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Catalytic Kinetic Resolution of Cyclic Secondary Amines

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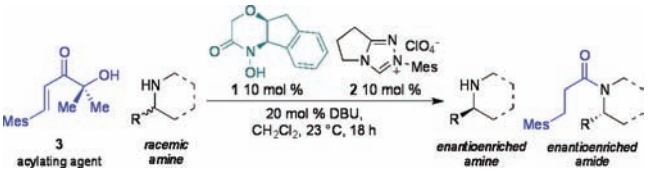
Supporting Information

ABSTRACT: The catalytic resolution of racemic cyclic amines has been achieved by an enantioselective amidation reaction featuring an achiral N-heterocyclic carbene catalyst and a new chiral hydroxamic acid cocatalyst working in concert. The reactions proceed at room temperature, do not generate nonvolatile byproducts, and provide enantioenriched amines by aqueous extraction.

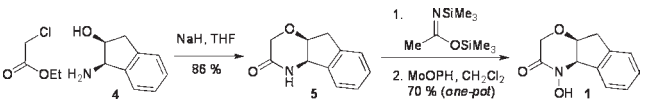
Enantiomerically pure amines are key constituents of pharmaceuticals and agricultural chemicals;[1] however, there are few methods for the catalytic resolution of racemic amines by either chemical reagents or biotechnological approaches.[2] This is particularly true of secondary amines, where the state of the art remains chromatography on chiral supports or classical resolution by diastereomer formation. In contrast, catalytic kinetic resolution[3] is often the method of choice for the preparation of other important chiral compounds, including secondary alcohols,[4] carboxylic acids,[5] and epoxides,[6] as kinetic resolutions have the advantage of reliably delivering enantiopure materials. In this report, we document the catalytic kinetic resolution of secondary amines by an enantioselective amide formation featuring two independent catalytic cycles that work in concert with complementary reactivity and chemoselectivity. Despite the complexity of the reaction mechanism, the resolution is operationally simple, proceeds at room temperature, produces no nonvolatile byproducts, and affords enantioenriched amines by aqueous extraction (Scheme 1).

The strong nucleophilicity of amines toward typical acylating reagents generally precludes the intervention of a chiral modulator necessary for achieving catalytic amine resolutions. Therefore, most approaches to kinetic resolution of amines require stoichiometric amounts of chiral acylating agents.[7] Fu has reported effective catalytic amine resolutions using bulky acylation reagents,[8] including the resolution of indolines.[9] Birman[10] and Miller[11] have resolved protected amine derivatives, including oxazolidinones and thioformylamides, with excellent selectivities, but this strategy precludes the use of secondary amines. Alternatively, low reaction temperatures and concentrations can suppress the background acylation, a strategy employed by Seidel[12] in a promising kinetic resolution of primary amines using standard acylating reagents and chiral cocatalysts; secondary amines, however, fail to react under these conditions. Important biocatalytic approaches include enantioselective carbamate formation,[13] amide formation,[14] deracemization,[15] and dynamic kinetic resolution,[16] but the application of these methods to cyclic secondary amines is limited to isolated examples;[17] the resolution of morpholines, piperazines, and azepanes has not been described.

Scheme 1. Catalytic Kinetic Resolution of Secondary Amines



Scheme 2. Synthesis of Hydroxamic Acid 1



The basis for our approach to amine resolution is the catalytic generation of acyl azoliums.[18] These species undergo rapid acylations with water, alcohols, and thiols but do not acylate amines.[19] We have devised methods for the catalytic generation of acyl azoliums from α-functionalized aldehydes by internal redox reactions promoted by N-heterocyclic carbenes (NHCs).[20] Catalytic amide formation requires an additive such as imidazole or 1-hydroxy-7-azabenzotriazole (HOAt) to convert the acyl azolium to a secondary activated species that acylates the amine.[21] Competing imine formation complicates the combination of aldehyde and amine, but we have overcome this problem by using α'-hydroxyenones as bench-stable surrogates for aldehydes to give clean, catalytic amidation reactions without imine formation and with no background rate in the absence of the additive.[22] These observations opened the possibility of catalytic kinetic resolutions of amines using an achiral NHC working in concert with a chiral acylation cocatalyst.

Using 2-methylpiperidine as a challenging substrate, we sought to identify reaction conditions and cocatalysts for the kinetic resolution of secondary amines. Chiral protic heterocycles, including imidazoles and triazoles, offered little or no enantioselectivity.[23] A search for alternative cocatalysts led us to hydroxamic acids.[24] While an initial screen of commercially available or previously reported chiral hydroxamic acids offered only modest selectivities,[25] the *cis*-(1*R*,2*S*)-aminoindanol-derived hydroxamic acid **1** gave excellent results. This novel catalyst can be readily prepared in two steps from either enantiomer of inexpensive amino alcohol **4** via known lactam **5** (Scheme 2).[26] Further optimization of the catalytic resolution conditions, including the use of mesityl-substituted α'-hydroxyenone **3** to deter NHC-catalyzed side

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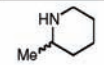
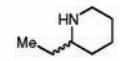
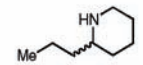
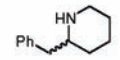
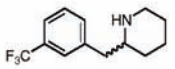
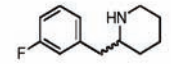
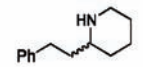
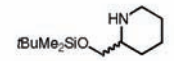
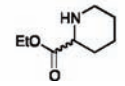
Table 1. Catalytic Kinetic Resolution of 2-Substituted Piperidines with Hydroxamic Acid 1

entry	*rac*-amine	conv.[a] (yield, %)[b]	*er* amine	*er* amide	*s*
1		55 (55)	94:6	86:14	17
2[c]		57 (57)	96:4	85:15	18
3		53 (53)	88:12	84:16	12
4[d]		49 (48)	16:84	15:85	11
5		48 (48)	88:12	91:9	23
6		34 (34)	70:30	94:6	23
7[e]		51	91:9	90:10	23
8		34 (34)	72:28	93:7	21
9		30 (30)	68:32	93:7	19
10		41 (41)	79:21	92:8	21
11		29 (28)	67:33	91:9	14
12[e]		46 (42)	83:17	91:9	20

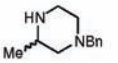
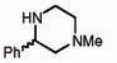
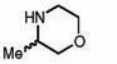
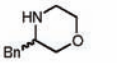
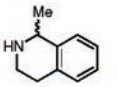
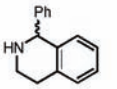
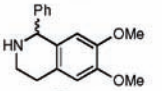
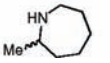
Conditions: Resolutions were carried out on a 0.25 mmol scale with amine (1.0 equiv), triazolium **2** (10 mol %), hydroxamic acid **1** (10 mol %), α'-hydroxyenone **3** (0.7 equiv), and DBU (0.2 equiv) in CH_2Cl_2 (0.1 M) at 23 °C for 18 h. [a] Calculated conversion.[28] [b] Isolated yield of amide. [c] 10 mmol scale. [d] The enantiomer (*ent*-**1**) of the hydroxamic acid cocatalyst was used. [e] 1.0 equiv of **3** was used.

reactions,[27] led to a robust enantioselective amidation of 2-methylpiperidine with synthetically useful selectivity (s = 17).

Treatment of racemic amines (1.0 equiv) with α'-hydroxyenone **3** (0.7 equiv), triazolium precatalyst **2** (10 mol %), chiral cocatalyst **1** (10 mol %), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 20 mol %) in CH_2Cl_2 (0.1 M) at 23 °C for 18 h produced enantiomerically enriched amides; the unreacted scalemic amines were recovered by extraction or carbamoylation. These conditions were tested for a range of substituted piperidines (Table 1), all of which gave good selectivities and the same sense of enantioselectivity. In addition to 2-alkylpiperidines, the synthetically important pipecolinic ester was resolved with excellent selectivity (entry 12). The resolution could be easily conducted on a gram scale (10.0 mmol of amine; entry 2) with quantitative recovery of hydroxamic acid **1**. As with any kinetic resolution, the enantiopurity of the recovered unreacted amine can be improved by higher conversions (entry 7).

We also evaluated other classes of cyclic amines. Substituted piperazines and morpholines, both of which are components of chiral pharmaceuticals, were resolved with s factors ranging from 11 to 23 (Table 2, entries 1−4). Tetrahydroisoquinolines (entries 6−8) were resolved with outstanding levels of selectivity (up to s = 74). It is noteworthy that in all cases the resolutions were conducted under identical reaction conditions; only minor variations in the reaction workup were made.

Table 2. Catalytic Kinetic Resolution of Piperazines, Morpholines, Tetrahydroisoquinolines, and Azepanes

entry	*rac*-amine	conv.[a] (yield, %)[b]	*er* amine	*er* amide	*s*
1		45 (45)	82:18	89:11	16
2[c]		53	94:6	89:11	23
3		40 (40)	79:21	93:7	24
4		41 (41)	76:24	87:13	11
5[c]		51 (51)	91:9	90:10	23
6		56 (47)	93:7	83:17	13
7		49 (49)	93:7	95:5	53
8		50 (50)	95:5	96:4	74
9		47 (40)	78:22	82:18	8

Conditions: Resolutions were carried out on a 0.25 mmol scale with amine (1.0 equiv), triazolium **2** (10 mol %), hydroxamic acid **1** (10 mol %), α'-hydroxyenone **3** (0.7 equiv), and DBU (0.2 equiv) in CH_2Cl_2 (0.1 M) at 23 °C for 18 h. [a] Calculated conversion.[28] [b] Isolated yield of amide. [c] 1.0 equiv of **3** was used.

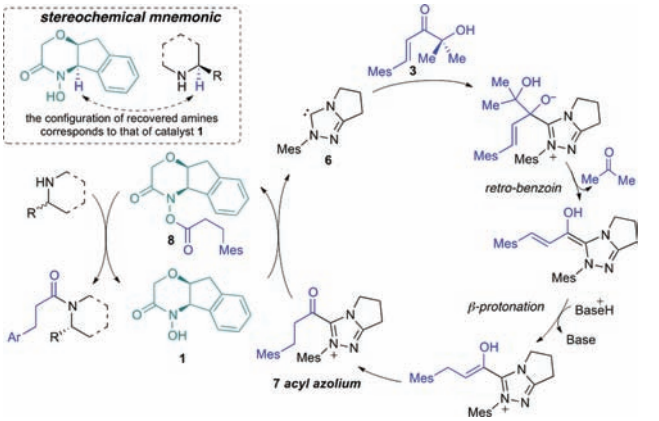


Figure 1. Proposed synergistic catalytic cycles for the kinetic resolution of amines and a stereochemical mnemonic.

Under the standard conditions, modest selectivities were observed in resolutions of 1-phenylethanamine, 2-methylpyrrolidine, 2-methylaziridine, and 3-methylpiperidine, and the reaction did not proceed in a preliminary evaluation of an acyclic secondary amine. It is probable that alternative catalyst designs will address these other substrates classes.

Monitoring the reaction by ^{1}H NMR spectroscopy showed that acylated intermediate **8** (Figure 1) was formed within

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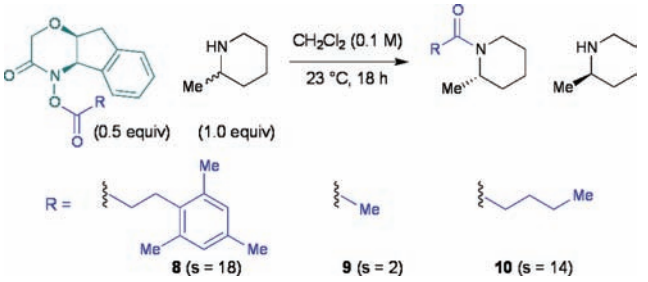
Scheme 3. Effect of the Acyl Substituent on the Selectivity



minutes. We confirmed **8** to be the active acylating agent by independently preparing this compound and employing it as a stoichiometric reagent, an experiment aided by the fact that **8** could be isolated and purified by column chromatography. Kinetic resolution of 2-methylpiperidine with 0.5 equiv of isolated **8** gave identical selectivity (s = 18). These results led us to propose the synergistic catalytic cycles shown in Figure 1. Hydroxamic acid **1** can be regarded as a chiral variant of commonly used N-acylation reagents such as *N*-hydroxysuccinimide or HOAt. Its success as a catalyst, however, depends on the ability of the NHC to generate synergistically the acylated hydroxamate via intermediate acylating agent **7** that does not itself react with the amine.[29]

In addition to high background rates, enantioselective acylations are known to be challenging because of the large number of potential transition states. Furthermore, cyclic chiral amines have many conformations that are energetically similar. We initially hypothesized that an acyl group containing an aryl moiety would be essential for controlling the number of available conformations and thereby enhancing the selectivity; a similar phenomenon has been observed in the kinetic resolution of secondary benzylic alcohols.[30] When we employed **9** (R = Me) as a stoichiometric reagent (Scheme 3), the selectivity factor dropped precipitously (s = 2) but recovered when reagent **10** (R = *n*Bu) was used (s = 14). These experiments demonstrate that there is no significant effect of the mesityl group on the stereoselectivity; its role is to deter the formation of side products that can arise from NHC-catalyzed dimerizations. They also suggest that fine-tuning of the acyl group can improve the selectivity or synthetic efficiency.

While we cannot at this point rationalize the high selectivity of acylations with hydroxamic acid **1**, the consistency in the absolute configuration of the acylated products allows us to propose the mnemonic shown in Figure 1 as a guide for predicting the stereochemical outcome of the reaction.

This catalytic resolution of amines is unique in that two independent catalytic cycles work in concert with complementary reactivity and chemoselectivity, thereby accomplishing an enantioselective reaction that would otherwise be plagued by competing background processes. The reaction itself is operationally simple, proceeds at room temperature, produces no nonvolatile byproducts, and affords enantioenriched amines by aqueous extraction. Chiral hydroxamic acids are a new class of acyl transfer agents that will be useful for other chemo- and enantioselective reactions.[31]

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data for all new compounds, NMR spectra for the products, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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