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Determination of the Absolute Configuration of *β*-Chiral Primary Alcohols Using the Competing Enantioselective Conversion Method

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Abstract

A method for determining the absolute configuration of *β*-chiral primary alcohols has been developed. Enantioenriched alcohols were acylated in the presence of either enantiomer of the enantioselective acylation catalyst HBTM, and the faster reaction was determined by measuring product conversion using ^{1}H NMR spectroscopic analysis. An empirical mnemonic was developed that correlates the absolute configuration of the alcohol to the faster reacting catalyst. Successful substrates for this method include primary alcohols that bear a "directing group" on the stereogenic center; directing groups include arenes, heteroarenes, enones, and halides.

Abstract
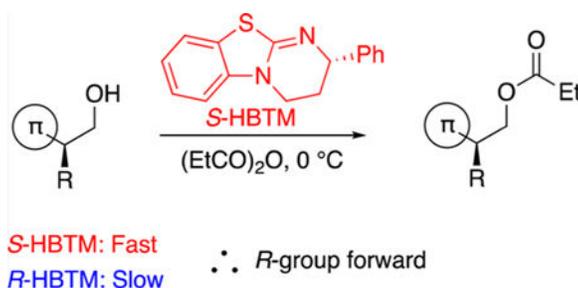
The determination of the absolute stereochemistry of small molecules remains an active challenge for researchers.[1] As of yet, there is no "one size fits all" analysis for absolute stereochemistry. Methods employed include chiral derivatization and NMR analysis,[2]

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01189.
Characterization of new compounds and experimental details for CEC analysis (PDF)

Notes

electronic and vibrational circular dichroism,[3] ECD methods,[4,5] and crystallographic analysis.[6] The method used depends on the functionality surrounding the stereogenic center as well as the availability and properties of substance.

Alcohols are common in natural product structures and are useful handles for absolute structure determination. While there are many reliable methods to determine the configuration of secondary alcohols, there are few methods for primary alcohols with stereogenic centers in the β-position (β-chiral primary alcohols). The Riguerda[7] and Seebach[8] groups have extended the modified Mosher's method to certain primary alcohols through ^{1}H and ^{19}F NMR analysis, respectively, and the Fukushi[9] group reported the derivatization and subsequent NOE analysis of β-chiral primary alcohols with chiral binaphthalene ester (MBCA) derivatives. Herein, we report our approach to this problem through the application of enantioselective acylation catalysts.

Our group has recently demonstrated that kinetic resolution catalysts can be used to identify the absolute configuration of optically pure molecules containing various functional groups. [10] The method utilizes the following process. An enantioselective catalyst developed for kinetic resolutions of a particular class of compounds is selected. Two reactions are set up in parallel containing an enantioenriched molecule of interest and either the R or S enantiomer of the enantioselective catalyst with the other necessary reagents to conduct the transformation. Many enantiopure substrates will react faster with one enantiomer of the catalyst. Once the reaction is stopped, the faster reacting catalyst is identified by measuring the relative conversion in each reaction. By comparing this result to an empirically derived mnemonic, the configuration in question can be determined. The CEC method is much less labor intensive than the Mosher's derivatization methods, for example, and has proven robust enough to be incorporated into an undergraduate laboratory experiment.[13c] The competing enantioselective conversion (CEC) method has been used to determine the configuration of primary amines,[11] lactams,[12] oxazolidinones,[12] and secondary alcohols. [10,13,14]

Birman has developed a number of enantioselective acylating catalysts,[15] including homobenzotetramisole[16] (HBTM) **1**, for kinetic resolutions of secondary alcohols.[17] Our group has previously employed HBTM as a catalyst for CEC methods for secondary alcohols[13] and other functional groups.[12] We sought to determine whether HBTM could be used for a CEC method with β-chiral primary alcohols by first probing its effectiveness in the kinetic resolution of racemic substrates. There have been sporadic reports of small molecule kinetic resolutions of these motifs previously.[18,19] Because HBTM and related catalysts have been proposed to interact with the substrates through π interactions,[20] alcohols bearing a π-group were tested initially. To our delight, we were able to resolve alcohols **1–3** with modest selectivities, as shown in Table 1. Though these selectivities are too low to be of practical synthetic utility, they are more than sufficient to make a stereochemical assignment based upon rate differences using the CEC method. One limitation was apparent as alcohol **4**, with the arene group γ to the alcohol, resulted in almost no selectivity. Optimization studies are presented in Tables S1 and S2. Other acylation catalysts were investigated (BTM and Cl-PIQ), but they did not provide superior selectivity in comparison to HBTM.[21] While the kinetic resolutions gave superior

selectivities at lower temperatures, 0 °C was selected as the standard temperature for CEC investigation due to the reproducibility and convenience inherent to ice–water baths.

Next, we investigated the order of the reaction with respect to the alcohol. Acylation reactions that are first order in alcohol are well behaved in the CEC method,[22] and the product conversions can be used to reliably identify the fast-reacting enantiomer. The acylation of enantiopure alcohol **5** was catalyzed by (*R*)- or (*S*)-HBTM in the presence of an excess of propionic anhydride and diisopropylethylamine (DIPEA); conversion was monitored by NMR analysis (Figure 1). The acylation of **5** was faster with (*S*)-HBTM and displayed first-order behavior with respect to alcohol with either catalyst, validating the assumption that relative conversions reflect relative reaction rates. This rate behavior simplifies the CEC analysis to a one-point conversion analysis. It reduces time and effort needed to identify the faster reacting catalyst and, therefore, the configuration of the stereocenter.

Finally, we turned our attention toward establishing a relationship between the absolute configuration of an enantioenriched alcohol and catalyst selectivity. Most of the enantioenriched alcohols in Scheme 1 were prepared by borane reduction of the corresponding acids, which were themselves prepared via enantioselective *α*-alkylations.[23] Alcohols **6–8** all react faster with (*S*)-HBTM. While methyl-bearing alcohol **6** shows higher rates of conversion, bulkier alcohols **7** and **8** show a slightly higher difference in conversion between parallel reactions. Both electron-rich and electron-poor arenes **10** and **11** are selective with (*S*)-HBTM. Because most of the alcohols we obtained had the same configuration with respect to R^1 and R^2, we compared enantiomers **5** and **12**. Both showed approximately equal and opposite conversions with (*R*)- and (*S*)-HBTM, serving as positive controls. Previous experience has shown, not unexpectedly, that a sample with lower enantiopurity will reduce the observed difference between the conversions.[13a] With the exception of compounds **13** and **21**, all of the samples are 89% ee, so the effect will be negligible. Gratifyingly, this CEC method also showed selectivity for scopolamine, **14**, demonstrating its utility for natural products containing this functional group array.

Emboldened by our success with *β*-aryl primary alcohols, we explored alcohols with different groups in place of the arene. Heteroaromatic alcohols **15** and **16** displayed significant differences in conversion, but unfortunately, indole **21** displayed conversions that were too close to confidently assign the faster reacting catalyst. A brief examination of nonaromatic *π*-systems revealed that enone **13** was an effective substrate. Interestingly, methyl ester **17** displayed selectivity opposite what was expected if the ester played the role of a directing group. We tentatively suggest that intramolecular hydrogen bonding could be altering the conformation of **17** and thus the selectivity. Curiously, we observed modest but reproducible selectivity for *β*-halide alcohols **18** and **19**. Lone pair–*π* interactions might account for the selectivity, but we are hesitant to endorse a physical rationale for this result without further experimental evidence. Phenyl alkyne **22** showed a slightly higher conversion with the (*S*)-HBTM catalyst, which was consistent with a directing group effect by the alkyne. The selectivity is modest enough to discourage its application to configuration assignments. Lastly, there was no selectivity for the negative control of alcohol **20**. This

outcome is consistent with models for the resolution of secondary alcohols by HBTM, which require a π-directing group.

Based upon the data, we have developed a mnemonic to determine the configuration of β-chiral primary alcohols, shown graphically in Figure 2. With the directing group (π system) drawn to the left of the page and the primary alcohol to the right of the page, if (S)-HBTM is the faster reacting catalyst, than the R group points out of the plane of the page. Conversely, if (R)-HBTM is the faster reacting catalyst, the R group points into the plane of the page. We posit a transition-state model analogous to that proposed by Birman and Houk,[20] which is consistent with the observed stereoselectivity. The alcohol approaches the face of the catalyst unencumbered by the bulky phenyl group and adopts a conformation in which the directing group interacts with the cationic π-system of acylated HBTM. An unfavorable steric interaction between the alcohol's R group and the catalyst imparts the observed stereoselectivity.

In summary, we have developed an empirical method to determine the absolute configuration of β-chiral primary alcohols using the enantioselective acylation catalyst HBTM. This report also describes the first example of the HBTM catalyst used in a kinetic resolution with β-chiral primary alcohols. This method is applicable to alcohols whose stereocenter bears a directing group. Experiments are underway in our laboratory to fully define the range of possible directing groups, which currently include arenes, some heteroarenes, enones, and halides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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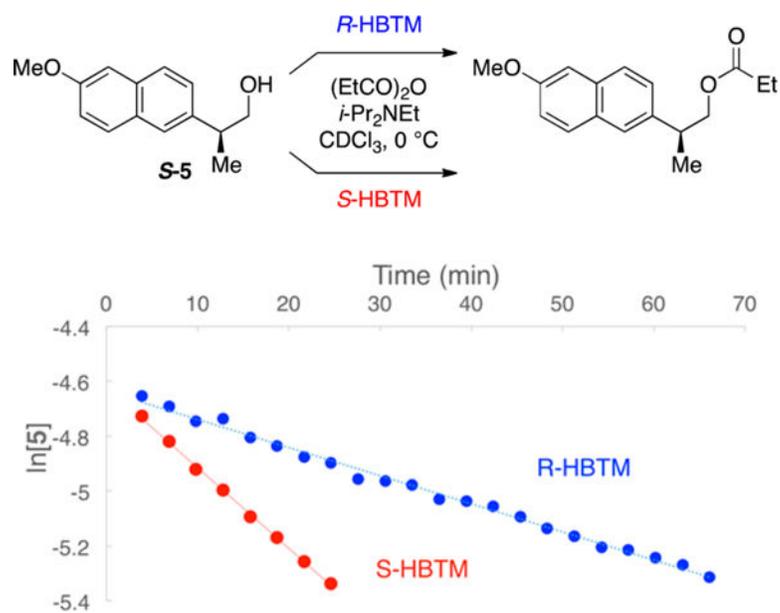
Figure 1.
Optically pure alcohol **5** was acylated with propionic anhydride and 20 mol % of either (*R*)- or (*S*)-HBTM. Reaction progress is plotted as ln[**5**] vs time, up to 50% conversion. Selectivity factor (*s*) from the ratio of slopes: (*S*)-HBTM/(*R*)-HBTM = –0.0294/–0.0102 = 2.9.[10]
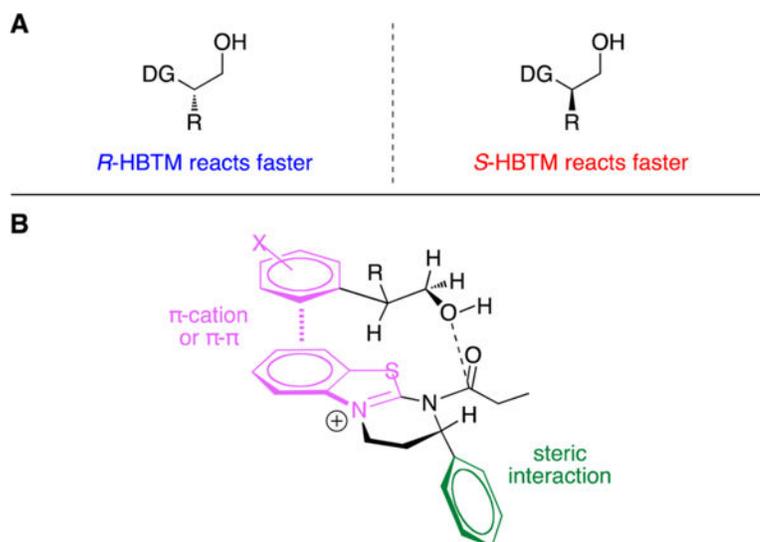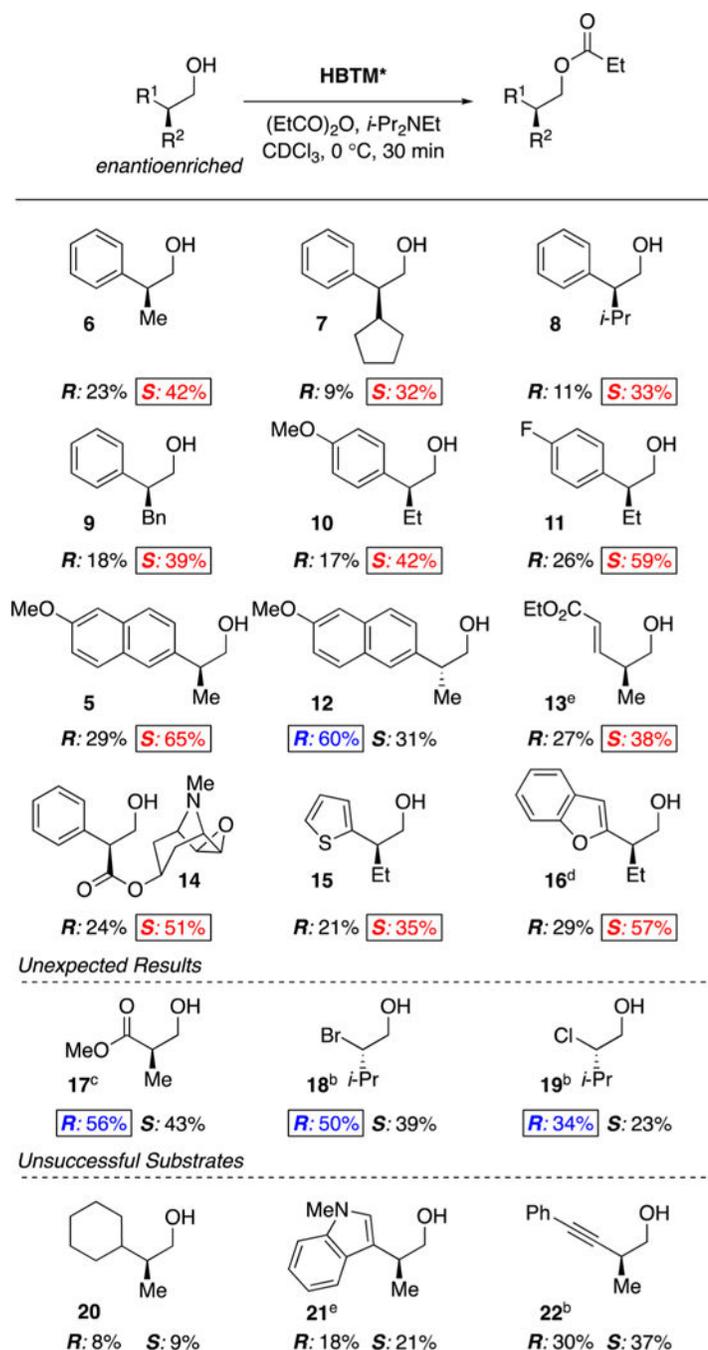
Figure 2.
(A) Mnemonic for determining the absolute configuration of stereocenters β to a primary alcohol. Aryl groups, certain heteroaromatic and nonaromatic π systems, bromines, and chlorines act as directing groups. (B) Proposed transition state between chiral primary alcohols and acylated (*S*)-HBTM.

Scheme 1. CEC Results for the Conversion of β-Chiral Primary Alcohols with (*R*)- and (*S*)-HBTM Acylation System[a,e]

[a]Optically enriched alcohols (0.015 M) were acylated with propionic anhydride (2 equiv) in the presence of (*R*)- or (*S*)-HBTM (10 mol %) and DIPEA (2 equiv) in CDQ_3 (400 μL total volume). After 30 min, the reactions were quenched by the addition of CD_3OD (50 μL). The reaction was diluted to 600 μL in $CDCl_3$, and percent conversion was determined by proton NMR analysis. The results from run to run were reproducible. [b]Percent conversions are the average of two trials [c]CEC reaction run with 0.020 M alcohol and 20 mol % of HBTM. [d]For
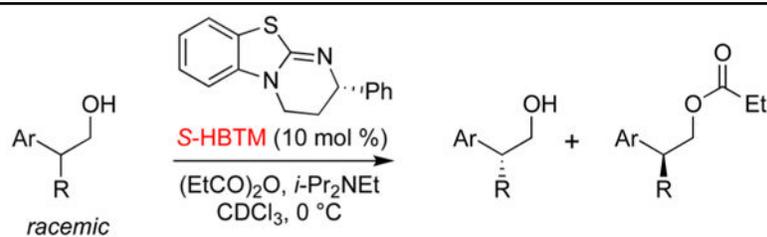
compound **16**, slightly overlapping peaks introduced small errors in the absolute values of the integrations. The relative conversions were consistent run to run, and no correction was applied. [e]The enantiomeric excess for all alcohols was 89%, except for **13** (83% ee) and **21** (84% ee).
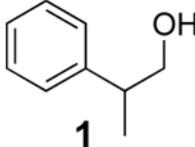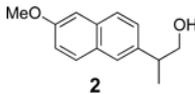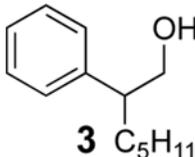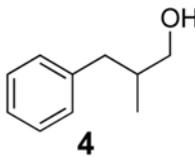
Table 1.

Kinetic Resolution of Racemic, β-Chiral Primary Alcohols[a]

substrate OH	Conversion[b]	Selectivity[b]
1	49%	3.8
2	52%	3.8
3 C₅H₁₁	35%	4.0
4	30%	1.2

[a] The alcohol (0.1 M), (S)-HBTM (10 mol %), and DIPEA (0.55 equiv) were combined in CDCl3, followed by the addition of propionic anhydride (0.55 equiv) at 0 °C. The reaction was quenched after 15 min by the addition of MeOH.

[b] The conversion and selectivity were calculated based upon the ee of the ester and remaining alcohol, which were determined using chiral HPLC analysis.[21]