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Stereoelectronic Basis for the Kinetic Resolution of N-Heterocycles with Chiral Acylating Reagents

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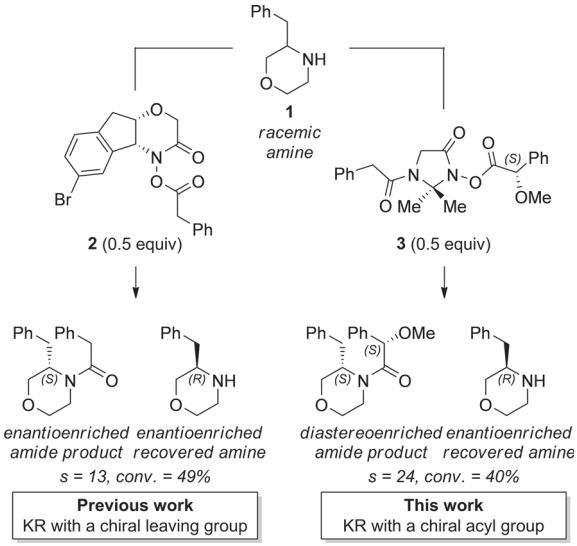
Abstract: The kinetic resolution of N-heterocycles with chiral acylating agents reveals a previously unrecognized stereoelectronic effect in amine acylation. Combined with a new achiral hydroxamate, this effect makes possible the resolution of various N-heterocycles by using easily prepared reagents. A transition-state model to rationalize the stereochemical outcome of this kinetic resolution is also proposed.

The kinetic resolution of racemic small molecules remains a valuable method for the preparation of enantioenriched materials, because it can always afford enantiopure materials by running the reactions to higher conversions.[1] The use of both stoichiometric reagents and catalysts for the kinetic resolution of alcohols, epoxides, and carboxylic acids is well established.[2] In contrast, reagents for the kinetic resolution of amines—particularly secondary amines—are underdeveloped, and the state of the art remains resolution by chromatography on chiral supports or diastereomeric salt formation and selective crystallization.[3] The latter can be relatively effective, but often requires the tedious screening of dozens or hundreds of salts and conditions for successful resolution.[3a] Enzymatic resolutions are highly developed for the resolution of alcohols, carboxylic acids, and primary amines, but their utility for separating the enantiomers of secondary amines is limited.[4]

We have recently documented a chiral hydroxamic acid effective for the resolution of piperidines, piperazines, diazepanes, morpholines, and tetrahydroisoquinolines.[5] The resolutions, with either catalytic or stoichiometric amount of the chiral hydroxamic acid, proceed at room temperature offering good selectivities (s) for the isolation of enantioenriched N-heterocycles.[6]

The catalytic kinetic resolution of 3-benzylmorpholine **1** with a chiral hydroxamic acid proceeds with good selectivity (s = 29).[5b] This is sufficient for isolating recovered starting material in enantiopure form,[1b] but is not suitable for preparing the amides with sufficient enantioselectivity or for dynamic kinetic resolutions. The use of other achiral acyl groups, such as 2-phenylacetate (**2**, Scheme 1) and 3-phenylpropanoate,[5c] generally gave somewhat inferior selectivities (s = 13–25). To further enhance the selectivity, we sought to identify an enantiomerically enriched acyl group that could be combined with the hydroxyamic acid catalyst, for example, a chiral acyl group generated by the action of a N-heterocyclic carbene (NHC) catalyst.[7] To establish whether such a strategy would be viable, we chose first to examine the effect of readily available chiral acyl groups on the kinetic resolution of secondary amines. These studies revealed a surprising stereoelectronic effect on the selectivity of amine acylation that has not been previously documented, as well as an effective method for amine resolution using a chiral acyl donor.



Scheme 1. Kinetic resolution (KR) of amine **1** with stoichiometric acylating agents.

For initial studies, we selected (*S*)-*O*-Me-mandelic acid, which is readily prepared[8] or commercially available. The stoichio-

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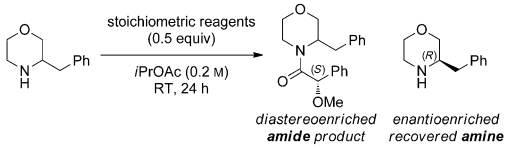
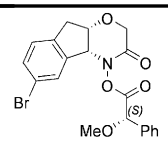
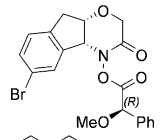
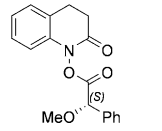
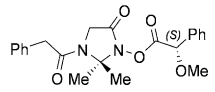
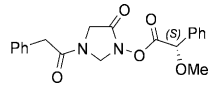
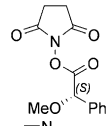
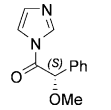
metric reagent prepared with (4a*R*,9a*S*)-hydroxamic acid[5b] gave a modest increase in selectivity (Table 1, entry 1). Surprisingly, the reagent prepared from (*R*)-*O*-Me-mandelic acid and

Table 1. Screening of leaving groups on stoichiometric reagents.[a]



Entry	Stoichiometric reagent	s	Conv. [%]	d.r.$_{amide}$[b]	e.r.$_{amine}$
1		30	50	92:8	92:8
2		1	50	50:50[c]	50:50
3		9	32	86:14[c]	67:33
4		24	40	93:7	79:21
5		8	40	84:16[c]	73:27
6		2	36	66:34[c]	59:41
7		1	50	50:50[c]	50:50

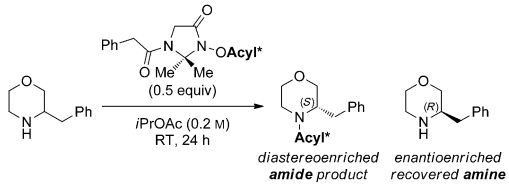
[a] Selectivity factor (s) and calculated conversion (conv.) were determined by Kagan's equation (see Ref. [6]). [b] See the Supporting Information for the determination of diastereomeric ratios (d.r.). [c] Epimerized amide products were observed (<10% for entries 2, 3, and 5; >30% for entries 6 and 7). See the Supporting Information for details.

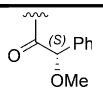
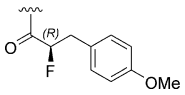
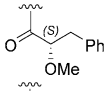
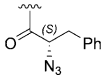
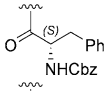
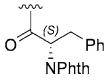
the (4a*R*,9a*S*)-hydroxamic acid was completely unselective (entry 2), prompting a further investigation into the nature of the leaving group.

A series of activated (*S*)-mandelic acid reagents were prepared, taking care to avoid epimerization in their formation. The chiral acylating agents from achiral, cyclic hydroxamic acids (Table 1, entries 3–5) were all effective for amine resolution. The bulky glycine derivative (Table 1, entry 4) gave a comparable selectivity to that of the chiral hydroxamic acid bearing an achiral acyl group (s = 24 vs. s = 13–29).[5] The more common activated carboxylates derived from *N*-hydroxysuccinimide (Table 1, entry 6) or imidazole (entry 7) were far less selective. These reagents also suffered from a greater degree of epimerization during the amine resolutions, resulting in a greater proportion of diastereomeric amide products. The poor results from these examples may be an underlying reason for the slow development of chiral reagents for amine resolution, which despite some notable successes from Fu and co-workers,[9] Krasnov and co-workers,[10] Mioskowski and co-workers,[11] Seidel and co-workers,[12] Spivey and co-workers,[13] and others,[14] has not kept pace with developments in other areas of asymmetric synthesis.

To differentiate the steric and electronic effects of the chiral acyl group, we prepared a series of acyl donors by using the achiral hydroxamic acid identified in Table 1 (entry 4). Replacing of the OMe with an isosteric Et moiety led to almost complete erosion of selectivity (Table 2, entry 2), suggesting an important role for the electronegative substituent. Unfortunately, the obvious substrate for probing this effect further, the reagent prepared from (*S*)-2-fluorophenylacetic acid, could not be prepared in enantiopure form. Therefore, we compared hydrocinnamate esters with α-(*R*)-fluoro (Table 2, entry 3), (*S*)-methoxy[15] (entry 4), (*S*)-azido[16] (entry 5), (*S*)-*N*-Cbz-[17] (entry 6),

Table 2. Screening of chiral acyl groups (Acyl*) on stoichiometric reagents.[a]



Entry	Acyl*	s	Conv. [%]	d.r.$_{amide}$	e.r.$_{amine}$
1		24	40	93:7	79:21
2		3	24	69:31	56:44
3[b]		11	36	12:88[c]	29:71
4		6	35	81:19	67:33
5		3	38	71:29	63:37
6		1	50	55:45	55:45
7		−2[d]	18	41:59	48:52

[a] Selectivity factor (s) and calculated conversion (conv.) were determined by Kagan's equation (see Ref. [6]). [b] α-(*R*)-Fluoroacyl hydroxamate (91% *ee*) was used. [c] See the Supporting Information for the determination of diastereomeric ratios. [d] Opposite relative diastereoinduction was observed.

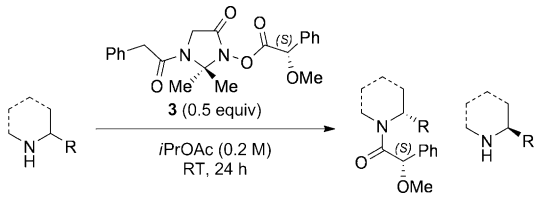
and (*S*)-*N*-phthaloyl[18] (entry 7) substituents. The fluorinated compound (Table 2, entry 3) proved to be the most selective, whereas the less electronegative amino acid derivative showed no selectivity. These results point to a previously unexploited stereoelectronic effect in diastereoselective acylations of chiral amines.

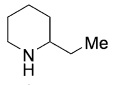
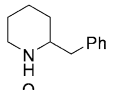
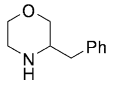
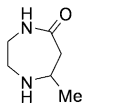
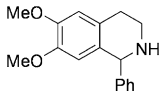
The (*S*)-mandelic acid derived reagent **3** is suitable for the kinetic resolution of several classes of racemic N-heterocycles (Table 3). Simply combining **3** and the amine in *i*PrOAc at room temperature for 24 h gave good conversions and acceptable selectivities for the resolution of 2-substituted piperidines (Table 3, entries 1 and 2), morpholine (entry 3), diazepanone (entry 4), and tetrahydroisoquinoline (entry 5). However, the selectivities in most cases were inferior to those obtained under catalytic conditions using a chiral hydroxamic acid derived from either enantiomer of *cis*-(1,2)-aminoindanol.[5a] Nevertheless, the low cost of (*S*)-mandelic acid and the ease of preparing the achiral hydroxamic acid may make these stoichiometric reagents preferable for certain applications (Scheme 2). In addition, the high selectivities and modular nature of the synthesis bodes well for future developments.

The most surprising aspect of this work is the identification of this unexploited stereoelectronic effect. Our stereochemical model to rationalize the selectivities obtained is presented in Figure 1. Ongoing mechanistic studies on the kinetic resolution of amines with chiral hydroxamic acids implicate a hydrogen-bonding interaction between the hydroxamate carbonyl and the amine proton. This interaction constrains the number of possible conformations to be considered, and the key alpha stereocenter on the electrophile ensures the addition occurs with high facial selectivity. The approach trajectory of the N-heterocycle with an equatorial nitrogen lone pair minimizes destabilizing steric interactions. The selectivity originates from the ability of only one enantiomer to approach with minimal destabilization due to its equatorial R group (Figure 1). Further discussion and alternative representations are presented in the Supporting Information.

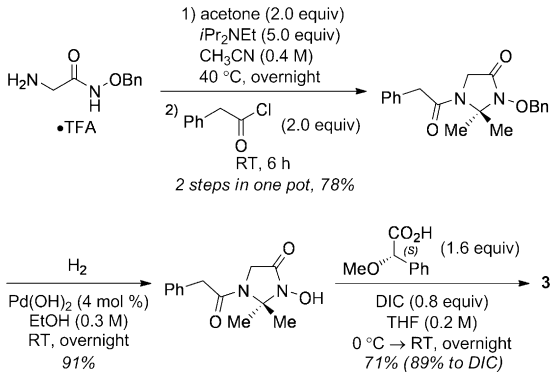
In summary, we have developed a chiral acyl hydroxamate reagent for kinetic resolutions of N-heterocycles. Optimization of reagent structure and a survey of acyl donors revealed that highly selective reactions can result from the stereoelectronic preferences of a proximal alpha stereocenter. This feature had not been previously exploited for enantioselective reactions of amines, and led to the development of a simple, highly selective reagent (s = 12 to 27) derived from (*S*)-mandelic acid. A model featuring this key stereoelectronic effect also predicts the stereochemical outcome. Collectively, this data provides crucial understanding to further improve selectivities and expand applicability of kinetic resolutions of amines.

Table 3. Kinetic resolutions using acyl hydroxamate **3**.[a]



Entry	Substrate	s	Conv. [%]	d.r.$_{amide}$[b]	e.r.$_{amine}$
1		12	39	88:12[c]	74:26
2		22	43	92:8[c]	82:18
3		24	40	93:7	79:21
4		27	38	94:6	77:23
5		18	36	92:8[c]	74:26

[a] Selectivity factor (s) and calculated conversion (conv.) were determined by Kagan's equation (see Ref. [6]). [b] See the Supporting Information for the determination of diastereomeric ratios. [c] Epimerized amide products were observed (< 5%). See the Supporting Information for details.



Scheme 2. Synthesis of acyl hydroxamate **3**. DIC = *N*,*N*′-diisopropyl-carbodiimide.

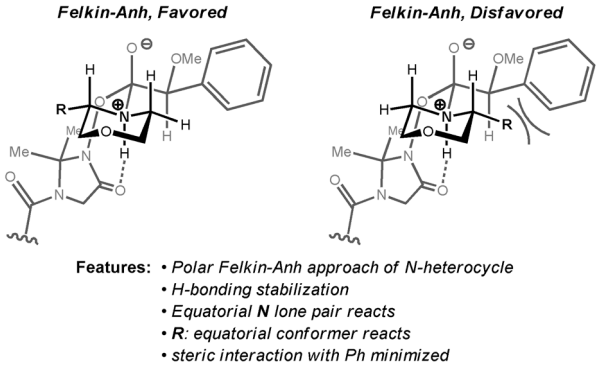


Figure 1. Proposed transition state model for kinetic resolution using **3**. See the Supporting Information for alternative approach trajectories.

Acknowledgements

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Keywords: hydroxamic acid · kinetic resolution · N-heterocycles · stereoelectronic effects · synthetic methods

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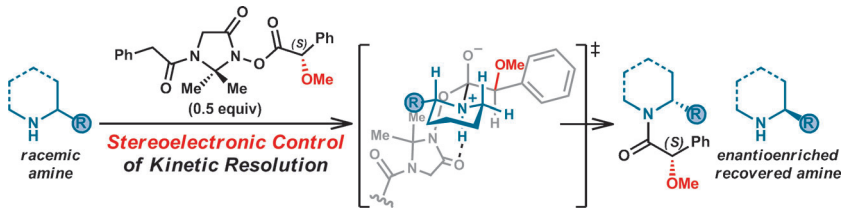

Look both ways! Esters of chiral acids and achiral hydroxyamic acids are just as effective for the kinetic resolution of N-heterocycles as those derived from a chiral hydroxyamic acid and achiral acids. The use of an inexpensive chiral acylating agent highlights the unique properties of hydroxyamic acids as leaving groups and reveals a previously unrecognized stereoelectronic effect in amine acylation (see scheme).

Synthetic Methods

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Stereoelectronic Basis for the Kinetic Resolution of N-Heterocycles with Chiral Acylating Reagents