Enhanced Molecular Recognition through Substrate–Additive Complex Formation in N-Heterocyclic-Carbene-Catalyzed Kinetic Resolution of α-Hydroxythioamides

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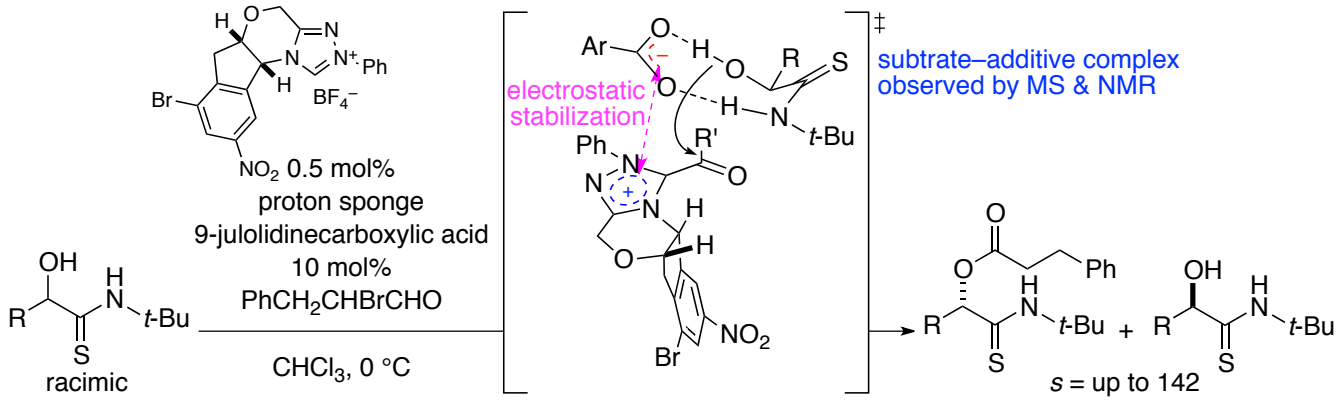


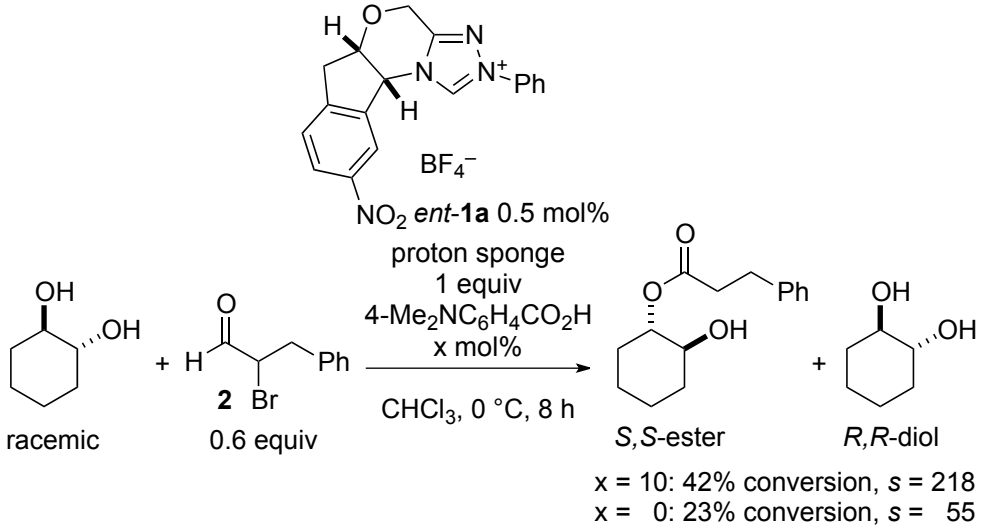
ABSTRACT. We describe a way of understanding enhanced molecular recognition through substrate–additive complex formation, and the development of the catalytic kinetic resolution of α-hydroxythioamides, which are versatile synthetic building blocks, using chiral N-heterocyclic carbene-catalyzed enantioselective acylation assisted by a carboxylate additive. Mass spectrometry provided evidence for the role of the additive, which forms a hydrogen-bonded complex with α-hydroxythioamide, resulting in both rate and selectivity enhancements. The synthetic applications of the resolved α-hydroxythioamides highlight the usefulness of the developed method.

KEYWORDS. organocatalysis/molecular recognition/catalytic kinetic resolution/α-hydroxythioamide/ N-heterocyclic carbene

Introduction

The development of catalytic asymmetric reactions is one of the most important objectives in synthetic organic chemistry. Significant effort has been devoted to achieving low catalyst loadings with satisfactory yields and enantioselectivities. In addition to developing new efficient catalysts, the identification of suitable additives has sometimes provided great improvement in catalytic performance.[1] Brønsted bases have been used as additives in several organocatalytic asymmetric reactions, where they mainly assist proton transfer,[2–5] act as acid scavengers,[6–9] or transform a less-efficient catalyst into a highly performing one.[10–13]

As a part of our research to develop organocatalytic reactions,[14–26] we reported the kinetic resolution of 1,2-*trans*-cycloalkanediols via asymmetric acylation catalyzed by chiral N-heterocyclic carbenes (NHCs).[27–29] The kinetic resolution of the diol proceeds with high enantioselectivity (selectivity factor, *s* = 218) with catalytic amounts of the chiral NHC precursor *ent*-**1a** and 4-dimethylaminobenzoic acid in the presence of 1,8-bis(dimethylamino)naphthalene (proton sponge) and 2-bromo-3-phenylpropanal **2** (Scheme 1). The use of the carboxylic acid as an additive significantly increases the reaction rate and the enantioselectivity of this reaction. Our working hypothesis for the role of the acid additive is as follows: (1) The carboxylic acid (pK_a = 5.03 in water[30]) is deprotonated by the strongly basic proton sponge (pK_a = 12.34 for the protonated form in water[31]) to generate a carboxylate anion. (2) The carboxylate anion forms a hydrogen-bonded complex with the diol. (3) In the transition state for acylation, the carboxylate anion acts as a general base that enhances the nucleophilicity of the diol. Although DFT calculations provided support for the proposed diol/carboxylate-anion interaction, we were previously unable to rationalize the increase in enantioselectivity afforded by this interaction. Here, we propose a new working hypothesis that rationalizes this increase in enantioselectivity.



Scheme 1. Our previous work: kinetic resolution of a diol.[27]

Namely, the formation of the hydrogen-bonded complex between the diol and the carboxylate anion enhances molecular recognition via an additional interaction with a chiral reaction partner (*vide infra*); this hypothesis can account for the observed increased enantioselectivity and is generalized in Figures 1. Compared to the usual interaction between a catalyst and substrate (Figure 1, mode A), the interaction between a catalyst and a complex formed by the substrate and an appropriate additive, which contains more recognition points than the substrate alone, can enable more precise recognition, with the targeted enantiomer selectively interacting with the catalyst (over the other enantiomer; mode B). Although several examples in which the addition of a Lewis or Brønsted acid enhances stereoselectivity in an NHC-catalyzed asymmetric reaction have been reported, this concept has not yet been proposed. Rovis et al. reported that a carboxylate salt, when used as a base to generate an NHC catalyst, enhanced rates and enantioselectivities during the asymmetric formation of *trans*-γ-lactams. They proposed that the in-situ-generated carboxylic acid activates the imine by protonation, while the carbonyl oxygen also interacts with a nucleophile through a hydrogen bond.[32] Scheidt et al. reported that the addition of lithium chloride dramatically increases diastereo- and enantioselectivity during spirooxyindole lactone formation from alkenals and *N*-alkylisatins, catalyzed by NHC.[33] Glorius et al. reported a similar improvement in diastereo- and enantioselectivity as a result of the addition of carboxylic acid.[34] They proposed that the *N*-alkylisatin and an *in situ* generated Breslow intermediate both coordinate to the lithium cation or form a hydrogen-bonded complex with the carboxylic acid, which control the orientation of the isatin and the Breslow intermediate in the transition state, resulting in high diastereo- and enantioselectivity. Zhong et al. evolved this chemistry to synthesize δ-spiro-lactones. They also proposed the formation of a hydrogen-bonded complex involving the carboxylic acid additive.[35] Huang and Chen reported that the rates and enantioselectivities for asymmetric addition of 1,3-diketones to nitroalkenes were improved by the addition of hexafluoroisopropanol. They suggested that the alcohol stabilizes the transition state by hydrogen bonding but proposed no specific structure for the transition state involving the alcohol.[36] In these reports, the enhanced rate and selectivity were explained in terms of transition state stabilization through coordination or hydrogen bonding; alternatively, it can be

considered that the formation of the additive-containing complex enables the substrates to interact with the reaction partners. In addition, to the best of our knowledge, there are no reports on the use of a Brønsted base additive to reinforce interactions with a catalyst through complex formation with a substrate.[37]

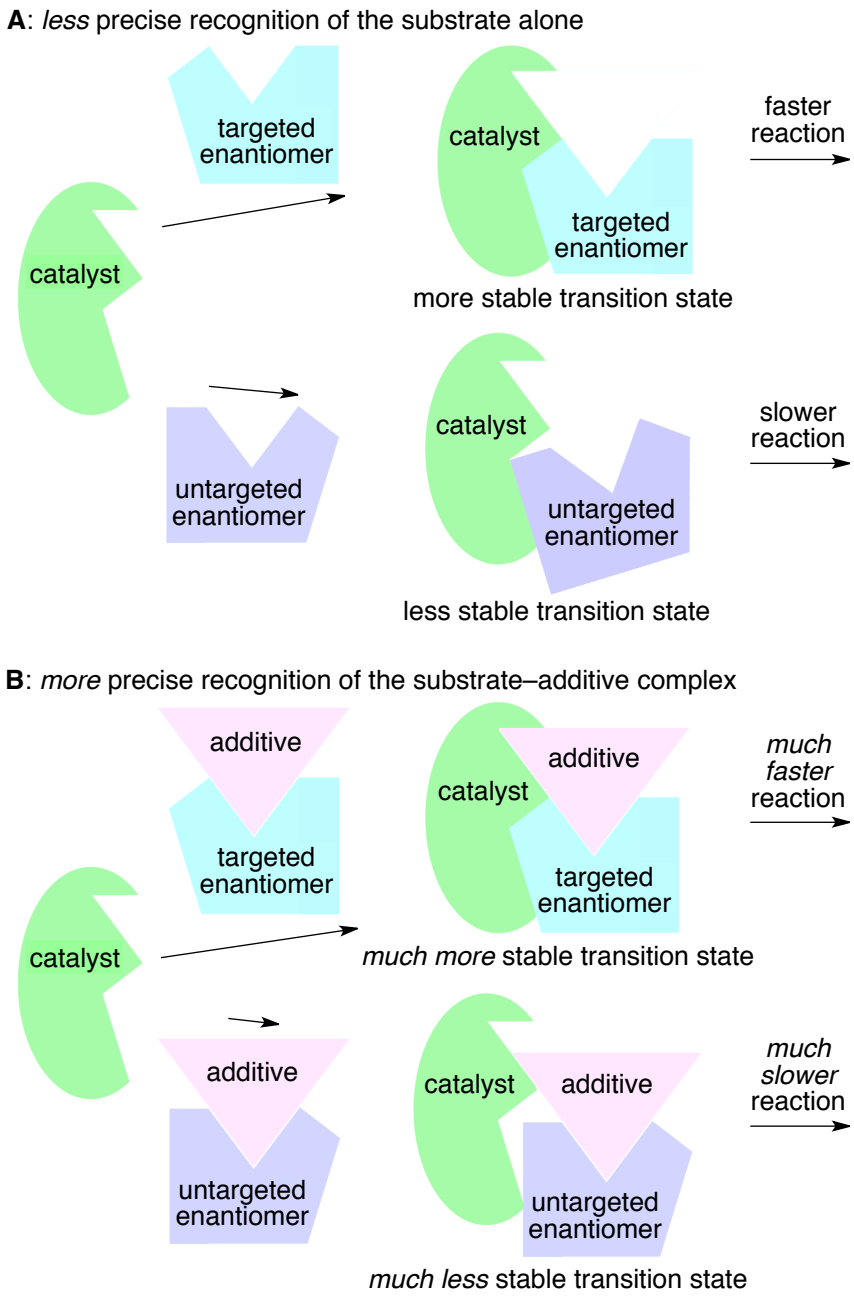


Figure 1. The concept of enhanced molecular recognition through substrate–additive complex formation.

Chiral α-hydroxycarboxylic acid derivatives are important building blocks in synthetic chemistry, and are found in biologically active compounds, such as cholesterol-lowering bestatin,[38] the cefamandole antibiotic,[39] the tesaglitazar PPARα/γ dual agonist,[40] and a renin inhibitor.[41] They also serve as building blocks of chiral ligands,[42,43] polymers,[44,45] and unnatural peptides and depsipeptides.[46,47] Among α-hydroxycarboxylic acid derivatives, the α-hydroxythioamide is an interesting and useful class of compound due to the versatility of the thioamide functionality (*vide infra*). Because chiral α-hydroxycarboxylic acid derivatives are important, tremendous effort has been directed to establishing enantioselective routes for their production.[48,49] Among these strategies, kinetic resolution is a reliable method for obtaining chiral compounds in optically pure forms and are sometimes attractive because both enantiomers can be obtained in high optical purities when the enantioselectivity is high. Although the kinetic resolutions of α-hydroxyesters[50] and α-hydroxyamides[51–53] have been reported, the lack of a method for the thioamide counterpart, as well as the utility of this functional group, encouraged us to develop such a method. Herein, we also report the first kinetic resolutions of α-hydroxythioamides and provide spectroscopic evidence for the formation of a substrate–additive complex.

Results and Discussion

To understand the role of the carboxylate additive in the previously reported kinetic resolution of 1,2-*trans*-cycloalkanediols, we first examined the B3LYP/6-31G** geometries of their transition-state models (Figure 2).[27] We found that the distances between the centers of the carboxylate oxygen atoms (anionic sites) and the triazolium pentagon (cationic sites) are shorter in the transition state of the faster-reacting *S,S*-diol (3.34 Å) than in the transition state of the slower-reacting *R,R*-diol (3.83 Å). Since the intensity of the electrostatic interaction is inversely proportional to the second power of the distance, these attractive interactions should differ by a factor of 1.3, which likely suggests that the transition state for the faster-reacting diol is more electrostatically stabilized than that of the slower-reacting diol. Furthermore, Morokuma–Kitaura energy decomposition analysis[54] of the transition-state geometries provided strong support for this hypothesized interaction; the calculated electrostatic energies between

the carboxylic acid moieties and the other parts in the transition states of the faster- and slower-reacting diols are –39.41 and –34.33 kcal/mol, respectively. Therefore, the difference in the energies associated with these electrostatic interactions are likely to contribute significantly to the free energy difference between the two transition states.

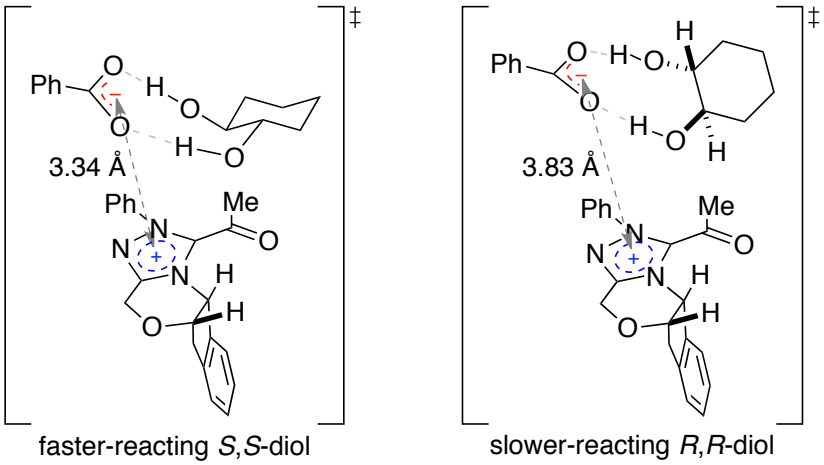


Figure 2. B3LYP/6-31G** transition-state models for the previously reported kinetic resolution of *trans*-cyclohexane-1,2-diol and proposed electrostatic interactions.

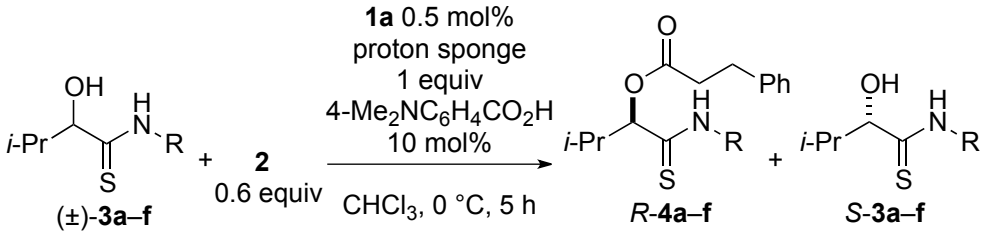
Based on the above analysis, we speculated that the carboxylate additive performs the following roles: (1) The carboxylate anion forms a hydrogen-bonded complex with the diol. (2) Owing to its anionic nature, the carboxylate-anion–containing, hydrogen-bonded complex attracts the acylating agent, which is a cationic acyltriazolium species generated *in situ*, to the diol. (3) In the transition state for acylation, the carboxylate anion acts as a general base that enhances the nucleophilicity of the diol, while concurrently stabilizing the transition state through electrostatic interactions with the cationic moiety of the acylating agent. Thus, the observed increase in enantioselectivity upon addition of the carboxylic acid is partly attributable to the enhanced chiral recognition of the chiral acylating agent through the formation of a substrate–additive complex, as illustrated in Figure 1. It is noteworthy that the

carboxylate additive participates in an additional through-space interaction, while the previously mentioned Lewis and Brønsted acids participate in through-bond interactions.[32–36]

To extend the scope of the concept, we investigated resolving α-hydroxythioamides that bear two adjacent hydrogen-bond-donor functionalities, namely OH and NH, and can form hydrogen-bonded complexes with carboxylate anions. We expected that the formation of the hydrogen-bonded complex would preferably overcome difficulties that may be caused by the conformational flexibility of the substrate.

We first examined the effect of the N-substituent on the thioamide, as it may significantly affect the strength of the hydrogen bond to the carboxylate, as well as steric interactions with the chiral acylazolium in the transition state. Hence, α-hydroxythioamide **3a** was acylated in chloroform at 0 °C using 2-bromo-3-phenylpropanal (**2**; 0.6 equiv.) and proton sponge (1 equiv.) in the presence of the NHC precursor **1a** (0.5 mol%) and 4-dimethylaminobenzoic acid (10 mol%) as catalysts (Table 1, entry 1). Acylated product *R*-**4a** was obtained in 26% yield and 79% enantiomeric excess (ee) after 5 h, along with unreacted *S*-**3a** (74% recovery, 27% ee; $s = 11$). Interestingly, the reaction of the corresponding *N*-phenyl α-hydroxyamide provided inferior result (8% conversion after 4 h, $s = 7$), indicating that the increased acidity of the NH in the thioamide is likely beneficial for the complex formation with the carboxylate anion. Slightly higher enantioselectivity was observed ($s = 12$; entry 2) when the *p*-methoxylphenyl-bearing thioamide **3b** was used in the reaction. In contrast, thioamide **3c** bearing the electron-deficient 3,5-bis(trifluoromethyl)phenyl group gave *R*-**4c** and *S*-**3c** with a dramatically lower selectivity ($s = 2$; entry 3). To our delight, aliphatic substituents led to better performance; the reactions of *N*-ethyl- and *N*-isopropylthioamides **3d** and **3e** proceeded with higher enantioselectivities (both $s = 24$; entries 4 and 5), while the *N*-*tert*-butylthioamide **3f** provided the best results, with *R*-**4f** and *S*-**3f** obtained with an s value of 68 (entry 6).

Table 1. Effect of the N-substituent in the NHC-catalyzed kinetic resolutions of α-hydroxythioamides.



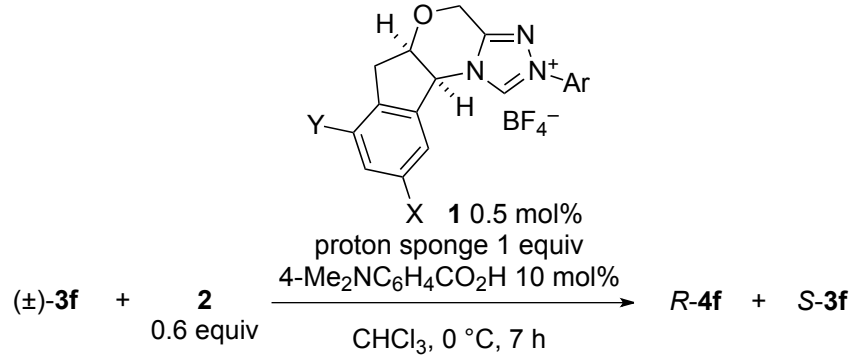
entry	**3**	R	**4**[a]	recovered **3**[a]	*s*[b]
1	**3a**	Ph	*R*-**4a** 26%, 79% ee	*S*-**3a** 74%, 27% ee	11
2	**3b**	4-$MeOC_6H_4$	*R*-**4b** 21%, 81% ee	*S*-**3b** 79%, 22% ee	12
3	**3c**	3,5-$(CF_3)_2C_6H_3$	*R*-**4c** 37%, 21% ee	*S*-**3c** 63%, 13% ee	2
4	**3d**	Et	*R*-**4d** 21%, 90% ee	*S*-**3d** 79%, 24% ee	24
5	**3e**	*i*-Pr	*R*-**4e** 33%, 88% ee	*S*-**3e** 67%, 44% ee	24
6	**3f**	*t*-Bu	*R*-**4f** 26%, 96% ee	*S*-**3f** 74%, 34% ee	68

[a] Isolated yields are shown. Enantiomeric excess (ee) was determined by chiral HPLC. [b] The selectivity factor, *s* was calculated as follows: $s = \ln[(1 - C)(1 - ee_3)]/\ln[(1 - C)(1 + ee_3)]$, where $C = ee_3/(ee_3 + ee_4)$.

We hypothesized that the electron density of the acylazolium is an important factor that determines the electrostatic interactions with the anionic α-hydroxythioamide–carboxylate complex. Hence, we next examined the effect of the N-substituent on the NHC (Table 2).[55] The use of the NHC derived from **1b**, which bears the electron-withdrawing pentafluorophenyl group, however, resulted in significantly lower reactivity and enantioselectivity (entry 1 vs 2), and gave *R*-**4f** in 24% conversion after 7 h with an *s* value of 9. This is possibly ascribable to differences in the preferred conformation of the acylazolium species in the *N*-phenyl- and *N*-perfluorophenyl-substituted systems.[56,57] The reaction was extremely slow and produced a negligible amount of *R*-**4f** when NHC precursor **1c**, bearing a phenyl group with

electron-donating groups at its 2,4,6-positions, was used (entry 3). Next, we investigated the effect of the substituent on the indane moiety. As expected, the newly developed bromo–nitro-substituted NHC precursor **1f** delivered outstanding reactivity (39% conversion) and selectivity (s = 92; entry 6), while the use of NHC precursors **1d** and **1e**, bearing less-electron-deficient indane moieties, led to slower reactions with lower selectivity factors of 15 and 35, respectively (entries 4 and 5).

Table 2. Substituent effects of the NHC precursor on the kinetic resolution of **3f**.



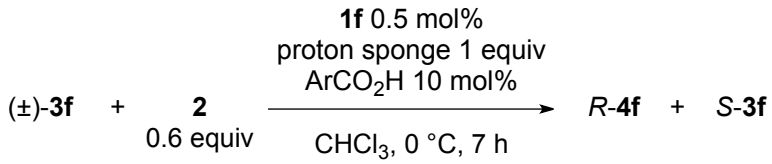
entry	**1**	Ar/X/Y	conv.[a]	*R*-**4f**[b]	*S*-**3f**[b]	s[c]
1[d]	**1a**	Ph/NO_2/H	26%	96% ee	94% ee	68
2	**1b**	C_6F_5/NO_2/H	24%	76% ee	24% ee	9
3	**1c**[e]	2,4,6-$Me_3C_6H_2$/NO_2/H	0%			
4	**1d**	Ph/H/H	3%	87% ee	3% ee	15
5	**1e**	Ph/Br/H	8%	94% ee	8% ee	35
6	**1f**	Ph/NO_2/Br	39%	96% ee	61% ee	92

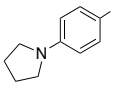
[a] Conversion, C was calculated as follows: $C = ee_{\mathbf{3f}}/(ee_{\mathbf{3f}} + ee_{\mathbf{4f}})$. [b] Ee was determined by chiral HPLC. [c] The selectivity factor, s was calculated as follows: $s = \ln[(1 - C)(1 - ee_{\mathbf{3f}})]/\ln[(1 - C)(1 + ee_{\mathbf{3f}})]$. [d] Data from Table 1, entry 6 for comparison. [e] Chloride was used in place of trifluoroborate.

Electrostatic interactions between the acylazolium and carboxylate moieties of the substrate–carboxylate complex stabilize the transition state for the predominantly reacting enantiomer in the hypothetical transition state, thereby increasing enantioselectivity. Therefore, with the aim of increasing the electron density of the carboxylate, we examined carboxylic acids bearing stronger electron-

donating substituents than 4-dimethylaminobenzoic acid (Hammett σ = –0.83;[58] Table 3). α-Hydroxythioamide (±)-**3f** was reacted with **2** in the presence of NHC precursor **1f**, proton sponge, and 4-pyrrolidinylbenzoic acid[59] (Hammett σ = –0.90[60]). As expected, *R*-**4f** was obtained in 15% yield with an improved *s* value of 117 after 7 h (entry 4). The use of the more electron-rich 9-julolidinecarboxylic acid[61] (estimated Hammett σ = –0.97) led to a significantly higher *s* value of 142 (entry 5). Conversely, the less-electron-rich benzoic acid performed less effectively to give *R*-**4f** in 8% yield with an *s* value of 71 (entry 2). Acylation proceeded at a moderate rate and with moderate selectivity in the absence of a carboxylic acid additive (entry 1).

Table 3. Substituent effect of the carboxylic acid additive on the kinetic resolution of **3f**.

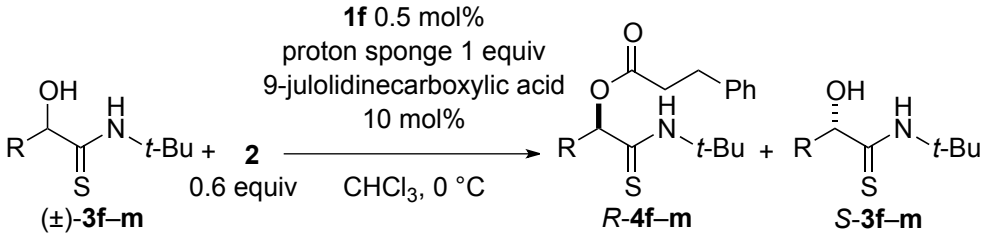


entry	$ArCO_2H$		conv.[b]	*R*-**4f**[c]	*S*-**3f**[c]	*s*[d]
	Ar	σ[a]				
1[e]	-	-	8%	94% ee	8% ee	35
2	Ph	0	8%	97% ee	8% ee	71
3[f]	4-$Me_2NC_6H_4$	–0.83	39%	96% ee	61% ee	92
4		–0.90	15%	98% ee	17% ee	117
5		–0.97	28%	98% ee	37% ee	142

[a] Hammett σ value of the substituent on the benzoic acid derivative. The σ in 9-julolidine was estimated as follows: $\sigma = \sigma_{p\text{-Me2N}} + 2\sigma_{m\text{-alkyl}} = (–0.83) + (–0.14) = –0.97$. See refs 58 and 60 [b] Conversion, *C* was calculated as follows: $C = ee_{\mathbf{3f}}/(ee_{\mathbf{3f}} + ee_{\mathbf{4f}})$. [c] Ee was determined by chiral HPLC. [d] The selectivity factor, *s* was calculated as follows: $s = \ln[(1 - C)(1 - ee_{\mathbf{3f}})]/\ln[(1 - C)(1 + ee_{\mathbf{3f}})]$. [e] Without $ArCO_2H$. [f] Data from Table 2, entry 7 for comparison.

With an efficient catalytic system in hand, we next investigated the scope of the reaction (Table 4). Thioamides bearing secondary alkyl groups as α-substituents (**3f**, **3i**, and **3j**) provided excellent selectivities (*s* = 142, 131, and 54; entries 3–5, respectively), although **3k** bearing a diphenylmethyl group still exhibited good, albeit lower, selectivity (*s* = 11; entry 6). Thioamides **3h** and **3l** bearing primary and tertiary alkyl substituents, respectively, were also good substrates that underwent kinetic resolution with high selectivity (*s* = 36 and 17; entries 2 and 7, respectively). Unfortunately, thioamide **3m** bearing a phenyl group as the α-substituent was not a suitable substrate, with low selectivity observed (*s* = 4; entry 8).

Table 4. Scope and limitations of the chiral NHC-catalyzed kinetic resolutions of α-hydroxythioamides.



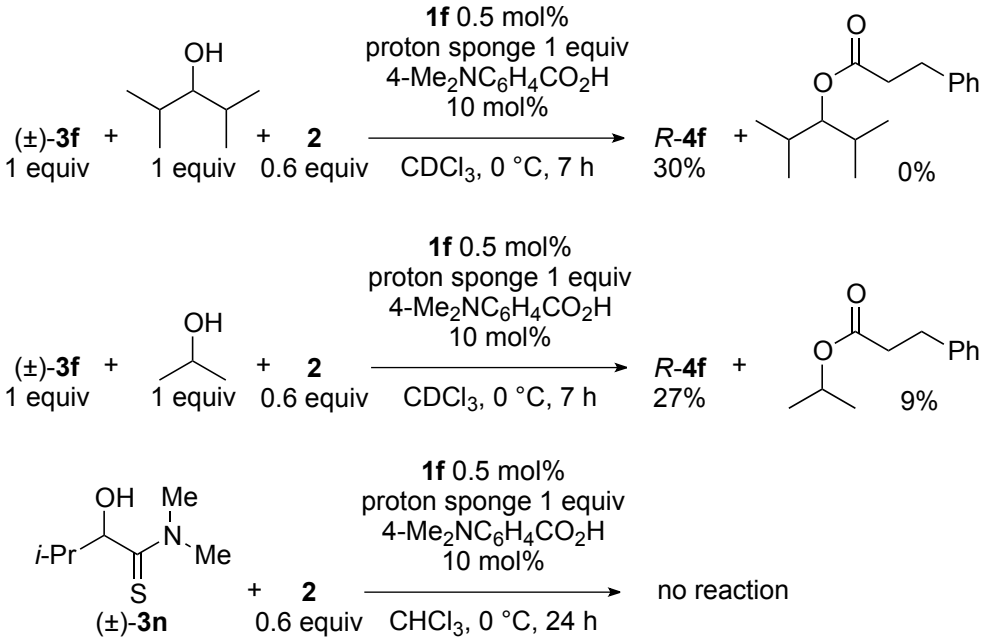
entry	**3**	R	time	*R*-**4**[a]	*S*-**3**[a]	*s*[b]
1[c]	**3g**	Me	15 h	*R*-**4g** 50%, 58% ee	*S*-**3g** 50%, 57% ee	7
2	**3h**	*i*-Bu	18 h	*R*-**4h** 49%, 78% ee	*S*-**3h** 51%, 98% ee	36
3[d]	**3f**	*i*-Pr	7 h	*R*-**4f** 28%, 98% ee	*S*-**3f** 72%, 37% ee	142
4	**3i**	*c*-Hex	7 h	*R*-**4i** 41%, 97% ee	*S*-**3i** 59%, 66% ee	131
5[e]	**3j**	*c*-Pr	18 h	*R*-**4j** 50%, 89% ee	*R*-**3j** 50%, 91% ee	54
6	**3k**	Ph_2CH	24 h	*R*-**4k** 31%, 78% ee	*R*-**3k** 69%, 34% ee	11
7	**3l**	*t*-Bu	48 h	*R*-**4l** 24%, 86% ee	*S*-**3l** 76%, 27% ee	17
8	**3m**	Ph	20 h	*R*-**4m**	*S*-**3m**	4

	44%, 44% ee	56%, 34% ee

[a] Ee was determined by chiral HPLC. [b] The selectivity factor, s was calculated as follows: $s = \ln[(1 - C)(1 - ee_3)]/\ln[(1 - C)(1 + ee_3)]$. [c] With **2** (1.5 equiv.), **1f** (1 mol%), and the carboxylic acid (20 mol%). [d] Data from Table 3, entry 5 for comparison. [e] Conducted at room temperature.

The following control experiments were used to gain additional evidence for the proposed transition-state enantiomer-recognition mode (Scheme 1). We first examined **3f** and 2,4-dimethylpentan-3-ol, which contain similarly sterically hindered hydroxy groups but with and without an adjacent hydrogen-bond donor group, respectively, in a competition experiment. When a solution of (±)-**3f** and the alcohol (1 equiv. each) in $CDCl_3$ was stirred at 0 °C for 7 h in the presence of **2** (0.6 equiv.), **1f** (0.5 mol%), proton sponge (1 equiv.), and 4-dimethylaminobenzoic acid (10 mol%), only **3f** was acylated to give *R*-**4f** in 30% yield without formation of the ester of 2,4-dimethylpentan-3-ol. Even when isopropanol, a much less sterically hindered competitor, was added, **3f** was acylated three-times faster than the alcohol to give *R*-**4f** in 27% yield along with the isopropyl ester in 9% yield. N-methylated α-hydroxythioamide **3n** failed to react, which also highlights the importance of the adjacent hydrogen-bond donor during the NHC–carboxylate-catalyzed asymmetric acylation.

Scheme 2. Highlighting the importance of an adjacent NH functionality.

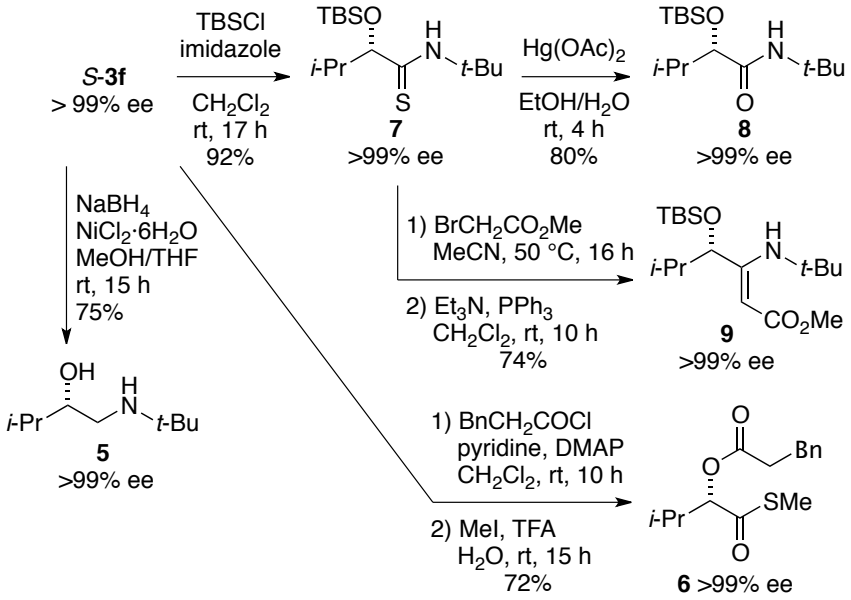


The postulated complex of hydroxythioamide and carboxylate anion was observed by mass spectrometry (MS). When a 10:10:1 mixture of (±)-**3f**, proton sponge, and 4-dimethylaminobenzoic acid was injected into a mass spectrometer operated in negative electron spray ionization mode, two anions $[(\pm)\text{-}\mathbf{3f} - \mathrm{H}]^-$ (*m/z* 188) and $[(\pm)\text{-}\mathbf{3f} + 4\text{-}Me_sNC_6H_4CO_2]^-$ (*m/z* 353) were observed. The molecular formula of the latter anion was further confirmed by high-resolution MS. It is noteworthy that the carboxylate anion (*m/z* 164) was not observed under this condition. The formation of the complex between (±)-**3f** and $4\text{-}Me_2NC_6H_4CO_2^-$ in solution is also supported by preliminary diffusion-ordered NMR spectroscopy data (see Supporting Information). These results provide strong evidence for our hypothesis that the hydroxythioamide forms an anionic complex with the carboxylate anion and attracts the cationic chiral acyltriazolium.

α-Hydroxythioamide *S*-**3f** was readily converted into other compounds without any loss in enantiopurity (Scheme 3). β-Amino alcohol **5** was obtained by reduction with $NiCl_2$–$NaBH_4$;[62] β-amino alcohols are common structural units in pharmaceutical agents[63–65] and useful ligands for metal catalysts.[66,67] Acylation to give *S*-**4f** followed by S-methylation[68] of the thioamide functionality and subsequent hydrolysis provided thioester **6**, which is transformable into a variety of carboxylic acid

derivatives, including aldehydes[69] and amides.[70] Amide **8** was also formed in 80% yield by desulfurization through the $Hg(OAc)_2$-promoted hydrolysis[71] of **7**, which was prepared by TBS-protection of the hydroxyl group. Dehydro-β-amino acid **9** was also obtained in 74% yield as a single diastereomer through the Eschenmoser sulfide contraction[72] of **7**.

Scheme 3. Applications of chiral hydroxythioamides.



Conclusion

We developed the first method for the catalytic kinetic resolutions of α-hydroxythioamides. We used a newly developed chiral bromo–nitro-substituent-bearing NHC catalyst, which realized highly enantioselective acylations with the assistance of a newly introduced 9-julolidinecarboxylate additive. MS provided additional evidence for the role of the additive in enhancing rate and selectivity by forming a hydrogen-bonded complex with the substrate, which we had previously suggested on the basis of density functional theory calculations. The experimental results support our working hypothesis that enhanced molecular recognition through electrostatic interactions is operative in this reaction. The versatility of the product highlights the usefulness of the reaction.

Supporting Information Available. Experimental details, characterization data of the new compounds, and details of the MS and NMR experiments (PDF). NMR charts and HPLC traces (PDF). These are available free of charge on the World Wide Web at http://pubs.acs.org.

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