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Using the Competing Enantioselective Conversion Method to Assign the Absolute Configuration of Cyclic Amines with Bode's Acylation Reagents

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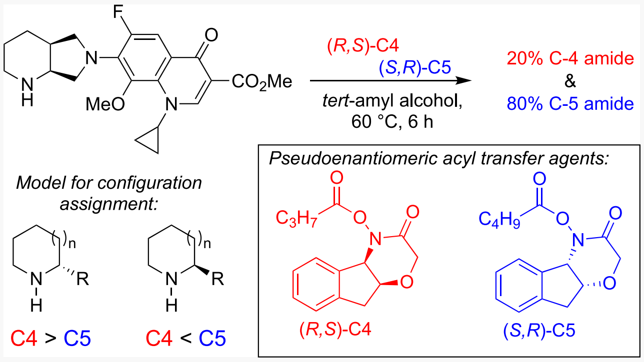
ABSTRACT: The competing enantioselective conversion (CEC) method is a quick and reliable means to determine absolute configuration. Previously, Bode's chiral acylated hydroxamic acids were used to determine the stereochemistry of primary amines, as well as cyclic and acyclic secondary amines. The enantioselective acylation has been evaluated for 4-, 5-, and 6-membered cyclic secondary amines, including medicinally relevant compounds. The limitations of the method were studied through computational analysis and experimental results. Piperidines with substituents at the 2-position did not behave well unless the axial conformer was energetically accessible, which is consistent with the transition state geometries proposed by Bode and Kozlowski. Control experiments were performed to investigate the cause of degrading selectivity under the CEC reaction conditions. The present study expands the scope of the CEC method for secondary amines and provides a better understanding of the reaction profile.



■ INTRODUCTION

Nitrogen-containing heterocycles are ubiquitous in active pharmaceutical ingredients and natural products. Alkaloids have long attracted the attention of medicinal and synthetic chemists due to their diverse biological activities and fascinating architectures. These structures have stimulated many new methods for the enantioselective installation of nitrogenous stereocenters.[1] Equally important in setting these stereocenters is the ability to accurately determine their absolute configuration. Frequently, this task is accomplished through new synthetic methodology to construct a compound of known absolute configuration and assigning other compounds by analogy. Also common is the use of computational predictions in conjunction with specific rotation or circular dichroism measurements.[2] However, there is rarely a straightforward method for assigning these newly formed stereocenters.

The gold standard in assigning absolute stereochemistry is generally considered to be X-ray crystallography. However, this requires the molecule of interest to be abundant and crystalline and frequently necessitates derivatization to establish absolute stereochemistry. The process of crystallization can also be arduous, as high-quality crystals of adequate size are required for reliable data to be obtained. Other approaches to assigning absolute configuration include chiral derivatization and subsequent NMR analysis,[3] vibrational and electronic circular dichroism coupled with DFT calculation,[4] and total synthesis.[5]

In 2011, our lab reported a method to determine absolute configuration based on the enantioselective acylation of chiral secondary alcohols, which was later coined the competing enantioselective conversion (CEC) method.[6] The method was inspired by the work of Horeau.[7] It is conducted with an enantioenriched substrate that is reacted with both enantiomers of an acyl transfer catalyst/reagent, generally in two separate vessels. After sufficient time, the reactions are quenched, and their conversions are assayed. The data are then compared to an empirically derived model, and the absolute configuration is assigned by analogy. The method is predicated on a meaningful energy difference between the two diastereomeric transition states, with the faster reaction identified as the matched case between the enantioselective reagent and enantiopure substrate.

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The CEC method has previously been applied to numerous substrate classes, including secondary alcohols,[6,8] β-chiral primary alcohols,[9] oxazolidinones, lactams,[10] primary amines, and cyclic secondary amines.[11] In our work on alcohols, the reactions were run separately, and the conversion of each reaction was determined by NMR. In some cases, we have been able to use pseudoenantiomeric reagents and run the competitive reactions in the same vessel.[11] One such example is the CEC method for primary amines, which used deuterated derivatives of Mioskowski's reagents.[12] The use of pseudoenantiomeric reagents allowed stereochemistry to be assigned by mass spectrometry. However, this method was not very general due to low reactivity of the reagents with secondary amines. Additionally, it was surprisingly difficult to achieve high levels of deuterium enrichment with Mioskowski's reagents, complicating data analysis. Seeking a more general solution that would allow for the assignment of secondary amines, we sought to make use of the high reactivity and selectivity of Bode's acyl transfer reagents.[13] Previously, we found that the enantiomeric hydroxamic acids can be acylated with butyryl chloride or valeroyl chloride to generate two pseudoenantiomers differing by a methylene unit (Figure 1).[11b] By searching for the mass of the resulting C4 and C5 amides by mass spectrometry, we were able to successfully assign absolute configuration with an operationally simple method.

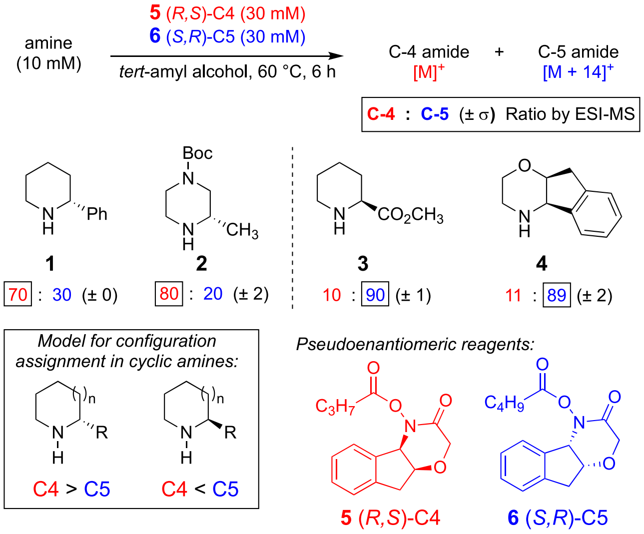


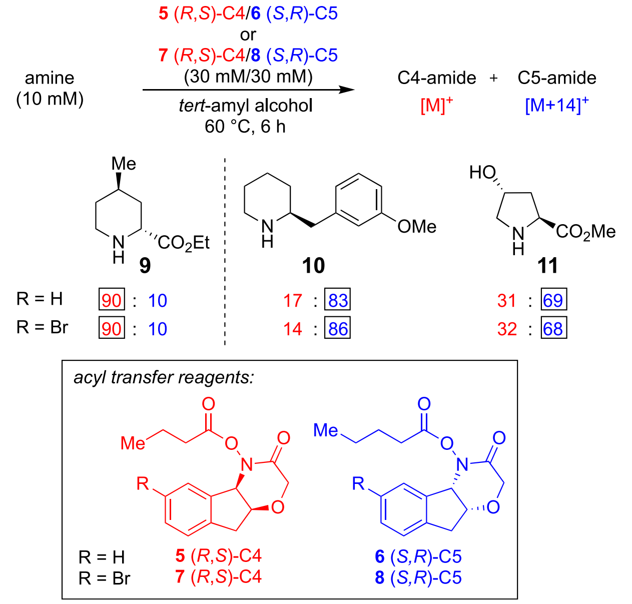
Figure 1. Basic CEC strategy for cyclic amines—published work with examples

In our original report, we detailed the development of effective reaction conditions and briefly investigated the scope of the method.[11b] However, we did not have a detailed understanding of the selectivity of the reaction or the limitations of the method. Bode has performed mechanistic investigations and carried out a thorough computational analysis in collaboration with Kozlowski; they concluded that the mechanism for enantioselective acylation of 6-membered cyclic amines proceeds through a concerted 7-membered transition state, forcing the alpha substituent into an axial configuration.[14] From this insight, one can imagine that the reaction would be either nonselective or unreactive in cases where the substituent cannot be placed in the axial position, and Bode's experimental work supports this conclusion. Herein, we report an extension of the CEC method for cyclic secondary amines focused on optimization of reaction conditions, expansion of substrate scope, and the effects of conformational preferences on the observed selectivity. We also investigate the origins of decaying selectivity through detailed kinetic modeling and control experiments.

RESULTS AND DISCUSSION

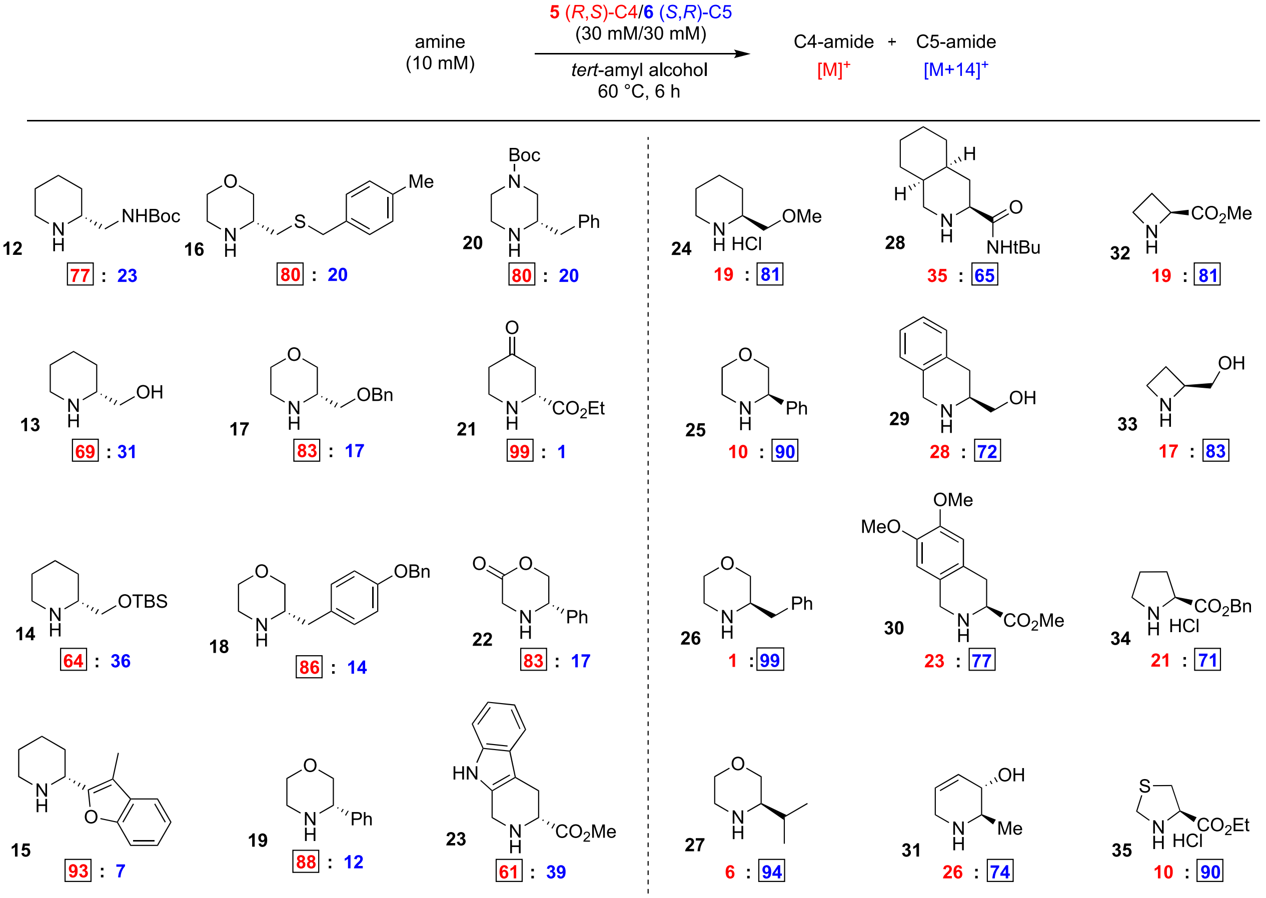
We began our investigations by exploring a new set of reagents to optimize the selectivity for the CEC reaction. Bode has reported that brominated acyl transfer reagents **7** and **8** give greater selectivity in the kinetic resolution of 6-membered cyclic amines.[13c] Using previously optimized conditions for the CEC of cyclic amines,[11b] the reaction of **9** and **10** exhibited equal selectivity with brominated and nonbrominated acyl transfer reagents (Scheme 1). We also observed reduced but equal selectivity for pyrrolidine **11** with both series of reagents. Our results indicate that the CEC method is equally effective with the brominated reagents. The brominated hydroxamic acids are commercially available, which makes preparation of the reagents a one-step process, compared with the 4-step synthesis of the nonhalogenated reagent. The brominated reagents will be more accessible for most laboratories. We elected to use the nonbrominated reagents for the majority of this work because we had multigram quantities of the acyl transfer reagents **5** and **6** on hand.

Scheme 1. Comparison of the Original and Brominated Acyl Transfer Reagents



The choice of pseudoenantiomers **5** and **6**, bearing C4 and C5 acyl groups, respectively, stems from the desire to perform absolute configuration analysis by mass spectrometry. Theoretically, any acyl group that produces amides differing in molecular weight would be effective. However, it is possible that the variance in the acyl chain would affect both the selectivity of the reagent, as well as the ionization potential of the amide products in the MS experiment. Bode has shown that a C5-acyl group is highly selective for this acyl transfer reaction, but the use of an acetyl group degrades the selectivity.[13e] With this in mind, we elected to synthesize **5 (*R*,*S*)-C4** and **6 (*S*,*R*)-C5**. In our previous report, we verified

Scheme 2. CEC Results for Cyclic Amines



that the C4 and C5 acyl chains display the same selectivity and reactivity in the CEC reaction. We also verified that the amide products had no difference in ionization potential.[11b]

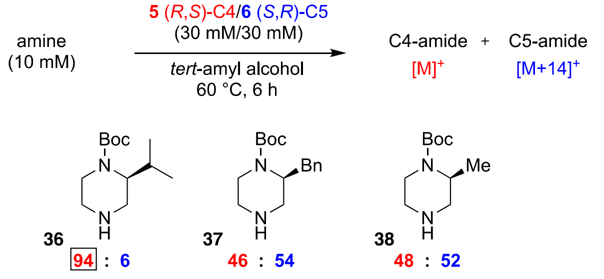
Previously, mass spectrometry for all of the CEC reactions was performed using a standard ESI-MS for simplicity and speed. However, one major drawback to this method of analysis is that at the end of the CEC reaction, there remain superstoichiometric amounts of the acyl transfer reagents. These large concentrations of acyl transfer reagents can make it difficult to achieve sufficient signal of the desired compounds in a standard ESI-MS experiment. More troubling is that substrates occasionally have the same molecular weight as the acyl transfer reagents, making data analysis impossible. To circumvent this issue, we performed mass spectrometry on a UPLC-QqQ-MS (see the Experimental Section for more information). The combination of UPLC and the triple quadrupole mass analyzers allowed us to cleanly analyze the ions corresponding to the amide products without interference from the acyl transfer reagents. While this system is specialized and may not be widely available, LC−MS analysis was also performed for selected substrates with very good agreement with the UPLC-QqQ-MS data. The excess of acyl transfer reagents is quite apparent in the LC−MS trace; however, extracted ion chromatograms (EICs) can be used to easily quantify the ion count of the compound in question so long as it does not have the same molecular weight as the acyl transfer reagents (see the Experimental Section and Supporting Information for further details).

In our previous report, we demonstrated that the CEC method outlined above is effective for various 5-, 6-, and 7-membered cyclic amines bearing chirality alpha to the amine. Seeking to more fully understand the scope and limitations of this method, we evaluated an array of 6-membered cyclic amines (Scheme 2). Alkyl-substituted piperidines **12−15** and **24** were evaluated, and all reacted smoothly and could be assigned with confidence, even in the presence of an unprotected primary alcohol (**13**). Morpholines **16−19** and **25−27** also proved to be competent substrates and were assigned with good selectivity. The method was not sensitive to other functional groups in the ring such as protected amines (**20**), ketones (**21**), esters (**22**), or alkenes (**31**). Substrate **23**, despite containing a potentially reactive indole, reacted with modest selectivity. Isoquinoline **28** and tetrahydroisoquinolines **29** and **30** were also successfully assigned using this method. Notably, piperidine **15**, bearing a benzofuran, reacted with excellent selectivity. Several piperidines with larger aryl groups were not selective. They are discussed later and presented in Table 1.

It has been reported that acyl transfer reagents **5** and **6** are less selective in reactions with azetidines and pyrrolidines. As such, we sought to evaluate if our method would be effective for smaller ring sizes. Azetidines **32** and **33** were subjected to standard CEC conditions, and each reacted with good selectivity. Pyrrolidine **34** was also a competent substrate, albeit with modest selectivity. Thiazolidine **35** displayed excellent selectivity, but the reaction took 48 h and only achieved low conversion.

With an array of successful cases in hand, we wondered if the same selectivity would be observed with other substitution patterns. As such, N-Boc piperazines with 3-alkyl substituents were investigated (Scheme 3). Surprisingly, we found that isopropyl bearing piperazine **36** reacted with exquisite selectivity. This selectivity quickly proved to be *sui generis*, as **37** and **38** bearing benzyl and methyl substituents, respectively, displayed almost no selectivity. We speculate that in its reactive conformation, the isopropyl group in **36** could place a methyl group in an optimal position to influence the selectivity of the reaction, while benzyl and methyl substituents do not fill this space. Interestingly, the selectivity observed with **36** was at odds with the empirical model previously developed for cyclic amines.[11b]

Scheme 3. CEC Results with 3-alkyl Pyrazoles

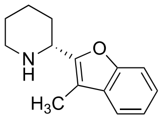
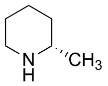
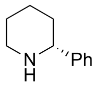
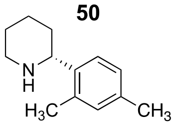
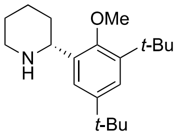
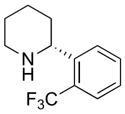


Following the success of the 6-membered substrates, we evaluated the utility of our method with biologically and medicinally relevant compounds (Scheme 4). Amines **39** and **42** are precursors to aprepitant (Emend) and solifenacin (Vesicare), respectively, and were successfully assigned with good selectivity. Mefloquine (**40**) was also assigned successfully but with diminished selectivity. This result is interesting, as Bode has previously reported a kinetic resolution of this compound with superior selectivity.[13e] The methyl ester of moxifloxacin (**41**), an antibiotic used to treat a number of bacterial infections, also displayed good selectivity with our method. Finally, the stereocenter adjacent to the amine in the natural product 1-deoxynojirimycin (**43**) was successfully assigned by CEC. Anabasine (**44**) exhibits low levels of selectivity in the expected direction, despite having a similar conformational energy to substrate **20**; we consider the CEC method unreliable in this case. Ritalin hydrochloride and the free amine were also tested but lead to very low selectivity and could not be assigned with this method.

During the course of our studies, we noticed that reactions that were allowed to reach high conversion (>70%) frequently resulted in lower levels of selectivity than those that proceeded to lower conversion (<70%). The CEC method was designed to be pseudo-first order with respect to the amine substrate, and the 1:3:3 ratio of amine to each acyl transfer reagent was previously shown to be effective. However, the ratio is too low to be truly pseudo-first order. We investigated the reduced selectivity because it seemed more significant than we would expect if it were simply a concentration effect.

To determine the underlying cause of this phenomenon, control experiments were performed in which the reaction of (*S*)-3-methylmorpholine was quenched at different time points, and the selectivity and conversion were assayed. The results are summarized in Figure 2. At low conversion, the selectivity of the reaction was high, but the selectivity slowly faded as the reaction progressed. Hypothesizing that the change in the concentration of acyl transfer reagents during the course of the reaction may play a key role, the CEC reaction was simulated using COPASI.[15] Consistent with the mechanism proposed by Bode, we simulated the data on the assumption that the reaction of each pseudoenantiomer of the acyl transfer reagents with the amine is a concerted, second order reaction. The rate constant (*k*) for the reaction of **5 (*R,S*)-C4** was set to be nine times that of the reaction of **6 (*S,R*)-C5**, in accordance with the experimental result observed at 17% conversion (Figure 2). The initial concentrations were set to reflect the experimental CEC conditions, and the simulated data and ratio of C4 amide to C5 amide are shown. The changing concentrations of acyl transfer reagents, based on these calculations, are likely to be a contributing factor, but the simulated data do not display a decrease large enough to be consistent with the experimental data.

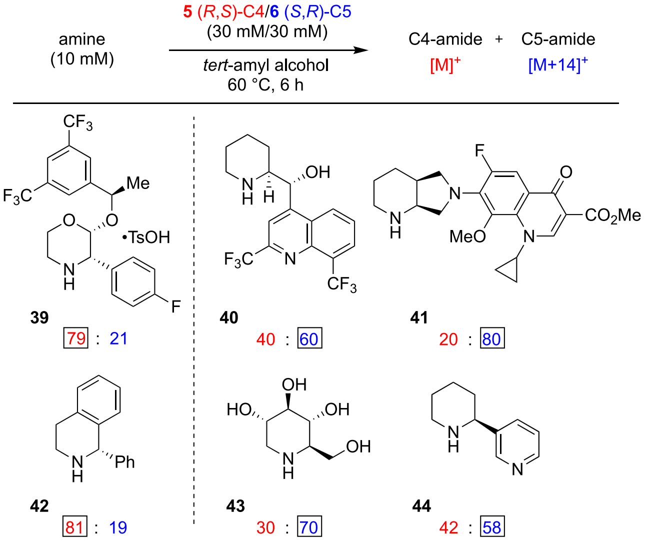
Table 1. Selectivity and Conversion Data with Calculated Axial Conformation Energy[a,b]

cyclic amine	conversion (%)	amide ratio	axial conf. (H-ax) kcal/mol	1st axial conf kcal/mol
 **30**	94	93 : 7	1.35	1.35
 **49**	–	78 : 22	2.32	2.14
 **50**	–	70 : 30	2.60	2.60
 **51**	24	45 : 55	3.96	3.96
 **52**	19	42 : 58	4.28	4.28
 **53**	0[b]	0 : 0	6.51	5.56

[a] Calculations were carried out using Spartan 18. Conformations were searched using the MMFF, and low-energy conformers were optimized using wB97xd/6-31G(d). The conformational energies in columns 4 and 5 are relative to the lowest energy conformation for each compound, which in all cases had the C2 subsitutent equatorial. Calculations were also carried out with Gaussian 16 and include solvation and free energy corrections; the conformational energies change a bit, but the ordering and rationale for selectivity do not. These more detailed calculations are included in Table S3 in the Supporting Information. [b] Determined by the insignificant ion counts of the C4 and C5 amides, compared to the C3 amide.

Mechanistically, the acyl transfer to the amine must generate the corresponding hydroxamic acid. At low conversion, this concentration will be negligible, but at high conversion, it is close to one equivalent of combined enantiomeric hydroxamic acids in solution. A possible complication is acyl transfer

Scheme 4. Examples with Clinically Relevant Cyclic Amines



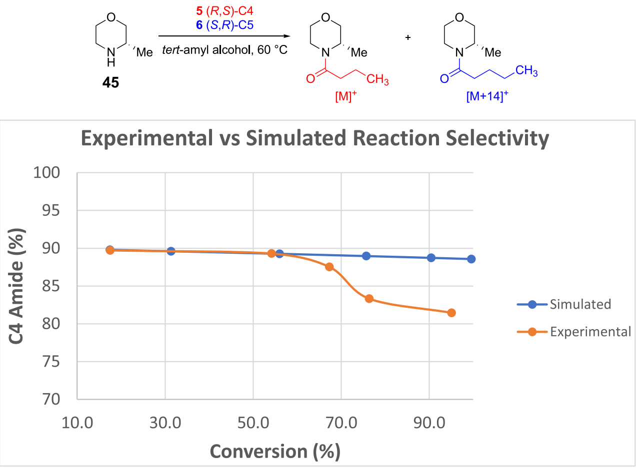
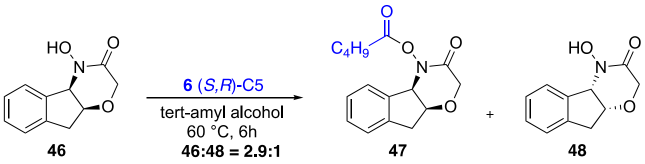


Figure 2. Acylation reaction and plot of experimental and simulated CEC data for (*S*)-2-methylmorpholine.

between the hydroxamic acid and the acylated hydroxamic acid. For example, if (*R,S*)-hydroxamic acid **46** were acylated by **6** (***S,R***)**-C5**, it would generate **47** (***R,S***)**-C5**. As shown, this enantiomer reacts faster with the amine substrate than **6** (***S,R***)**-C5**. A buildup of **47** during the course of the reaction could artificially inflate the amount of C5 amide observed, leading to a lower ratio of C4/C5 amides. To test this hypothesis, we designed an experiment to determine if acyl transfer is possible under the reaction conditions (Scheme 5).

(*R,S*)-hydroxamic acid **46** was mixed with an equimolar amount of **6** and was diluted to 30 mM in *tert*-amyl alcohol. This mixture was heated to 60 °C for 6 h to simulate the CEC reaction conditions, and subsequently, an aliquot was diluted and subjected to HPLC analysis. Consistent with acyl transfer, **46** and **48** were observed in a 2.9:1 ratio. We assume that the change in concentration over the reaction course, in addition to a slow scrambling of the acyl groups among hydroxamic esters, accounts for the declining selectivity observed with long reaction times.

Scheme 5. Hydroxamic Acid Crossover Experiment



Piperidine **30**, bearing a benzofuran, reacts with excellent selectivity. Previously, we reported that **49** reacts to provide a 78:22 ratio of C4 to C5 amides. In accordance with the reactive conformation proposed by Bode and Kozlowski,[14] the 2-substituent and the proton on the nitrogen will adopt axial orientations during the acyl transfer. However, this mechanistic modality places an upper limit on the size of substituents that can be tolerated in the CEC reaction with 2-substituted piperidines. To further probe this effect, the relative energy for the axial conformation was calculated for the substrates shown in Table 1. Larger substituents lead to higher relative energies for the axial conformations. For piperidine **30**, the first conformation that places both the proton and substituent axial (column 4) occurs at a relative conformational energy of 1.35 kcal/mol. Additionally, this conformer also represents the lowest energy conformation that places the aryl substituent axial (column 5). With respect to the previously reported piperidine **49**, the lowest energy axial conformation occurs at 2.14 kcal/mol, while the lowest energy conformation that places both the proton and methyl groups axial is 2.32 kcal/mol. The difference in energy between **30** and **49** likely explains the variance in selectivity observed between these two substrates. We have observed that as the relative energy increases, both selectivity and reaction conversion will dramatically decrease (Table 1). Compound **50**, displaying a slightly higher axial conformational energy, reacts in a decreased ratio with respect to **49**. As energies increase toward 4 kcal/mol (**51** and **52**), the reaction is no longer selective, and reaction conversion diminishes. As energies reach beyond 6 kcal/mol (**53**) the reaction does not proceed at all. Based upon the observed data from these substrates, we posit that if the substituent requires a relative energy around 3 kcal/mol or greater to adopt an axial conformation, then the CEC reaction is unlikely to be successful. This conformational energy requirement represents a limitation of the CEC method.

■ CONCLUSIONS

We have shown that the CEC method is a useful tool for assigning absolute configuration of secondary cyclic amines and have extended the scope of the original method. Control experiments have helped to clarify the reaction profile and make sense of a slow erosion in selectivity at long reaction times. The Bode and Kozlowski model requires the C2 substituent and the proton on nitrogen to occupy axial positions in the reactive conformation for cyclic 6-membered amines. Our experimental and modeling results support this model and suggest an upper limit on the conformational energy for an effective CEC reaction (and kinetic resolution) using Bode's acyl transfer reagents. The present study expands the scope of the CEC method for cyclic secondary amines and provides a better understanding for predicting and analyzing these enantioselective acyl transfer reactions.

■ EXPERIMENTAL SECTION

General Experimental Details. All volumetric glassware and NMR tubes were oven-dried prior to use. The ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at 298.0 K unless stated otherwise. Chemical shifts (δ) were referenced to the residual solvent peak (7.26 ppm for

$CHCl_3$) for ^{1}H NMR and $CDCl_3$ (77.16 ppm) for ^{13}C{^{1}H} NMR. The ^{1}H NMR spectral data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex = sextet, oct = octet, m = multiplet, app. = apparent, and br. = broad), coupling constant(s) in hertz (Hz), and integration. High-resolution mass spectrometry was performed using ESI-TOF. Mass spectrometry for CEC reactions was performed on a UPLC-QqQ-MS system using an Acquity UPLC and a Quattro Premier XE QqQ-MS mass analyzer. LC−MS was performed using a Waters Acquity QDA UPLC−MS system.

Unless otherwise stated, synthetic reactions were carried out in flame- or oven-dried glassware under an atmosphere of argon. All CEC reactions were carried out under air, in 700 μL amber mass spectrometry vials preloaded with 3 μmol of each acyl transfer reagent. All commercially available reagents were used as received unless stated otherwise. Solvents were purchased as ACS grade or better and as HPLC-grade and passed through a solvent purification system equipped with activated alumina columns prior to use. Thin layer chromatography (TLC) was carried out using glass plates coated with a 250 μm layer of 60 Å silica gel. TLC plates were visualized with a UV lamp at 254 nm or by staining with *p*-anisaldehyde, potassium permanganate, phosphomolybdic acid, or vanillin. Liquid chromatography was performed using forced flow (flash chromatography) with an automated purification system on prepacked silica gel (SiO_2) columns.

Chemicals. All purchased chemicals were used without further purification unless otherwise noted. $CDCl_3$ was purchased from Cambridge Isotope Laboratories. UPLC grade water and MeCN were purchased from Fisher. Acyl transfer reagents **5**−**8**,[13b,c] **14**,[16] **30**,[17] and **41**[18] were synthesized according to known literature procedures. All piperidines were benzyl protected when acquired and were debenzylated for CEC analysis. All morpholines were synthesized according to a known preparation.[19] All other compounds were purchased commercially.

■ GENERAL PROCEDURE 1

Morpholine Synthesis.[19] The respective amino alcohol was dissolved in CH_2Cl_2 (0.4 M) and cooled to 0 °C. Triethylamine (1.2 equiv) in CH_2Cl_2 (50 mL) was added, and the solution was stirred for 10 min. Chloroacetyl chloride (1.2 equiv) in CH_2Cl_2 (0.9 M) was slowly added over 1 h. The resultant mixture was kept at 0 °C for 30 min and then was slowly warmed to room temperature. When the reaction was complete by TLC, the reaction was quenched with water (1.3 mL/mmol). The organic phase was separated, and the aqueous phase was exacted twice with CH_2Cl_2 (1.3 mL/mmol). The combined organic phase was then washed twice with brine and dried over Na_2SO_4. The solution was then concentrated in vacuo and the crude material was used in the next reaction without further purification.

Sodium hydride (60% in mineral oil) (1.5 equiv) was suspended in THF (0.6 M with respect to NaH) and was kept at −10 °C for 10 min. The crude acetamide was dissolved in THF (0.5 M), and the solution was slowly added over 1 h. The reaction was stirred for another 30 min and was then slowly warmed to room temperature. After the reaction completed, water (2 mL/mmol) was carefully added followed by ethyl acetate (1.3 mL/mmol). The organic phase was separated, and the aqueous phase was exacted with ethyl acetate three times. The organic phase was combined, dried over Na_2SO_4, and concentrated in vacuo.

The crude product was dissolved in THF (0.4 M), and the solution was slowly added to the suspension of $LiAlH_4$ (3 equiv) in THF (1 M) at 0 °C. The reaction mixture was refluxed for 2 days and then cooled to −10 °C. Water was carefully added to quench the reaction, and then, 2 N NaOH was slowly added upon vigorously stirring. The white solid was filtered through Celite and washed six times with ethyl acetate. After drying with Na_2SO_4, the solvent was removed under vacuum and further purified via column chromatography to give the respective morpholine.

(*R*)-3-(((4-Methylbenzyl)Thio)Methyl)Morpholine (16). (R)-3-(((4-methylbenzyl)thio)methyl)morpholine was prepared according to General Procedure 1 using the following amounts of reagents. **Step 1:** S-(4-tolyl)-L-cysteinol (0.200 g, 0.888 mmol), triethylamine (0.149 mL, 1.067 mmol), chloroacetyl chloride (85 μL, 1.07 mmol), and CH_2Cl_2 (6.49 mL). **Step 2:** sodium hydride (60% in mineral oil, 0.035 g, 0.001 mmol) and THF (6.10 mL). **Step 3:** $LiAlH_4$ (0.171 g, 4.494 mmol) and THF (8.10 mL). The title compound was isolated as a white solid: 4.0 mg, 1.9% yield over three steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 3.81−3.71 (m, 2H), 3.69−3.65 (m, 2H), 3.55−3.45 (m, 1H), 3.15 (dd, *J* = 10.9, 9.4 Hz, 1H), 2.88 (dd, *J* = 7.1, 3.0 Hz, 2H), 2.82 (tdd, *J* = 9.3, 4.4, 3.0 Hz, 1H), 2.42 (dd, *J* = 13.4, 4.4 Hz, 1H), 2.33 (s, 3H), 2.03 (s, 1H); **^{13}C{1H} NMR** (101 MHz, $CDCl_3$) δ 137.0, 135.0, 129.4, 128.9, 72.0, 67.6, 53.2, 46.0, 36.2, 33.7, 21.2; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{13}H_{19}NOSH$ $(M + H)^+$: 238.1261, found 238.1253; $[\alpha]^{21}_D$ = −35.5 (*c* 4.75, MeOH).

(*S*)-3-((Benzyloxy)Methyl)Morpholine (17). (S)-3-((benzyloxy)methyl)morpholine was prepared according to General Procedure 1 using the following amounts of reagents. **Step 1:** *O*-benzyl-L-serinol hydrochloride (0.200 g, 0.92 mmol), triethylamine (0.154 mL, 1.1 mmol), chloroacetyl chloride (88 μL, 1.1 mmol), and CH_2Cl_2 (6.49 mL). **Step 2:** sodium hydride (60% in mineral oil, 0.020 g, 0.50 mmol) and THF (6.10 mL). **Step 3:** $LiAlH_4$ (0.053 g, 1.4 mmol) and THF (8.10 mL). The title compound was isolated as a white solid: 8.6 mg, 4.5% yield over three steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35−7.30 (m, 5H), 4.52 (s, 2H), 3.79 (dd, *J* = 11.2, 3.0 Hz, 2H), 3.55 (ddd, *J* = 11.2, 9.0, 4.1 Hz, 1H), 3.47−3.28 (m, 3H), 3.17−3.07 (m, 1H), 2.97−2.92 (m, 2H), 2.66 (br s, 2H); **^{13}C{1H} NMR** (101 MHz, $CDCl_3$) δ 138.0, 128.6, 128.0, 127.9, 73.7, 70.6, 69.3, 67.4, 54.5, 45.2; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{12}H_{17}NO_2H$ $(M + H)^+$: 208.1333, found 208.1327; $[\alpha]^{21}_D$ = +7.4 (*c* 4.15, MeOH).

(*S*)-3-Phenylmorpholine (19). (S)-3-phenylmorpholine was prepared according to General Procedure 1 using the following amounts of reagents. **Step 1:** L-phenylglycinol (0.200 g, 1.45 mmol), triethylamine (0.244 mL, 1.75 mmol), chloroacetyl chloride (0.139 mL, 1.75 mmol), and CH_2Cl_2 (6.49 mL). **Step 2:** sodium hydride (60% in mineral oil, 0.0508 g, 1.27 mmol) and THF (6.10 mL). **Step 3:** $LiAlH_4$ (0.171 g, 4.494 mmol) and THF (8.10 mL). The title compound was isolated as an amorphous white solid: 53.0 mg, 22.4% yield over three steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41−7.37 (m, 2H), 7.36−7.31 (m, 2H), 7.30−7.25 (m, 1H), 3.92 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.87 (ddt, *J* = 11.2, 3.1, 1.2 Hz, 1H), 3.82 (dd, *J* = 11.0, 3.2 Hz, 1H), 3.65 (td, *J* = 11.3, 2.7 Hz, 1H), 3.39 (dd, *J* = 11.0, 10.1 Hz, 1H), 3.13 (td, *J* = 11.6, 3.3 Hz, 1H), 3.00 (ddd, *J* = 11.8, 2.7, 1.5 Hz, 1H), 1.90 (s, 1H); **^{13}C{1H} NMR** (101 MHz, $CDCl_3$) δ 140.7, 128.6, 127.9, 127.3, 73.8, 67.4, 60.7, 46.7; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{10}H_{13}NOH$ $(M + H)^+$: 164.1070, found 164.1063; $[\alpha]^{21}_D$ = +52.2 (*c* 3.26, MeOH).

(*R*)-3-Phenylmorpholine (25). (R)-3-phenylmorpholine was prepared according to General Procedure 1 using the following amounts of reagents. **Step 1:** *D*-phenylglycinol

(0.200 g, 1.46 mmol), triethylamine (0.24 mL, 1.75 mmol), chloroacetyl chloride (0.14 mL, 1.75 mmol), and CH_2Cl_2 (6.49 mL). **Step 2:** sodium hydride (60% in mineral oil, 0.062 g, 2.60 mmol) and THF (6.10 mL). **Step 3:** $LiAlH_4$ (0.149 g, 3.93 mmol) and THF (8.10 mL). The title compound was isolated as a white solid: 23.2 mg, 14.2% yield over three steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41−7.32 (m, 5H), 4.15 (dd, *J* = 8.1, 6.5 Hz, 1H), 3.98−3.95 (m, 2H), 3.90−3.85 (m, 2H), 3.03 (ddd, *J* = 12.9, 10.4, 5.4 Hz, 1H), 2.76 (dt, *J* = 13.0, 1.9 Hz, 1H); **^{13}C{1H} NMR** (101 MHz, $CDCl_3$) δ 132.4, 130.0, 129.4, 128.1, 68.8, 63.4, 59.1, 43.5; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{10}H_{13}NOH$ $(M + H)^+$: 164.1070, found 164.1064; $[\alpha]^{22}_D$ = −0.7 (*c* 3.26, MeOH).

(*R*)-3-Benzylmorpholine (26). (R)-3-benzylmorpholine was prepared according to General Procedure 1 using the following amounts of reagents. **Step 1:** D-phenylalaninol (0.200 g, 1.32 mmol), triethylamine (0.22 mL, 1.56 mmol), chloroacetyl chloride (0.13 mL, 1.56 mmol), and CH_2Cl_2 (6.49 mL). **Step 2:** sodium hydride (60% in mineral oil, 0.053 g, 0.002 mmol) and THF (6.10 mL). **Step 3:** $LiAlH_4$ (0.127 g, 3.35 mmol) and THF (6.10 mL). The title compound was isolated as a white solid: 17 mg, 7.4% yield over three steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.93 (m, 1H), 7.35−7.27 (m, 3H), 7.19−7.15 (m, 2H), 3.98 (ddd, *J* = 12.7, 3.9, 2.1 Hz, 1H), 3.87 (ddt, *J* = 12.8, 7.0, 3.0 Hz, 2H), 3.66 (dd, *J* = 12.7, 9.9 Hz, 1H), 3.47 (dt, *J* = 11.9, 6.3 Hz, 1H), 3.26 (dt, *J* = 13.0, 2.5 Hz, 1H), 3.22−3.14 (m, 1H), 3.10 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.83 (dd, *J* = 13.6, 9.8 Hz, 1H); **^{13}C{1H} NMR** (101 MHz, $CDCl_3$) δ 134.3, 129.2, 129.2, 127.8, 68.0, 63.7, 55.8, 43.4, 35.6; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{11}H_{15}NOH$ $(M + H)^+$: 178.1227, found 178.1219; $[\alpha]^{22}_D$ = +31.2 (*c* 3.55, MeOH).

(*R*)-3-Isopropylmorpholine (27). (R)-3-isopropylmorpholine was prepared according to General Procedure 3 using the following amounts of reagents. **Step 1:** D-valinol (0.200 g, 1.94 mmol), triethylamine (0.33 mL, 2.33 mmol), chloroacetyl chloride (0.19 mL, 2.328 mmol), and CH_2Cl_2 (6.49 mL). **Step 2:** sodium hydride (60% in mineral oil, 0.069 g, 2.859 mmol) and THF (6.10 mL). **Step 3:** $LiAlH_4$ (0.136 g, 3.595 mmol) and THF (8.10 mL). The title compound was isolated as a white solid: 3.1 mg, 1.2% yield over three steps. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.04 (dd, *J* = 12.6, 3.5 Hz, 1H), 3.98−3.92 (m, 1H), 3.82 (ddd, *J* = 12.8, 11.8, 2.6 Hz, 1H), 3.63 (dd, *J* = 12.7, 10.8 Hz, 1H), 3.24 (dt, *J* = 13.0, 2.2 Hz, 1H), 3.13 (ddd, *J* = 12.9, 11.8, 3.9 Hz, 1H), 2.95 (ddd, *J* = 10.8, 7.5, 3.5 Hz, 1H), 1.92 (m (8), *J* = 6.9 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); **^{13}C{1H} NMR** (101 MHz, $CDCl_3$) δ 67.2, 63.7, 60.5, 44.0, 28.6, 18.8, 18.4; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_7H_{15}NOH$ $(M + H)^+$: 130.1227, found 130.1221; $[\alpha]^{21}_D$ = +16.0 (*c* 2.58, MeOH).

■ GENERAL PROCEDURE 2

Debenzylation of Piperidines. Benzylated piperidine and Pd/C (5 or 10 wt %, 0.5 equiv) were suspended in either ethyl acetate, absolute ethanol, or a mixture of the two. Aqueous HCl (1 or 2 M, 1.2−1.5 equiv) was added, and the mixture was sparged with hydrogen for 10 min. The mixture was then allowed to stir under an atmosphere of hydrogen until the reaction was complete as monitored by ESI-MS. Upon completion, the reaction mixture was filtered through a pad of Celite, and aqueous NaOH was added. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Products were purified by flash chromatography on silica gel (0−10% MeOH in CH_2Cl_2).

(*R*)-2-(2,4-Dimethylphenyl)Piperidine (51). Following General Procedure 2, benzylated piperidine (58.7 mg, 0.210 mmol) and 10% Pd/C (111.8 mg, 0.105 mmol) were suspended in ethyl acetate (2.10 mL), and 2 M HCl (0.15 mL) was added. Subsequently, the mixture was sparged with hydrogen for 10 min and was allowed to stir under a hydrogen atmosphere for 36 h. Upon completion of the reaction as monitored by ESI-MS, the mixture was filtered through a pad of Celite. Subsequently, 1 M NaOH (3 mL) was added, and the mixture was stirred for 20 min. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 x 5 mL). The product was isolated as stated to afford **51** as a yellow oil (21.3 mg, 54% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.95 (s, 1H), 3.76 (d, *J* = 10.5 Hz, 1H), 3.21 (d, *J* = 11.6 Hz, 1H), 2.81 (dt, *J* = 11.7, 2.6 Hz, 1H), 2.29 (s, 3H), 1.89 (d, *J* = 11.9 Hz, 1H), 1.78−1.64 (m, 3H), 1.62−1.41 (m, 3H).; **^{13}C{1H} NMR** (126 MHz, $CDCl_3$) δ 140.7, 136.1, 134.7, 131.1, 127.0, 125.9, 58.1, 48.3, 34.0, 26.2, 25.8, 21.0, 19.2; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{13}H_{19}NH$ $(M + H)^+$: 190.1591, found 190.1591; $[\alpha]^{22}_D$ = +68.9 (*c* 2.13, $CDCl_3$).

(*R*)-2-(3,5-di-*tert*-Butyl-2-Methoxyphenyl)Piperidine (52). Following General Procedure 2, benzylated piperidine (41.5 mg, 0.105 mmol) and 10% Pd/C (56.1 mg, 0.053 mmol) were suspended in ethanol (0.8 mL) and ethyl acetate (0.26 mL), and 2 M HCl (0.08 mL) was added. The product was isolated as stated to afford **52** as a white sticky solid (17.9 mg, 56%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.5 Hz, 1H), 7.24 (d, *J* = 2.6 Hz, 1H), 3.95 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.22−3.16 (m, 1H), 2.83 (td, *J* = 11.6, 2.9 Hz, 1H), 1.95−1.88 (m, 1H), 1.80−1.71 (m, 2H), 1.69−1.64 (m, 1H), 1.63−1.52 (m, 2H), 1.40 (s, 9H), 1.31 (s, 9H); **^{13}C{1H} NMR** (126 MHz, $CDCl_3$) δ 154.8, 146.0, 141.5, 137.9, 123.1, 63.0, 56.0, 48.5, 35.5, 34.8, 34.5, 31.7, 31.4, 26.3, 26.0; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{20}H_{33}NOH$ $(M + H)^+$: 304.2635, found 304.2628; $[\alpha]^{22}_D$ = +34.8 (*c* 1.79, $CDCl_3$).

(*R*)-2-(2-Trifluoromethylphenyl)Piperidine (53). Following General Procedure 2, benzylated piperidine (67.2 mg, 0.210 mmol) and 10% Pd/C (112 mg, 0.105 mmol) were suspended in ethanol (1.6 mL) and ethyl acetate (0.53 mL), and 2 M HCl (0.15 mL) was added. The product was isolated as stated to afford **53** as a yellow oil (34.7 mg, 72%). **^{1}H NMR** ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 3.98 (app. d, *J* = 9.3 Hz, 1H), 3.18 (app. d, *J* = 11.4 Hz, 1H), 2.83 (td, *J* = 11.7, 2.6 Hz, 1H), 2.01 (s, 1H), 1.92−1.83 (m, 1H), 1.81−1.74 (m, 1H), 1.71−1.65 (m, 1H), 1.59 (qt, *J* = 12.3, 4.0 Hz, 1H), 1.54−1.45 (m, 2H); **^{13}C{1H} NMR** (151 MHz, $CDCl_3$) δ 144.4, 132.2, 128.9, 127.6 (q, *J* = 29.5 Hz), 127.0, 125.5 (q, *J* = 5.9 Hz), 124.7 (q, *J* = 273.7 Hz), 77.2, 57.8, 48.0, 34.9, 25.8, 25.5; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{12}H_{14}F_3NH$ $(M + H)^+$: 230.1152, found 230.1149; $[\alpha]^{22}_D$ = +50.9 (*c* 3.47, $CDCl_3$).

Methyl (*R*)-2,3,4,9-Tetrahydro-1*H*-Pyrido[3,4-*b*]-Indole-3-Carboxylate (23). (*R*)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (30 mg, 0.14 mmol) was dissolved in methanol (1.4 mL), and thionyl chloride (15 μL, 0.21 mmol) was added. The mixture was heated to 80 °C for 2 h and was then evaporated in vacuo. The amine salt was suspended between a mixture of CH_2Cl_2 (1 mL) and saturated aq. $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford analytically pure **12** (26 mg, 80%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.47 (dd, J = 7.6, 1.3 Hz, 1H), 7.27 (dd, J = 8.1, 1.0 Hz, 1H), 7.15 (dd, J = 8.1, 1.4 Hz, 1H), 7.10 (td, J = 7.4, 1.1 Hz, 1H), 4.13−4.03 (m, 2H), 3.83−3.75 (m, 4H), 3.13 (dd, J = 15.3, 1.2 Hz, 1H), 2.90 (ddt, J = 15.3, 9.6, 1.9 Hz, 1H), 2.19 (s, 1H); **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 173.9, 136.1, 132.1, 127.3, 121.8, 119.6, 117.9, 110.9, 107.5, 56.0, 52.3, 42.2, 25.5; **HRMS (ESI-TOF)** *m* / *z* calcd for $C_{13}H_{14}N_2O_2H$ $(M + H)^+$: 231.1129, found 231.1130; $[\alpha]^{22}_D$ = +68.3 (*c* 4.60, $CHCl_3$).

GENERAL PROCEDURE 3

CEC Reactions. The amine was weighed in a volumetric flask and diluted to volume with methanol to make a 200 mM amine stock solution. This solution was subsequently diluted with *tert*-amyl alcohol to make a 10 mM stock solution for CEC reactions. This solution (100 μL (1 μmol)) was added to an amber mass spectrometry vial, which had been preweighed with 3 μmol of each acyl transfer reagent, and the vial was sealed with an aluminum cap and shaken lightly to mix the contents. If the amine substrate was a salt, Et_3N (1 μL) was added to liberate the free amine in situ. The mixture was allowed to stand for the designated amount of time, at the designated temperature, after which the cap was removed and 100 equivalents of propionic anhydride was added. The mixture was allowed to stand for 15 min, after which the contents of the vial were pipetted into a dram vial.

For analysis, 3 μL of the CEC reaction mixture was diluted to 3 mL with 30% $MeCN/H_2O$ (UPLC grade solvents) to make a 10 μM stock solution. This solution was diluted to 1 and 3 μM in LC−MS vials, and the 1, 3, and 10 μM solutions were subjected to mass spectrometry analysis using an optimized method on a UPLC-QqQ-MS. Samples were subjected to UPLC using an Acquity UPLC system equipped with a C18 column eluted with a gradient of MeCN with 0.2% acetic acid (A1 buffer) in a mixture of 98:1.8:0.2 H_2O/MeCN/acetic acid (B1 buffer) from 10−90% of A1 buffer/B1 buffer. This system was coupled to a Quattro Premier XE QqQ MS using a learning method, allowing the user to input the expected ionic masses in each sample. The instrument then optimizes itself to look for the desired mass transition through the QqQ.

As proof of concept, analysis was also performed for substrates **19**, **25**, and **30** using a Waters Acquity QDA UPLC-MS system. For analysis, 5 μL of the CEC reaction mixture was diluted to 1 mL with 10% H_2O/MeCN (UPLC grade solvents) to make a 50 μM mass spectrometry sample. Samples were subjected to UPLC using a Waters Acquity UPLC system equipped with a C4 column eluted with a gradient from 0−100% $MeCN/H_2O$ + 0.1% formic acid. The TIC chromatogram was then used to prepare extracted ion chromatograms (EICs) for the $[M + H]^+$ peak of the C3, C4, and C5 amides in question. Data for these substrates are reported in the Supporting Information and are in excellent agreement with the data from the UPLC-QqQ-MS.

Hydroxamic Acid Crossover Experiment. (4a*S*,9a*R*)-3-oxo-2,3,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-4(4a*H*)-yl pentanoate (**6 (*S*,*R*)-C5**) (5.3 mg, 0.018 mmol) and (4a*R*,9a*S*)-4-hydroxy-4,4a,9,9a-tetrahydroindeno[2,1-*b*][1,4]-oxazin-3(2*H*)-one (**46**) (3.8 mg, 0.018 mmol) were added to a dram vial equipped with a stir bar, and *t*-amyl alcohol (0.6 mL, 0.03 M) was added. The mixture was heated to 60 °C for 6 h to replicate the CEC reaction conditions. The reaction mixture was cooled to room temperature, and a 240 μL aliquot was diluted to 2 mL with a solution of 10% *i*PrOH/hexanes (both HPLC grade). This mixture was characterized by HPLC using a Chiralcel AD column (w/o guard) eluted with 15% *i*PrOH/hexanes with a flow rate of 1.0 mL/min. The two hydroxamic acids were observed as a 2.9:1 ratio of **46**/**48**. HPLC traces can be found in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01275.

Experimental details, NMR spectra, mass spectrometry data, computational details, and HPLC traces (PDF)

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Notes

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