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Determination of the Absolute Configuration of Cyclic Amines with Bode's Chiral Hydroxamic Esters Using the Competing Enantioselective Conversion Method

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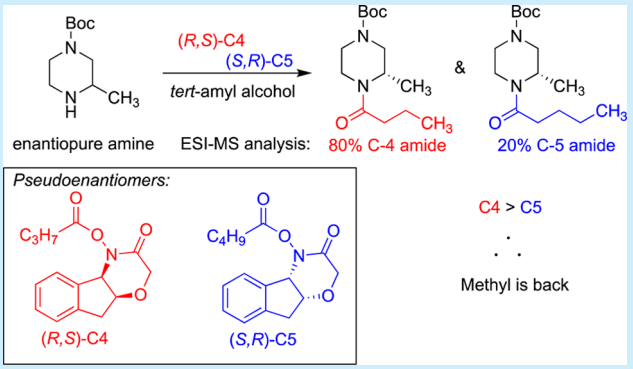
Supporting Information

ABSTRACT: The competing enantioselective conversion (CEC) strategy has been extended to cyclic amines. The basis for the CEC approach is the use of two complementary, enantioselective reactions to determine the configuration of the enantiopure substrate. Bode's chiral acylated hydroxamic acids are very effective enantioselective acylating agents for a variety of amines. Pseudoenantiomers of these acyl-transfer reagents were prepared and demonstrated to react with enantiopure cyclic amines with modest to high selectivity. The products were analyzed by ESI-MS to determine selectivity, and the results were used to assign the configuration of the amine substrate. The method was applicable to a variety of cyclic amines as well as primary amines and acyclic secondary amines. The method is limited to amines that are unhindered enough to react with the reagents, and not all amine substitution patters lead to high selectivity.



Determination of absolute configuration is an important step in structure determination and has a significant role in natural product analysis, enantioselective methods development, and medicinal chemistry.[1] Many different methods have been used to assign absolute configuration to organic molecules, including chiral derivatization followed by NMR spectroscopy,[2] vibrational circular dichroism (CD) combined with density functional theory simulations,[3] X-ray diffraction of single crystals,[4] the exciton chirality method with electronic CD,[5] and specific rotation combined with computer simulations.[6] Our laboratory developed the competing enantioselective conversion (CEC) method to assign configuration based on the relative rates of reaction with enantioselective reagents.[7,8] We reported a CEC method to analyze primary amines, but it was not effective with secondary amines or cyclic amines because of the low reactivity of the enantioselective reagents.[9] Inspired by Bode's recent development of a broadly applicable kinetic resolution method for cyclic amines,[10,11] we developed and now report a CEC method to assign configuration to cyclic amines.

Chiral amines are common in natural product structures and often associated with biological activity. Chiral amines are important building blocks in medicinal chemistry. Aside from the physical methods for determining absolute configuration, amines have been analyzed most often by derivatization with chiral reagents.[12] Other methods have been reported,[5f,13] including a new approach using induced conformational chirality that is detected by exciton-coupled circular dichroism.[14] A CEC strategy complements these other methods and has the potential to provide good substrate scope and selectivity with an operationally simple analysis.

The CEC method makes use of enantioselective reagents or catalyzed reactions to derivatize the targeted functional group in an enantiopure substrate. It was inspired by the work of Horeau, who used a kinetic resolution to assign configuration.[15] Most commonly, two parallel reactions are used, with one enantioselective reagent/catalyst system in each reaction. The fast reacting reagent is identified, and the absolute configuration of the unknown substrate is assigned based on the known preferences of the enantioselective catalyst or reagent.[7] In a few cases it has been possible to use pseudoenantiomeric reagents and run the competitive reactions in a single flask. The CEC method for primary amines used deuterated pseudoenantiomers of Mioskowski's reagents as shown in Figure 1.[7] Unfortunately, these acyl-transfer reagents were not reactive enough to derivatize more hindered amines or secondary amines. Bode has recently investigated enantioselective acyl transfer reagents based on chiral hydroxamic esters and shown that they demonstrate good enantioselectivity and work well with a wide variety of cyclic amines.[9,10] These enantioselective reagents appeared to be ideal for a new CEC method for cyclic amines.

We envisioned using pseudoenantiomeric reagents designed around Bode's hydroxamic acid: **6**(*R,S*)-C4 and 7(*S,R*)-C5. The goal was to use two complementary enantioselective reagents in

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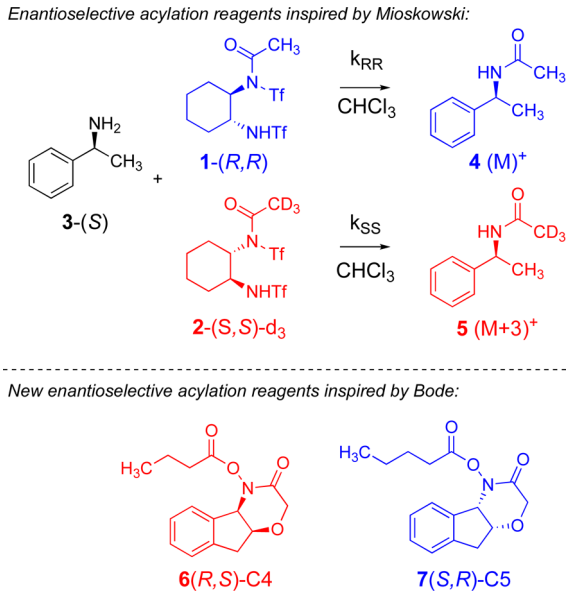
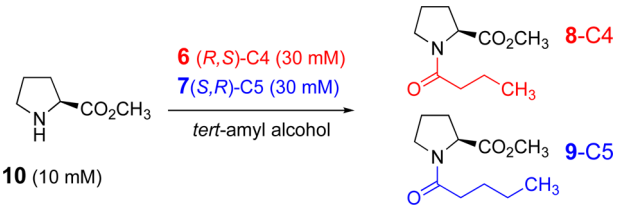


Figure 1. Enantioselective and pseudoenantiomeric acylation reagents inspired by Mioskowski's work were used in a prior competing enantioselective conversion method for primary amines.[7] The current project uses enantioselective acylation reagents inspired by Bode's work.[9]

the same flask at essentially the same concentration and have them compete to derivatize the enantiopure amine substrate. As long as the reactions are nearly first-order in substrate, in this case the amine, the ratio of products formed will be very similar to the selectivity of the enantioselective reagent. Measuring the product ratios will identify the fast-reacting reagent, and that can be used with a mnemonic to assign absolute configuration. In prior work, the two different enantiomeric reagents and products formed from them were marked with deuterium labels.[8] Bode demonstrated that the hydroxamic esters reagents are most selective with propionic or longer carboxylic acids.[10a] The corresponding isotopically labeled compounds are very expensive and probably unnecessary. Instead, the (*R*,*S*) reagent was prepared with butanoic acid and the complementary (*S*,*R*) reagent was prepared with pentanoic acid. These pseudoenantiomeric reagents are shown in Figure 1.

The enantioselective acylation reaction was optimized using (*S*)-proline methyl ester (**10**) as a test substrate. An excess of a 1:1 mixture of **6**(*R*,*S*)-C4 and **7**(*S*,*R*)-C5 was reacted with **10** in different solvents and concentrations. These initial screening reactions are documented in Table S1 of the Supporting Information. They showed that the reaction was faster and more selective in *tert*-amyl alcohol than in ethereal or aromatic solvents. Optimization of the temperature and time for the reactions is shown in Table 1. The conversion was measured by acylating the remaining amine with propionic anhydride, and the analysis was carried out by measuring the ratios of C3, C4, and C5 amides by ESI-MS.[16] The reaction was found to be relatively slow at 20 °C and only resulted in about 37% conversion after 6 h (entry 3). Heating the reaction at 60 °C for 6 h (entry 9) resulted in nearly complete conversion. The selectivity observed for the reactions was lower at 60 °C than at 20 °C (entry 9 vs entry 3), but the effect was modest. The concentration, temperature, and time for entry 9 were selected as the standard for the CEC evaluation of other substrates.[17]

Table 1. Optimization of Reaction Time and Temperature Using (*S*)-Proline Methyl Ester[a,b]



entry	time (h)	temp (°C)	$[M]^+$:$[M + 14]^+$	σ^c	conv (%)
1	1	20	4:96	3	7
2	3	20	8:92	2	22
3	6	20	7:93	1	37
4	1	40	9:91	2	16
5	3	40	8:92	1	43
6	6	40	9:91	2	68
7	1	60	12:88	1	52
8	3	60	11:89	0	89
9	6	60	13:87	0	98
10[d]	6	60	51:49	0	

[a]The reactions were run at the indicated concentrations, times, and temperatures. The total reaction volume was 100 μL. Percentages are based on the sum of the ion counts for the M + H and M + Na peaks. [b]Percent conversion was obtained by quenching the reaction with propionic anhydride and using the ion count of the three-carbon amide formed to quantify the unreacted **10**. [c]Standard deviation of major peak intensity based on three trials. [d]This experiment was run with racemic proline methyl ester.

If the rate of acylation with the C4 reagent **6** was faster than the rate of reaction with the C5 reagent **7**, it would lead to excess formation of the C4 amide with each enantiomer of the substrate. Combining both enantiomers (using the racemate) would lead to more than 50% of the C4 amide in the product. The question was addressed with the experiment in entry 10 of Table 1. This example used racemic proline methyl ester and resulted in a 51:49 ratio of the C4:C5 amides as measured by the ESI-MS method. The observed ratio of C4:C5 amides is very close to 50:50, and it puts an upper limit on the difference in rate between the reagents **6** and **7** with this substrate. We conclude that the difference in rate between the C4 and C5 reagents is negligible.

The results with a variety of cyclic amines are presented in Scheme 1. The reactions were run in small vials with 100 μL of solvent; each evaluation used 1.0 μmol of substrate (e.g., 0.16 mg of amine **11**). Six-membered ring structures **11**−**18** showed reasonable selectivity regardless of the adjacent substituent's identity or the presence of other heteroatoms in the ring. The five-membered ring pyrrolidine examples **10** and **19**−**23** showed larger variations in their selectivity. The minimally substituted 2-methylpyrrolidine (not shown)[18] led to very low and reversed selectivity. The low selectivities with methyl and phenyl (**20**) substituents represent a limitation of this CEC method for pyrrolidines. The hydrochloride salt **23** was used directly in the reaction by adding Et_3N to liberate the free amine in situ. Finally, azepane **24** resulted in selectivity similar to the corresponding piperidine **11**. The predictive mnemonic for cyclic amines is apparent by inspection of Scheme 1.

The previously reported CEC method worked well for primary amines. The current method was evaluated against a small number of primary and secondary amines as shown in Scheme 2. Primary amines are much more reactive than

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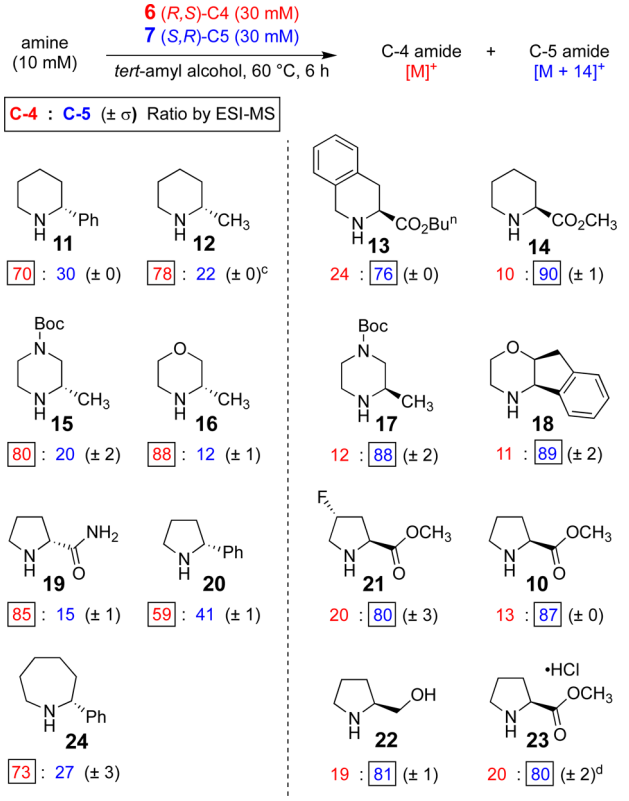
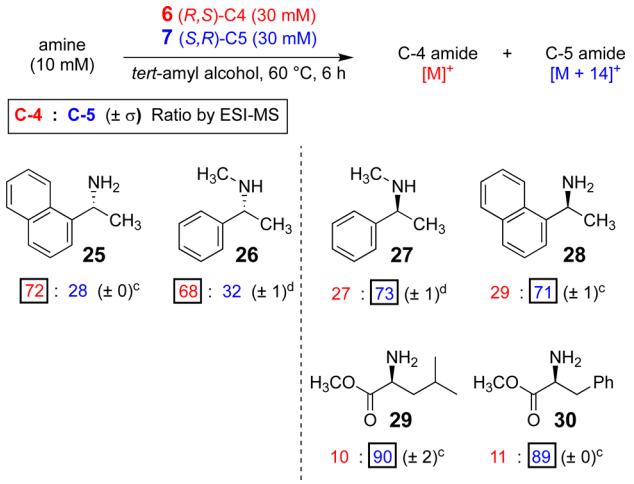
Scheme 1. CEC Evaluation of Cyclic Amines with Adjacent Stereogenic Centers[a,b]



[a]The reactions were run at the indicated concentrations, times, and temperatures. The total reaction volume was 100 μL. Percentages are based on the sum of the ion counts for the M + H and M + Na peaks. [b]Standard deviation based on three trials. [c]Calculated based on M + H peaks only. [d]Triethylamine (1.0 μL) was added to the reaction mixture.

Scheme 2. CEC Evaluation of Acyclic Primary and Secondary Amines[a,b]



[a]The reactions were run at the indicated concentrations, times, and temperatures. The total reaction volume was 100 μL. Percentages are based on the sum of the ion counts for the M + H and M + Na peaks. [b]Standard deviation based on three trials. [c]The primary amine reactions were run at 20 °C for 1 h. [d]Calculated based on M + Na peaks only.

secondary amines, and the acylation reaction with **6** and **7** proceeded to completion at 20 °C in 1 h with the other reaction conditions unchanged. All of the examples investigated had structures in which the amine carbon was bracketed with an sp^2 and sp^3 substituent. The selectivities were modest but reproducible. Amino acid esters **29** and **30** were acylated with good selectivity. Secondary amines with similar structural features were also investigated. *N*-Methylamines **26** and **27** showed the same sense of selectivity as the similar primary amines.[19] The corresponding *N*-benzylamines were unreactive under the standard conditions. The limited number of examples investigated here is not enough to establish a reliable and well-documented reactivity pattern for primary amine configuration assignment, but the simple pattern of selectivity is very encouraging.

A predictive mnemonic for using the relative reactivity of reagents **6** and **7** to assign absolute configuration is illustrated in Figure 2. The cyclic cases appear to be relatively robust based on the data presented here and Bode's resolution work.[10] A tentative mnemonic for amines that are not part of a ring is also shown. The cyclic structure **31** emphasizes the similarity in selectivity between the two models. Bode and Kozlowski have developed a detailed mechanistic model for the acylation of piperidines in which the 2-subsitutent preferentially adopts an axial position.[11] Their computational and experimental work suggests that the mnemonic for cyclic amines should be analyzed with care for more complex, conformationally restricted cyclic amines. The predictive mnemonics for cyclic and acyclic amines will be useful in assigning absolute configuration of enantiopure amines.

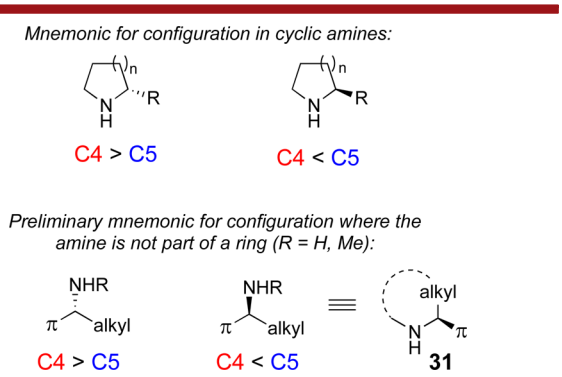


Figure 2. Preliminary mnemonic for assigning absolute configuration using the **6**(*R,S*)-C4 and **7**(*S,R*)-C5 reagents illustrated in Figure 1.

A new CEC method has been developed for cyclic amines; it shows good results with five-, six-, and seven-membered rings. The method is based on the chiral hydroxamic esters developed by Bode's group. Easily accessible pseudoenantiomeric reagents **6**(*R,S*)-C4 and **7**(*S,R*)-C5 were reacted with the amines and the product ratios were analyzed by ESI-MS. The method is sensitive, and preliminary results suggest that it can be used with acyclic amines. The procedure should be useful to assign absolute configuration in medicinal chemistry and natural products chemistry. We will continue to develop the scope of the method.

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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.7b01748.

Characterization of new compounds and experimental details for CEC analysis (PDF)

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Notes

The authors declare no competing financial interest.

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(16) The ratio of C4 and C5 amides was measured with a test substrate using known concentrations. The ESI-MS results showed an excellent correlation with the solutions' concentrations. These results are presented in the Supporting Information.

(17) In most cases, the propionic anhydride treatment was omitted from the standard conditions. The same C4:C5 ratio was observed with or without the propionic anhydride step.

(18) Bode labeled 2-methylpyrrolidine a "difficult substrate" (ref 10a).

(19) One would expect the selectivity for secondary amines **26** and **27** to be equal and opposite. The precise conversions do not match, which could indicate varying levels of ee in the amines, a rate difference between C4 and C5 esters with these substrates, or other effects. The fast and slow reactions are easily identified, but the different level of selectivity suggests further investigation would be of interest.

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