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Determination of Absolute Configuration Using Kinetic Resolution Catalysts

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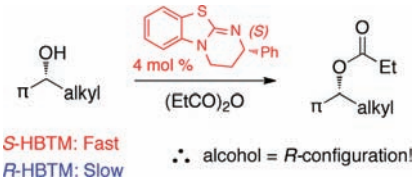
ABSTRACT



A new method was developed to assign the absolute configuration of molecules using kinetic resolution catalysts. Secondary alcohols were acylated in the presence of Birman's *S*-HBTM and *R*-HBTM catalysts, and the fast-reacting catalyst was identified by NMR analysis of the reaction mixture. A mnemonic was developed to assign configuration based on the identity of the fast-reacting catalyst. The method uses only 1−3 mg of alcohol, and it is more convenient than the Mosher method. The kinetic resolution strategy may be extended to other classes of molecules.

Establishing the absolute configuration of a molecule is an important step in the characterization of a natural product or a new synthetic entity,[1] and it is a necessary prerequisite to meaningfully analyzing its interactions with other chiral entities such as enzymes and receptors. The advanced Mosher method is the most widely used strategy for assigning the configuration of a molecule and depends on the derivatization of a secondary alcohol followed by purification and NMR analysis of the resulting esters.[2] The Mosher method is limited to secondary alcohols that are not too sterically hindered and where the ester is stable and isolable. A number of other methods have been developed for absolute configuration assignment including the exciton chirality method[3,4] and Kishi's NMR methods.[5] We describe a new strategy for the assignment of absolute configuration and actualize the strategy as a practical method for the assignment of chiral secondary alcohols.[6]

The crux of the new strategy is to derivatize the optically pure molecule in question with each enantiomer of a chiral catalyst. The relative rates of the two reactions will be measured, and the identity of the fast-reacting catalyst will allow the configuration of the molecule to be assigned based on an empirical correlation with similar molecules. Enzymatic derivatizations have been proposed as a

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(3) For example, see: (a) Zhou, P.; Zhao, N.; Rele, D. N.; Berova, N.; Nakanishi, N. *J. Am. Chem. Soc.* **1993**, *115*, 9313–9314. (b) Mori, Y.; Sawada, T.; Sasaki, N.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 1651–1656.

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(5) (a) Ghosh, I.; Zeng, H.; Kishi, Y. *Org. Lett.* **2004**, *6*, 4715–4718. (b) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Tetrahedron Lett.* **2003**, *44*, 7489–7491. (c) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2002**, *4*, 411–414.

(6) Various kinetic methods have been developed for assigning enantiomeric excess to compounds but not for assigning absolute configuration: (a) Reetz, M. T.; Becker, M. H.; Klein, H.-W.; Stockigt, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1758–1761. (b) Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1755–1758. (c) Korbel, G. A.; Lalic, G.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 361–362. (d) Young, B. L.; Cooks, R. G. *Int. J. Mass Spectrom.* **2007**, *267*, 199–204. (e) Muller, C. A.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3363–3366. (f) Muller, C. A.; Markert, C.; Teichert, A. M.; Pfaltz, A. *Chem. Commun.* **2009**, 1607–1618. (g) Matsumoto, T.; Urano, Y.; Takahashi, Y.; Mori, Y.; Terai, T.; Nagano, T. *J. Org. Chem.* **2011**, *76*, 3616–3625.

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method to assign configuration, but without having both enantiomers of the enzyme available, subtle differences in rate cannot be identified.[7] The method is empirical, as is the Mosher's advanced method,[2] and empirical rules need to be developed for each catalyst system. This strategy is a modern implementation of Horeau's method[8] but one in which the derivatization involves a chiral catalyst rather than a chiral substrate. Horeau's method depends on an analysis of the unreacted 2-phenylbutyric acid, but that strategy cannot work with an achiral anhydride. We have turned the analysis around and instead examine the relative rates of reaction using two different enantiomers of a chiral catalyst.

The tremendous advances in enantioselective catalysis and kinetic resolution in the last decades make the strategy potentially very general.[10] It can be applied to any functional group for which there is a good kinetic resolution catalyst. Our initial focus is on secondary alcohols, which is one of the most widely distributed functional groups in synthetic routes and in natural products. The proof of principle reported below validates the general strategy for other kinetic resolution catalysts.

Many enantioselective acylation catalysts have been reported,[11−13] but Birman's homobenzotetramisole (HBTM) catalysts are of special interest because of their broad substrate scope, generally good selectivity, and relative ease of synthesis.[14] Both enantiomers of the catalyst were prepared, and they were used to catalyze the acylation of a model alcohol **1**. Birman's optimized conditions use low temperatures and solvent mixtures;[14] for convenience, we have focused on room temperature reactions in $CDCl_3$. The initial results are shown in Figure 1, where the reactions catalyzed by 5 mol % of HBTM were monitored by ^{1}H NMR analysis in an NMR tube. The conversion was measured by integration of the protons on the carbon adjacent to the oxygen atom, and the results were evaluated assuming pseudo-first-order conditions.[15]

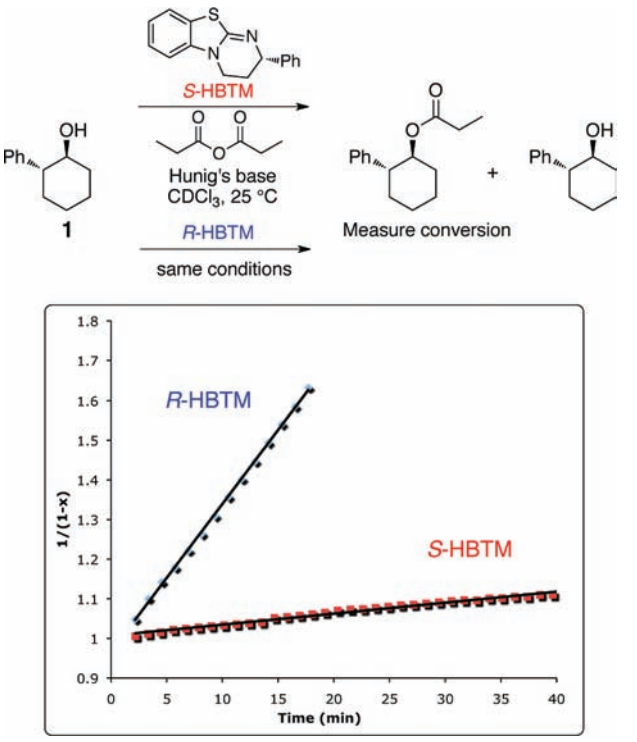


Figure 1. Optically pure alcohol **1** was reacted with propionic anhydride and either 5 mol % of *S*-HBTM or 5 mol % of *R*-HBTM catalyst. The conversion was monitored directly by NMR spectroscopy, and the conversion, x, was plotted as $1/(1 - x)$ versus time to determine a rate constant for each catalyst enantiomer.[9] The *R*-HBTM was faster than *S*-HBTM by a factor of 13.5, which is consistent with the relative reactivity reported by Birman. Thus the configuration of alcohol was confirmed to be 1*S*,2*R*.

In contrast to the Mosher method, the ester itself does not need to be stable because the reaction can be monitored by loss of the starting alcohol. Thus this kinetic resolution method can be applied to chemically sensitive alcohols.[6g] The plots in Figure 1 yield relative rates of 13.4, where *R*-HBTM is the fast-reacting catalyst.[9] Using Birman's rate data,[14a] one can assign the configuration of alcohol **1** as 1*S*,2*R*.

The example in Figure 1 demonstrates the concept, but the kinetic method requires both instrument time and significant material to assign a configuration. It is only necessary to identify the fast-reacting catalyst for a particular alcohol, and that can be done without measuring precise reaction rates. All of the subsequent conversion data were determined by running side-by-side reactions in a common water bath for a fixed length of time. The reactions were set up in 100 μL of $CDCl_3$, and the reactions were terminated[16] by adding 400 μL of $CDCl_3$ followed by NMR analysis. Each reaction used 10 μmol of alcohol, 0.4 μmol of catalyst, and ca. 1.3 equiv of the other reagents for pseudo-first-order kinetics (at modest conversion).[14c]

(7) For a review, see: Jing, Q.; Kazlauskas, R. J. *Chirality* **2008**, *20*, 724–735.

(8) (a) Horeau, A. In *Stereochemistry, Fundamentals and Methods*; Fiaud, J., Horeau, A., Kagan, H. B., Eds.; Georg Thieme: Stuttgart, 1977; Vol. 3, pp 51−94. (b) Horeau, A. *Tetrahedron Lett.* **1961**, 506–512. (c) Schoofs, A.; Horeau, A. *Tetrahedron Lett.* **1977**, 3259–3262. (d) Horeau, A.; Nouaille, A. *Tetrahedron Lett.* **1990**, *31*, 2707–2710. (e) Koenig, W. A.; Gehrcke, B.; Weseloh, G. *Chirality* **1994**, *6*, 141–147.

(9) From the data in Figure 1, the k_{obs} rate for the *R*-HBTM catalyst was 6.2×10^{-4} s^{-1} and the corresponding rate for the *S*-HBTM catalyst was 4.6×10^{-5} s^{-1}.

(10) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974–4001.

(11) (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412–420. (b) Fu, G. *Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2007; pp 186−190. (c) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570–5595.

(12) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499–1505.

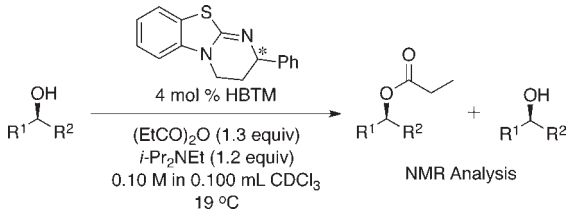
(13) (a) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351–1354. (b) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859–4861. (c) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537. (d) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227.

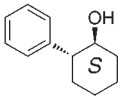
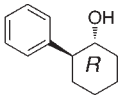
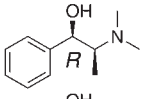
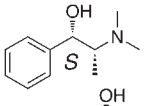
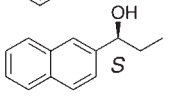
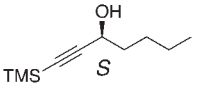
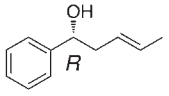
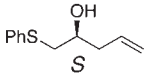
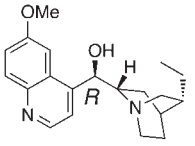
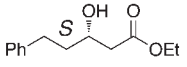
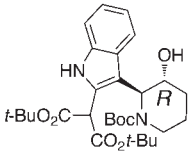
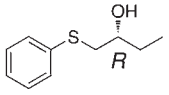
(14) (a) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115–1118. (b) Zhang, Y.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2525–2529. (c) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347–4350.

(15) At high conversion, the reactions deviate from pseudo-first-order conditions. For calculating relative reactions rates, we only considered data for $< 40\%$ conversion.

(16) The catalyzed acylation is a bimolecular reaction and should slow down by a factor of roughly $5^2 = 25$ on 5-fold dilution.

Table 1. Determination of the Fast-Reacting Catalyst for a Series of Optically Pure Secondary Alcohols[a]



entry	substrate	time (h)	% conversion *S*-HBTM[b]	% conversion *R*-HBTM[c]
1		0.75	4	49
2		0.75	53	6
3		0.75	10	24
4		0.75	28	9
5		0.5	8	71
6		0.5	28	76
7		0.75	40	15
8		0.75	21	30
9		0.75	28	50
10		4	24	25
11		4	43	16
12		4	60	33

[a] The reaction conditions are given in the text. [b] *S*-HBTM er = 97.4:2.6. [c] *R*-HBTM er = 98.2:1.8.

The method uses a total of 20 μmol of alcohol in the determination. The results with a variety of secondary alcohols are presented in Table 1.

Most alcohols with activating π-substituents produce sufficient conversion in 30–45 min to identify the fast-reacting catalyst. The fast-reacting catalyst for each entry is circled in Table 1. The enantiomeric pairs (entries 1, 2 and 3,4) showed the expected complementary reactivity. The less active substrates (entries 11 and 12) were run for 4 h to achieve sufficient conversion to determine the fast-reacting HBTM catalyst. The designation of "less active" substrates is a bit arbitrary: the alcohols in entries 8 and 12 show similar reactivities, but entry 12 was run for a longer time to give higher conversion. In only one case (entry 10) was the reactivity of the two catalysts too close to make a clear assignment of the fast-reacting catalyst. The HBTM catalyst system does not differentiate between the ester chain and the phenethyl chain. A different enantioselective acylation catalyst might be used to make this assignment.

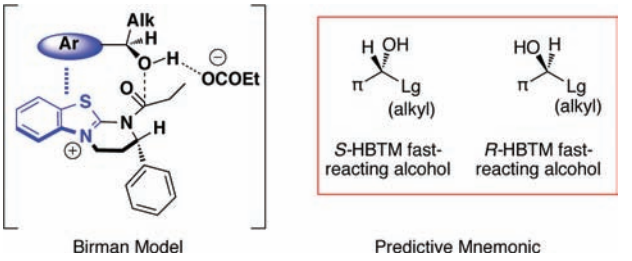


Figure 2. Birman's transition state model predicts the fast-reacting alcohol structure with the *S*-HBTM catalyst (left.) A more general mnemonic (right) places the small or π-substituent on the left and the large group on the right. The alcohol preferred by the *S*-HBTM catalyst is back, whereas the alcohol preferred by the *R*-HBTM catalyst is forward.

In order to use the observed rate difference to assign configuration, a clear relationship needs to be identified between the fast-reacting chiral catalyst and the three-dimensional structure of the alcohol. Birman examined a number of substrates and proposed the model shown in Figure 2.[14] His transition state model predicts that the *S*-HBTM catalyst will react faster than the *R*-HBTM when the aryl group is over the benzotriazole ring, and the alkyl group is pointing up and away from the complex. We propose a mnemonic based on our more extensive results and Birman's TS model, which is shown in Figure 2. The dominant π-group is placed to the left, and the larger (alkyl) group is drawn to the right. When the *S*-HBTM catalyst reacts faster, the hydroxyl group is back. When the *R*-HBTM catalyst reacts faster, then the hydroxyl group is forward. The substrates in Table 1 are drawn in this orientation, and the general suitability of the mnemonic is substantiated by inspection. The trend from the data for the π-dominant group is shown below:

$$\text{aryl} > \text{propargyl} > \text{homothiophenyl} \approx \text{benzyl} > \text{allyl} \approx \text{crotyl} > \text{alkyl}$$

This simple mnemonic predicts the HBTM selectivity for all of the alcohols presented, but it will not be adequate to

predict the reactivity of all secondary alcohols. Birman has shown that the HBTM catalyst and the closely related BTM catalyst are effective in the kinetic resolution of a variety of secondary alcohols including those with benzylic, propargylic, allylic, and cyclohexyl structures.[13,14] All of these alcohols can be analyzed with our proposed mnemonic or by direct analogy to specific example.

One goal of future work is to systematically broaden the scope of this method by studying different classes of secondary alcohols and refining our predictive mnemonic. Further refinements in catalyst structure,[14b,17] reaction conditions, and analytical strategy may be helpful in making this method more convenient and more widely applicable. The simple procedure described herein for determining the fast-reacting enantiomer of the HBTM catalyst, combined with the mnemonic based on Birman's model, will make this new method a valuable tool for assigning the configuration of secondary alcohols.

The method has been developed for secondary alcohols, but the general strategy should be applicable to any functional group for which an effective kinetic resolution catalyst has been developed. We will extend the strategy to assign the configuration of molecules based on functional groups not subject to common analytical methods.

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Supporting Information Available. Experimental procedures for the acylation reactions, NMR data for the relative rate determination, and kinetic data from compound **1** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.