentration of catalyst **3** shows a linear correlation (Figure 2), indicative of a reaction that is first order in catalyst **3**.

An additional method for verifying the validity of the conclusion that the reaction is first order in catalyst **3** is an analysis of the turnover frequency (TOF, reaction rate/[**3**]) relative to the concentration of **1**.[16] The TOF was plotted for each experiment (Figure 3).[17] The result of the plot is an overlay of points on a line for all four of the experiments, which provides conclusive evidence that the reaction is first order with respect to catalyst **3**.[18]

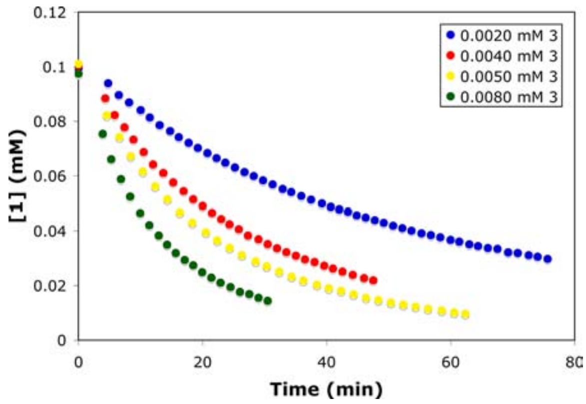


Figure 1. Experiments measuring the concentration of alcohol **1** with respect to time for a series of reactions at varied concentrations of catalyst **3**. Each experiment contained 2.0 mol equiv of anhydride **2** and 2.0 mol equiv of *N*,*N*-diisopropylethylamine relative to the initial amount of **1**.

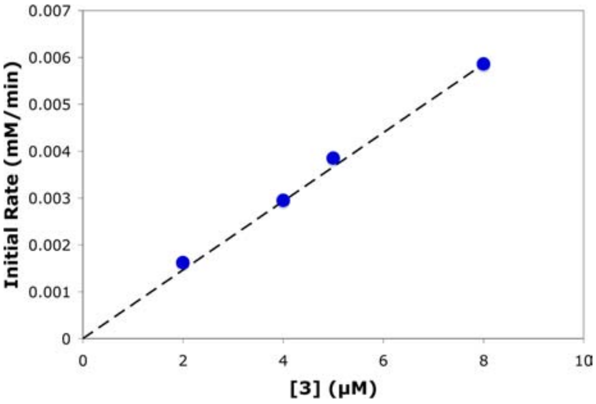


Figure 2. A plot of the correlation between initial rate and concentration of catalyst **3**.

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(8) (a) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436.

(9) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751.

(10) Larionov, E.; Mahesh, M.; Spivey, A. C.; Wei, Y.; Zipse, H. *J. Am. Chem. Soc.* **2012**, *134*, 9390.

(11) Vedejs, E.; Daugulis, O.; Harper, L. A.; MacKay, J. A.; Powell, D. R. *J. Org. Chem.* **2003**, *68*, 5020.

(12) Kiesewetter, M. K.; Scholten, M. D.; Kirn, N.; Weber, R. L.; Hedrick, J. L.; Waymouth, R. M. *J. Org. Chem.* **2009**, *74*, 9490.

(13) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347.

(14) Enantiopure alcohol **1** was previously tested with the CEC method in ref 5a (4 mol% HBTM, 1.3 equiv of **2**, 1.2 equiv of *i*-Pr$_2$NEt, 0.1 M in CDCl$_3$ for 45 min at rt) and was found to have a conversion to the ester product of 53% for (*S*)-HBTM and 6% for (*R*)-HBTM.

(15) Control studies showed no reaction over 60 min without catalyst **3**.

(16) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302.

(17) The aforementioned plot (Figure 3) uses the reaction rate for a specific time point during the course of the reaction. This rate was calculated using the negative slope of a linear regression of the concentration of **1** from three sequential time points, where the slope found for the three time points pertained to the reaction rate of the middle time point.

(18) A two-point analysis was also conducted, and the resulting plot is included in the Supporting Information (SI) for comparison. The sequential two-point analysis also shows an overlay of the resulting data sets from the four reactions.

(19) A plot of the progress of the reaction vs time for different initial concentrations of anhydride **2** is found in Figure SI-1 in the SI.

(20) Mathew, J. S.; Klussmann, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E. A. C.; Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711.

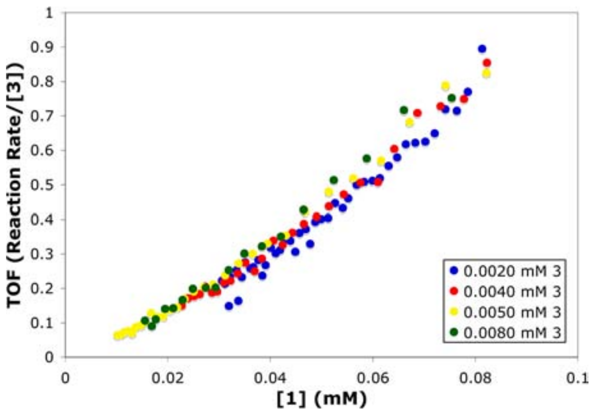


Figure 3. A plot of the turnover frequency (TOF) of catalyst **3** relative to the concentration of alcohol **1**.

The next set of experiments examined the effect of the concentration of anhydride **2** on the rate of the loss of alcohol **1** over time (Figure SI-1).[19] An increase in the concentration of anhydride **2** resulted in an increase in the rate of loss of alcohol **1**. A plot of the correlation between the initial rate and the concentration of **2** revealed a linear relationship, indicating that the reaction is first order in anhydride **2** (Figure 4).

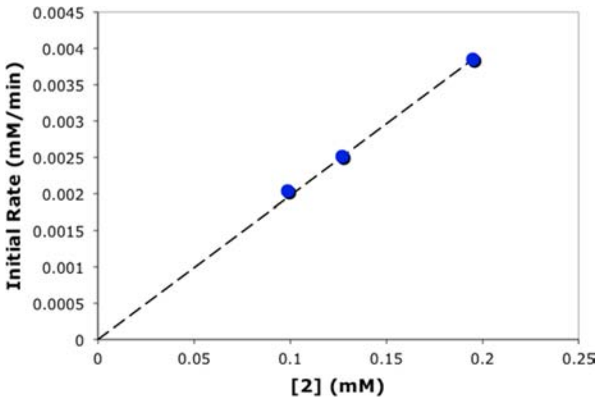


Figure 4. A plot of the correlation between initial rate and concentration of anhydride **2**.

In order to confirm the conclusion of first order in anhydride **2** and to determine the order with respect to alcohol **1**, the data from Figure SI-1 were analyzed in accordance with the "different excess" protocol of Reaction Progress Kinetic Analysis (RPKA) developed by Blackmond.[20] The different excess analysis assumes that every molecule of alcohol **1** uses up one molecule of anhydride **2** in order to make one molecule of ester product. The order of both **1** and **2** can be investigated through this process, with the intent being to find an overlap with a straight line between the different experiments. The desired overlap was only present when the exponents for the concentrations of **1** and **2** were both set to 1, indicating first order in **2** (as previously concluded) and first order in **1** (Figure 5).[17,18]

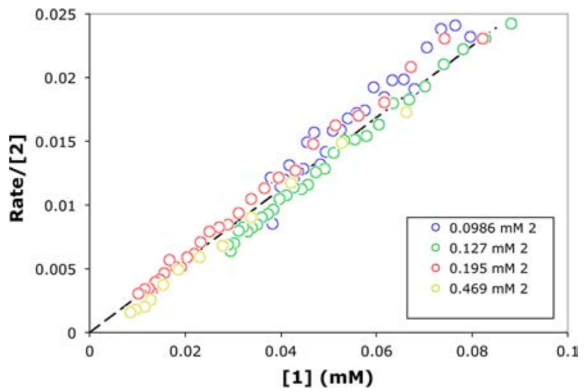
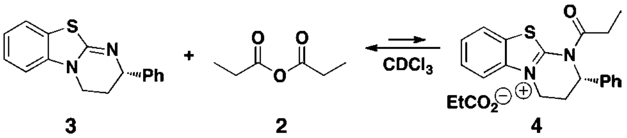


Figure 5. "Different excess" analysis of the experiments from variations in the concentration of anhydride **2** (Figure SI-1).

The finding of first order in **2** was interesting for this system, as we had originally hypothesized this reaction would display a Michaelis–Menten type relationship between anhydride **2** and catalyst **3**. In this scenario, saturation of catalyst **3** would preclude **2** from having an impact on the rate of the reaction in the range of concentrations of **2** that is utilized in this reaction.[21] To investigate this finding, we examined the equilibrium between catalyst **3** and acylated-HBTM intermediate **4** (Scheme 2).

Scheme 2. Equilibrium Reaction between HBTM (**3**), Propionic Anhydride (**2**), and Acylated-HBTM Intermediate **4**



3 **2** **4**

$$K_{eq}\,(25\ °C) = \frac{[4]}{[3][2]} = 0.25 \pm 0.1$$

The equilibrium between catalyst **3**, anhydride **2**, and acylated intermediate **4** was evaluated at six different concentrations in CDCl$_3$ at 25 °C. The calculated equilibrium constant is reported in Scheme 2, along with the equilibrium equation.[22] The acylated intermediate **4** is a tight ion pair and behaves as a single entity in the

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(21) Johnson, K. A.; Goody, R. S. *Biochemistry* **2011**, *50*, 8264.

(22) Details of the equilibrium measurements between **2**, **3**, and **4** are provided in the SI.

(23) Baxter, R. D.; Sale, D.; Engle, K. M.; Yu, J.-Q.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 4600.

(24) The presence of 0.49 mM propionate anion at the halfway point in trial 1 does not inhibit the reaction compared with trial 2 (Figure 7). Apparently the tight ion pair **4** is not directly influenced by the presence of the excess propropionate anion.

equilibrium expression. Under relevant conditions, a doubling of the propionic anhydride concentration results in a doubling of the concentration of the acylated intermediate **4**. These results are consistent with a rapid pre-equilibrium formation of **4** and explains the first-order dependence on anhydride concentration in the kinetics expression.

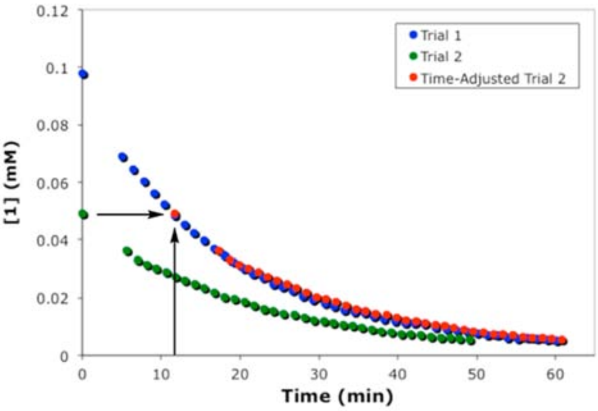
One additional component of the reaction is the consistency of the catalyst rate over the course of the reaction. Using the "same excess" protocol from RPKA, two experiments were conducted that contained the same excess of anhydride **2** relative to alcohol **1** (Figure 6).[23] The difference between the trials is the starting concentration of **1**.

Both experiments were run, and the corresponding data for the loss of **1** with respect to time were collected. After the data were tabulated, a time-adjusted profile for trial 2 was developed. This adjustment places the starting concentration of trial 2 at the same concentration in trial 1 along with the corresponding time that this concentration occurs in trial 1. The main difference between the two trials is that, in trial 1, catalyst **3** has already been utilized for the conversion of half of the material present in the reaction.

The time-adjusted profile for trial 2 overlays with trial 1.[23] This outcome shows that the catalyst operates at the same rate whether it has converted half of alcohol **1** to product (in trial 1) or is just starting to convert material (in trial 2). These experiments demonstrate that the catalyst does not decompose over the course of the reaction. The "same excess" experiments also indicate that the ester product, propionic acid byproduct, and amine byproduct do not alter the rate of reaction through competing side reactions with the catalyst or product inhibition of the catalyst.[24]

As a result of the experiments performed, the following catalytic cycle is proposed (Figure 7). The first step is a rapid and reversible acylation of the catalyst to produce acylated intermediate **4** as a tight ion pair. The second step is a slow addition of the secondary alcohol, resulting in intermediate **5**. The difference in energy between diastereomeric transition states to form intermediate **5** likely determines the selectivity factor in kinetic resolutions with this catalyst. Rapid deprotonation of **5** and subsequent collapse of the tetrahedral intermediate generate the ester product and regenerate catalyst **3**. The amine removes the propionic acid from the reaction. The catalytic cycle is well behaved and does not show product inhibition or any significant side reactions.

In summary, we have presented a kinetic analysis of the HBTM-mediated esterification of enantioenriched secondary alcohol **1**. The analysis reveals that the reaction is first order in alcohol **1**, first order in anhydride **2**, and first order in catalyst **3**. The acyl-HBTM intermediate (**4**) is formed in a rapid pre-equilibrium followed by slow acylation of alcohol **1**. A "same excess" plot showed no noticeable catalyst decomposition or product inhibition. A catalytic cycle has been proposed based on the collective kinetic data reported herein. These experiments validate the assumptions of the CEC method and provide useful information for HBTM kinetic resolutions. Additional kinetic studies will be performed to further our understanding of these enantioselective catalytic reactions.



trial	[**1**]° (mM)	[**2**]° (mM)	[**3**]° (mM)	[**2**]° - [**1**]°
1	0.0979	0.198	0.0050	**0.100**
2	0.0490	0.149	0.0050	**0.100**

Figure 6. "Same excess" plot of the concentration of **1** with respect to time for trials 1 and 2. The initial concentrations of reagents in the two trials are listed above.

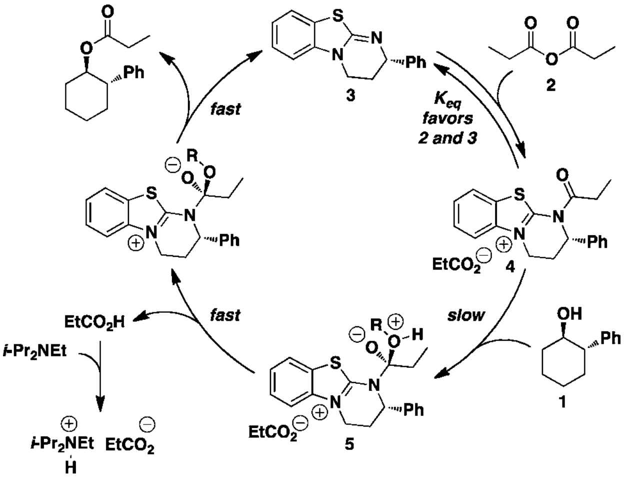


Figure 7. Proposed catalytic cycle for the HBTM-mediated esterification of **1**.

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Supporting Information Available. Experimental procedures for the reactions performed (Figures 1, SI-1, and 6), tables of [**1**] versus time, two-point rate plots (Figures 3 and 5), first-order integrated rate-law plots (for **2** and **3**), and equilibrium experiments (Scheme 2). This material is available free of charge via the Internet at http://pubs.acs.org.
