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Expanded substrate scope and catalyst optimization for the catalytic kinetic resolution of N-heterocycles†

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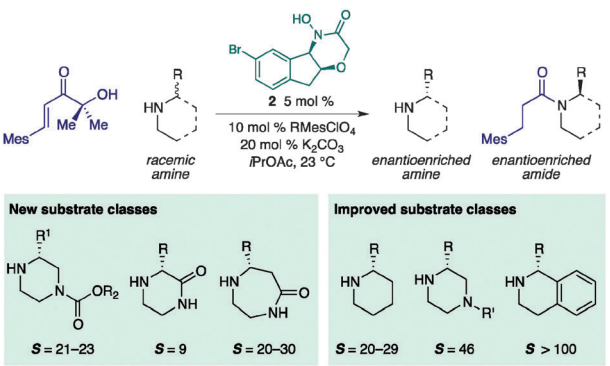
The scope, reactivity, and selectivity of the chiral hydroxamic acid-catalyzed kinetic resolution of chiral amines are improved by a new catalyst structure and a more environmentally friendly reaction protocol. In addition to increasing selectivity across all substrates, these conditions make possible the resolution of N-heterocycles containing lactams or other basic functional groups that can inhibit the catalyst.

Enantiopure amines are important components of pharmaceuticals and other biologically active molecules.[1] Synthetic methods for the preparation of enantioenriched primary amines include nucleophilic addition to substrates bearing a chiral auxiliary,[2] asymmetric hydroamination,[3] asymmetric hydrogenation,[4] and kinetic resolution.[5] Acyclic chiral secondary amines can often be prepared from the corresponding primary amines by alkylation. In contrast, enantiopure cyclic secondary amines such as piperidines, morpholines, diazepanes and piperazines are often difficult to obtain by enantioselective synthesis;[6] classical resolution by diastereomeric salt formation and chromatography on chiral supports remain the state of the art.[7,8] In seeking to address this well-known deficiency in asymmetric synthesis, we have developed a new catalytic kinetic resolution of N-heterocycles by the combination of a chiral hydroxamic acid acylation catalyst coupled with the catalytic generation of an acylating agent with an achiral N-heterocyclic carbene.[9]

During the course of our studies, we identified three limitations of our original conditions to the resolution of chiral N-heterocycles. First, some substrates gave unexpectedly poor selectivity. Although enantiopure recovered starting material can be obtained from any selectivity level, *S*-factors of 20 or higher are desired for practical use.[11] Some of our most important substrates, for example 2-ethyl piperidine (S = 12), fell slightly short of this goal. Second, N-heterocycles containing lactam substructures or pendant amines with carbamate protecting groups or bulky substituents gave poor conversions. Third, the use of chlorinated solvents and relatively high catalyst loadings diminished the appeal of these conditions. In this communication we report optimized catalyst **2** and improved reaction conditions (0.2 M *i*PrOAc, K_2CO_3, 5 mol% chiral catalyst) that increase selectivity and make possible resolutions of substrates unreactive under our prior conditions (Scheme 1).

Chiral hydroxamic acid catalyst **1** is prepared from (1*R*, 2*S*)-aminoindanol in two steps.[9,12] Our first task was therefore to identify a variant of this catalyst that improved the selectivity of substrates such as 2-ethyl piperidine. Substitution of the aromatic ring provided the most easily executed route to catalyst tuning. Using standard protocols we prepared 6-bromo, 6,7-dibromo, and 6-nitro-substituted variants **2–4** (Table 1).[13] A different route, beginning from the amino indanol, was used to prepare *N*-hydroxycarbamate **5**.[14] Upon screening these catalysts for the resolution of 2-ethyl piperidine (Table 1), we were pleased to find that 6-bromo-substituted catalyst **2** led to a marked increase in selectivity.

Our original conditions were not suitable for the resolution of substrates bearing lactam or *N*-carbamate groups. Diazepanones and others (**6–8**, Scheme 2a and b) showed poor reactivity. We speculated that these substrates form hydrogen bonds to the hydroxamic acid, thereby deactivating the catalyst. To test this hypothesis we conducted the resolution of 2-methylpiperidine – an excellent substrate under normal conditions – in the presence of 1 equiv. of δ-valerolactam (**9**, Scheme 2c). We observed significantly lower conversion and reaction rate, pointing to an unproductive interaction between the chiral catalyst and the added lactam. NMR titration of hydroxamic acid **1** with δ-valerolactam **9** proved informative. Upon addition of **9** to a $CDCl_3$ solution of **1**, we observed a significant change of the chemical shift of the OH proton of the hydroxamic acid in the NMR spectra, indicative of a hydrogen bonding interaction of



Scheme 1 New hydroxamic acid catalyst **2** and reaction conditions for catalytic kinetic resolution of secondary cyclic amines.

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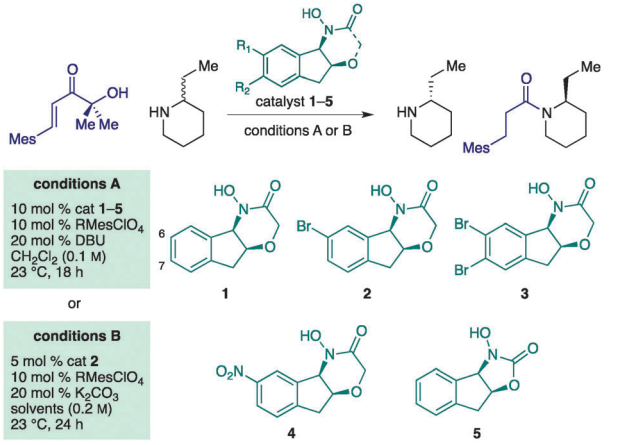
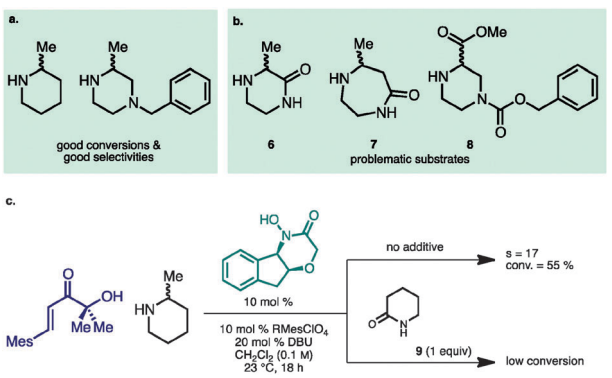
Table 1 Screening of catalysts **1–5** in CH_2Cl_2 *vs.* *i*PrOAc[a]



Entry	Condition	Catalyst	S^b	Conv.[c] (%)	*er* amine[d]	*er* amide[d]
1	A	**1**	12	53	88 : 12	84 : 16
2	A	**2**	25	52	93 : 7	90 : 10
3	A	**3**	9	51	83 : 17	82 : 18
4	A	**4**	12	47	82 : 18	86 : 14
5	A	**5**	1	20	51 : 49	54 : 46
6	B, CH_3CN	**2**	16	37	74 : 26	91 : 9
7	B, THF	**2**	> 23	59	> 99 : 1	84 : 16
8	B, *i*PrOAc	**2**	21	57	97 : 3	86 : 14

[a] $RMesClO_4$ = 2-(2,4,6-trimethylphenyl)-2,5,6,7-tetrahydropyrrolo[2,1-*c*] [1,2,4]triazol-4-ylium perchlorate. [b] Calculated selectivity.[10] [c] Calculated conversion. [d] Determined by SFC on a chiral support.



Scheme 2 (a) Substrates that show good conversion and selectivity in CH_2Cl_2. (b) Substrates with lactam or carbamate substructures that show low conversion in CH_2Cl_2. (c) The addition of 1 equiv. of δ-valerolactam inhibits the catalytic amine resolution.

the lactam with the cyclic hydroxamic acid **1**. Standard methods were used to calculate an association constant of 100 M^{-1}.[15]

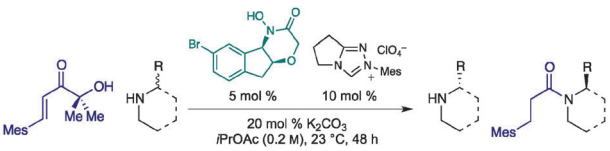
This finding suggested that a more polar solvent could disrupt this interaction and free the hydroxamic acid to participate in the synergistic catalytic cycle. This theory was tested by performing the same titration experiment in CD_3CN. We observed a linear relationship indicating very little hydrogen bonding interaction and no association was detected within experimental error.

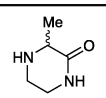
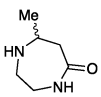
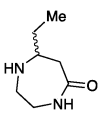
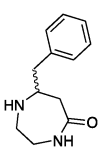
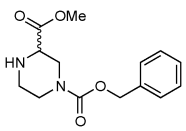
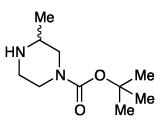
A screen of alternative solvents for the catalytic kinetic resolution revealed *i*PrOAc as a suitable alternative (Table 1, entries 6–8). Furthermore, we found that these conditions allowed the use of K_2CO_3 as the base, which simplified the reaction workup; the DBU used in our original procedure was sometimes difficult to separate from the recovered, enantio-enriched amine. The improved reactivity offered by Br-substituted catalyst **2** and these alternative reaction conditions also allowed us to reduce the loading of chiral hydroxamic acid catalyst **2** to 5 mol% (Table 1, entry 8).

These new conditions were applied to the resolution of a number of valuable amines that were unreactive or not effectively resolved with our original procedure (Table 2). Most importantly, the use of *i*PrOAc allowed us to resolve substrates containing a lactam, including 3-alkyl-piperazinones (entry 1) and 7-substituted 1,4-diazepanones (entries 2–4). Furthermore, it also significantly improved both the reactivity and selectivity of piperazines bearing *N*-carbamate protecting groups. These valuable substrates had proven to be problematic under our original conditions.

We have also evaluated these improved conditions for the resolution of piperidines, morpholines, tetrahydroisoquinolines, and azepanes, including both previously tested substrates as well as new examples (Table 3). In comparison to our original conditions, we obtained better selectivity in all cases examined.

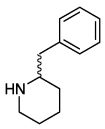
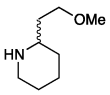
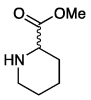
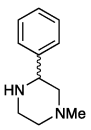
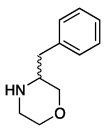
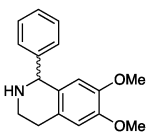
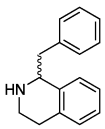
Table 2 Kinetic resolutions of substrates containing lactam and carbamate functional groups



Entry	Substrate	S^a	Conv.[b] (%)	*er* amine[c] yield[d] (%)	*er* amide[c] yield[d] (%)
1[e]		9	58	90 : 10 (42)	79 : 21 (56)
2		22	54	95 : 5 (43)	88 : 12 (54)
3		> 20	64	> 99 : 1 (34)	78 : 22 (48)
4[e]		30	41	81 : 19 (39)	94 : 6 (40)
5[e]		23	45	84 : 16 (55)	92 : 8 (44)
6		21	57	97 : 3 (35)	86 : 14 (21)

[a] Calculated selectivity. [b] Calculated conversion. [c] Determined by supercritical fluid chromatography or HPLC on a chiral support. [d] Isolated yield after column chromatography. [e] 10 mol% hydroxamic acid.

Table 3 Kinetic resolution of piperpidines, piperazines, morpholines, isoquinolines, and azepanes with 5 mol% **2** in *i*PrOAc[a]

Entry	Substrate	S[b]	Conv.[c] (%)	*er* amine[d] yield[e] (%)	*er* amide[d] yield[e] (%)
1		21	57	97 : 3 (40)	86 : 14 (55)
2		> 22	61	> 99 : 1 (39)	82 : 18 (50)
3		29	52	94 : 6 (27)	91 : 9 (44)
4		26	52	94 : 6 (46)	90 : 10 (51)
5		20	33	71 : 29 (61)	93 : 7 (31)
6		46	55	99 : 1 (27)	90 : 10 (51)
7		29	46	87 : 13 (45)	93 : 7 (43)
8		127	51	98 : 2 (36)	97 : 3 (51)
9		16	46	83 : 17 (45)	89 : 11 (43)
10		9	46	79 : 21 (24)	84 : 16 (35)

[a] 5 mol% hydroxamic acid, 24 h. [b] Calculated selectivity. [c] Calculated conversion. [d] Determined by supercritical fluid chromatography or HPLC on a chiral support. [e] Isolated yield after column chromatography.

In summary, we have identified improved conditions and catalysts for the catalytic kinetic resolution of cyclic secondary amines. A remote substituent on the chiral hydroxamic acid catalyst improved selectivities of 6- and 7-membered N-heterocycles in the range needed for practical resolutions and the use of *i*PrOAc allowed us to expand the substrate scope to piperazinones and diazepanones, which were unreactive under our prior conditions.

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