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Absolute Configuration of Lactams and Oxazolidinones Using Kinetic Resolution Catalysts

Matthew A. Perry, Jonathan V. Trinidad, and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, Irvine, California 92697, United States

srychnov@uci.edu

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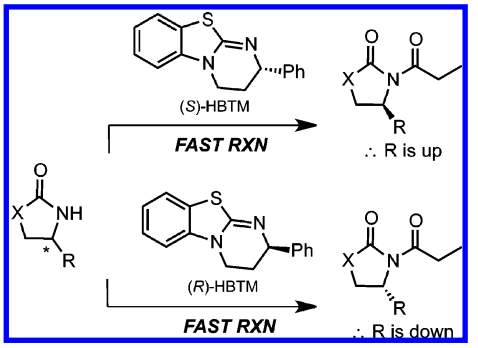
ABSTRACT



A simple method for determining the absolute configuration of oxazolidinones, lactams, and their derivatives using kinetic resolution catalysts is described. The optically pure substrates were acylated using the (*S*)-HBTM and the (*R*)-HBTM catalyst, and the faster reaction was determined. An empirical mnemonic was developed for the assignment of the absolute configuration based on the fast-reacting catalyst.

The assignment of relative and absolute configuration is an essential aspect of synthetic organic chemistry. The functional group present about the chiral center under investigation dictates the use of specific methods for configuration analysis. A wide variety of reliable methods are available for secondary alcohols and primary and secondary amines.[1] Fewer methods are available for chiral amides and congeners. Current strategies include circular dichroism (ECD and VCD) with TD-DFT calculations,[2] NMR shift reagents (e.g., $Eu(hfc)_3$,[3] 1,5,7-trimethyl-3-azabicyclo[3.1.1]-nonan-2-one,[4] or 2,2,2-trifluoro-1-(9-anthryl)ethanol[5] (Pirkle's alcohol)), and derivatization with achiral or chiral reagents followed by X-ray analysis.[6] Described herein is a simple method for the determination of absolute configuration of lactams and oxazolidinones using kinetic resolution catalysts.

Our strategy uses an enantiomeric pair of acylation catalysts to analyze an optically pure substrate of unknown configuration (Scheme 1). The first step is to determine the relative reactivity of the substrate with each catalyst; the second step is to use an empirical mnemonic to assign the configuration.

The selectivity is determined by setting up two parallel acylation reactions using diisopropylethylamine, propionic anhydride, the two enantiomeric catalysts, and the chiral substrate. After a time selected to allow sufficient conversion, the reaction mixtures are diluted and the conversion is evaluated by ^{1}H NMR analysis. The difference in conversion between the two reactions identifies the fast reacting catalyst and leads to a configuration assignment based on the empirically derived mnemonic. We previously developed

(1) Review articles: (a) Wenzel, T. J.; Chisholm, C. D. *Chirality* **2011**, *23*, 190–214. (b) Jing, Q.; Kazlauskas, R. J. *Chirality* **2008**, *20*, 724–735.

(2) (a) Tedesco, D.; Zanasi, R.; Guerrini, A.; Bertucci, C. *Chirality* **2012**, *24*, 741–750. (b) Woznica, M.; Kowalska, P.; Lysek, R.; Masynk, M.; Gorecki, M.; Kwit, M.; Furche, F.; Frelek, J. *Curr. Org. Chem.* **2010**, *14*, 1022–1036.

(3) Hudhomme, P.; Duguay, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1891–1900.

(4) Bauer, A.; Bach, T. *Tetrahedron: Asymmetry* **2004**, *15*, 3799–3803.

(5) Pirkle, W. H.; Robertson, M. R.; Hyun, M. H. *J. Org. Chem.* **1984**, *49*, 2433–2437.

(6) Tarui, A.; Kondo, K.; Taira, H.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Heterocycles* **2007**, *73*, 203–208.

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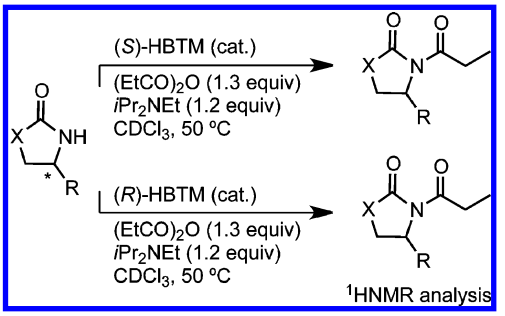
a similar strategy for secondary alcohols.[7] We have also reported the determination of absolute configuration of primary amines using proto and deutero chiral acylating reagents and mass spectrometry.[8]

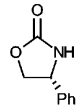
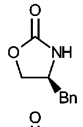
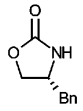
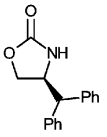
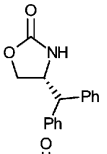
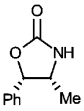
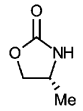
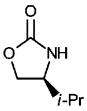
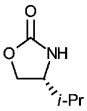
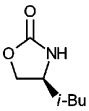
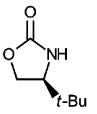
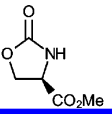
Scheme 1. Parallel Acylation Reactions Were Used To Identify the Fast-Reacting Catalyst for Each Substrate



Herein, we describe our results with chiral α-substituted oxazolidinones, lactams, and thiolactams. This class of molecules has found widespread use in stereoselective chemical transformations,[9] natural product synthesis,[10,11] and pharmaceutical targets.[12] Birman has reported the resolution of some oxazolidinones and lactams using different catalysts that were more capable for each class.[13] We prefer Birman's HBTM catalysts,[14] which are less selective but can be applied to a wider variety of substrates with adequate and predictable selectivity. The HBTM catalyst allows a single catalyst to be used in the determination of absolute configuration for a variety of substrate classes.[7]

The reaction conditions vary based on the class of substrates under consideration. The observed reactivity trend is consistent with the acidity of the nitrogen proton. As acidity increases, reactivity increases. Most oxazolidinones provided sufficient conversion at 3 h and 50 °C. Lactams showed the greatest variability with the reactivity decreasing with increased ring size. Simple β-lactams showed reactivity comparable to the oxazolidinone cases. The γ- and δ-lactams were the least reactive substrates requiring longer reaction times and increased catalyst loading. The thiolactams, oxazolidine-2-thione, and thiazolidine-2-thione required shorter reaction times, decreased temperatures, and in some cases, decreased reaction concentration. In all cases, the presence of an

Table 1. Identification of Fast-Reacting Catalyst for Enantiopure Oxazolidinones

entry[a]	substrate	time, temp	% conversion[f] (S)-HBTM	% conversion[f] (R)-HBTM
1		1 h, 25 °C	22	**36**
2		3 h, 50 °C	**53**	34
3[b]		3 h, 50 °C	37	**57**
4		3 h, 50 °C	**39**	7
5[c]		3 h, 50 °C	6	**28**
6		3 h, 50 °C	40	**53**
7		3 h, 50 °C	24	**34**
8		3 h, 50 °C	**10**	5
9		3 h, 50 °C	9	**14**
10		8 h, 50 °C	**27**	14
11[d]		43 h, 50 °C	**13**	2
12[e]		1.5 h, 25 °C	**48**	34

[a] All conversions are averages of triplicate runs unless otherwise stated. [b] % conversion at 1 h: (*S*) = 12, (*R*) = 21. [c] Average of duplicate runs are reported. [d] 10 mol % catalyst loading. [e] Reaction mixture diluted 5-fold from the standard conditions. [f] Standard deviation range for % conversion: (*S*) = 0 – 2.8, (*R*) = 0.6–2.9. Details are provided in the Supporting Information.

(7) Wagner, A. J.; David, J. G.; Rychnovsky, S. D. *Org. Lett.* **2011**, *13*, 4470–4473.

(8) Miller, S. M.; Samame, R. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2012**, *134*, 20318–20321.

(9) Zappia, G.; Cancelliere, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. *Curr. Org. Chem.* **2007**, *4*, 238–307.

(10) Babu, K.; Reddy, R.; Rao, S.; Palnati, V.; Gutta, M. *Synth. Commun.* **2012**, *42*, 2624–2631.

(11) (a) Takao, K.; Aoki, S.; Tadano, K. *J. Synth. Org. Chem., Jpn.* **2007**, *65*, 460–469 and references therein. (b) Zappia, G.; menendez, P.; Delle Giuliano, M.; Mesiti, D.; Nevola, L.; Botta, B. *Mini-Rev. Med. Chem.* **2007**, *7*, 389–409. (c) Gulder, T. A. M.; Moore, B. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9346–9367.

(12) Konaklieva, M. I.; Plotkin, B. J. *Curr. Med. Chem.: Anti-Infect. Agents* **2003**, *2*, 287–302.

(13) (a) Yang, X.; Bumbu, V. D.; Liu, P.; Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, W.; Jiang, X.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2012**, *134*, 17605–17612. (b) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870–2871.

(14) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115–1118.

electron-withdrawing group as the α-substituent increased reactivity.

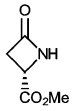
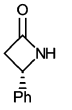
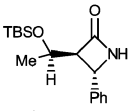
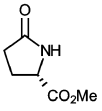
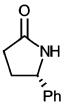
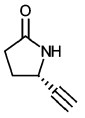
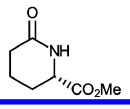
The oxazolidinone class was examined first and is shown in Table 1. Most substrates exhibited sufficient conversion and complementary reactivity at 3 h and 50 °C. The fast-reacting catalyst was identified in each case and indicated with a box. Compounds containing aryl groups reacted faster than the alkyl counterparts as predicted by Birman's proposed π-cation interaction in the transition state.[13a,14] The different substituents lead to a wide range of rates for the acylation reaction. Structures containing a phenyl or benzyl substituent (entries 1−5) showed greater differentiation than methyl or branched alkyl side chains (entries 6−11). Remarkably, the methyl substituent in entry 7 was sufficient to discriminate between competing catalysts. The sterically encumbered *tert*-butyloxazolidinone example showed selectivity but pushed the limit of reactivity (entry 11). The methyl ester derivative showed increased reactivity and comparable selectivity to the aryl examples (entry 12). In most cases, the relative reactivity of the oxazolidinones followed a consistent trend.

A series of lactams were also inspected as indicated in Table 2. The reactivity between substrates varied substantially. Regardless, all cases displayed sufficient differences in conversion rates and the same sense of selectivity as the oxazolidinone examples. Due to the strain induced reactivity of small ring lactams, the reactivity decreased with increased ring size ($\beta > \gamma > \delta$).

Additional substitution at the 3-position of the β-lactam in entry 3 confirms the usefulness of this method for more complex molecules. Simple γ-lactams with π-systems also show great selectivity (entries 4−6). Unfortunately, γ-lactams containing allyl or *n*-propyl side chains showed either no reactivity or reacted with no selectivity, respectively.[15] In all but the (*S*)-methyl 6-oxopiperidine-2-carboxylate case (entry 7), the δ-lactams showed no conversion with longer reaction times (>24 h) and increased catalyst loading (10 mol %).[15] The method works well for most substrates, but low reactivity and the occasional lack of selectivity limit the scope.

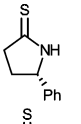
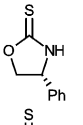
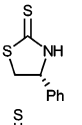
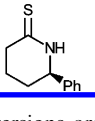
Various thio-derivatives were investigated to determine the feasability of our method with this more reactive class of compounds. Three of the four cases showed increased reactivity and comparable selectivity to their amide counterparts (Table 3, entries 1−3). The thioamide derivative of the previously unreactive (*R*)-6-phenylpiperidin-2-one showed a reasonable improvement in reactivity with no distinguishable selectivity (entry 4).

Table 2. Identification of Fast-Reacting Catalyst for Enantiopure Lactams

entry[a]	substrate	time, temp	% conversion[c] (*S*)-HBTM	% conversion[c] (*R*)-HBTM
1		10 min, 50 °C	50	75
2		3 h, 50 °C	28	40
3[b]		8 h, 50 °C	14	33
4		3 h, 50 °C	38	89
5[b]		18 h, 50 °C	6	30
6[b]		18 h, 50 °C	39	67
7		24 h, 50 °C	10	49

[a] All conversions are averages of triplicate runs unless otherwise stated. [b] 10 mol % catalyst loading. [c] Standard deviation range for % conversion: (*S*) = 0.6−2.1, (*R*) = 0.6−3.2. Details are provided in the Supporting Information.

Table 3. Identification of Fast-Reacting Catalysts for Thiolactams and Derivatives

entry[a]	substrate	time, temp	% conversion[d] (*S*)-HBTM	% conversion[d] (*R*)-HBTM
1[b]		3 h, 25 °C	73	100
2[c]		10 min, 25 °C	31	52
3[c]		90 min, 25 °C	63	82
4		6 h, 50 °C	26	27

[a] All conversions are averages of triplicate runs unless otherwise stated. [b] Average of duplicate runs are reported. [c] Reaction mixture diluted 5-fold from the standard conditions. [d] Standard deviation range for % conversion: (*S*) = 1.2−1.7, (*R*) = 0−2.1. Details are provided in the Supporting Information.

From the empirical data above and an analogous transition state calculated by Birman and Houk,[13a] a predictive mnemonic was developed. The transition state shown in Figure 1 predicts that the analogous (*S*)-HBTM catalyst will react faster when the aryl group is placed over the benzotetramisole ring with the proton facing toward the acyl group of the catalyst. We propose a general mnemonic

(15) See the Supporting Information for details concerning the acylation of propyl and allyl γ-lactams and other lactams.

based on our results in line with Birman and Houk's proposed TS model. The compound under investigation is oriented with the α-nitrogen substituent to the right. When the (*R*)-HBTM catalyst reacts faster, the R group is back. When the (*S*)-HBTM catalyst reacts faster, the R group is forward. For clarity, the examples described herein are oriented in this fashion. Our mnemonic accurately predicts the sense of HBTM selectivity for the examples we have investigated. Continued use of this method will help broaden the scope of applicable lactams and derivatives thereof.

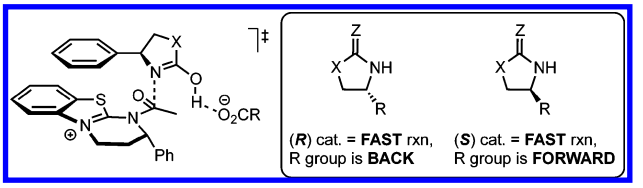


Figure 1. Assignment of absolute configuration is predicted by our extrapolation of Birman and Houk's TS model. Our mnemonic dictates that the R group is up when the (*S*)-HBTM catalyst reaction is fast and the R group is down when the (*R*)-HBTM catalyst reaction is fast.

In summary, a method for determining the absolute configuration of oxazolidinones and lactams using Birman's acylation catalyst has been developed. This method was utilized to provide a predictive mnemonic based on the conversion difference observed between (*R*)- and (*S*)-HBTM-catalyzed acylation. Oxazolidinone substrates work well while lactams show a more limited scope due to lower reactivity. Derivatization to thiolactams can increase reactivity and the selectivity is maintained in most cases. Assignment of configuration using this kinetic resolution strategy requires milligram quantities of substrate, the analysis is carried out by ^{1}H NMR spectroscopy, and the process is simple and convenient. We continue to explore the scope of this method for the assignment of configuration to chiral molecules containing other functional groups.

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

The authors declare no competing financial interest.