Kinetic Resolution of α-Hydroxyamide via N-Heterocyclic Carbene-Catalyzed Acylation

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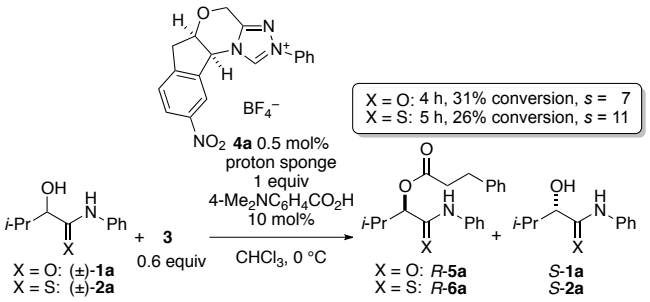
Abstract: The effect of N-substituent of α-hydroxyamides on the performance of chiral N-heterocyclic carbene-catalyzed kinetic resolution was examined. *N-tert*-Butyl-α-hydroxyamides provided the best performance and underwent enantioselective acylation with α-bromo aldehyde by chiral N-heterocyclic carbene/carboxylate anion co-catalysis to realize kinetic resolution in high selectivity factor up to 128.

Introduction

Chiral α-hydroxycarboxylic acid derivatives are synthetically useful building blocks and abundantly found in biologically signficant compounds, e.g., renin inhibitor,[1] cholesterol-lowering agent,[2] PPARα/γ dual agonist,[3] and antibiotic.[4] They are also found as a substructure of chiral ligands,[5,6] polymers,[7,8] and unnatural peptides and depsipeptides.[9,10] Due to the importance of this class of compounds, tremendous effort has been devoted to development of the synthetic method for optically active α-hydroxycarboxylic acid derivatives.[11,12] Among the strategies for asymmetric synthesis, kinetic resolution is a reliable method to obtain chiral compounds in optically pure forms. Besides, both enantiomers can be obtained from a racemic mixture in high optical purities when the enantioselectivity is sufficiently high. To date, the kinetic resolutions of α-hydroxyesters[13,14] and α-hydroxyamides[13–16] have been achieved with high efficiency.

As a part of our research to develop organocatalytic reactions,[17–27] we recently reported the kinetic resolution of α-hydroxythioamides using asymmetric acylation catalyzed by chiral N-heterocyclic carbenes[28] (NHCs).[29–32] In the previous study, we found that the kinetic resolution of thioamide **2a** showed slightly better selectivity (selectivity factor, *s* = 11) than that of the corresponding amide **1a** (*s* = 7) in the presence of 2-bromo-3-phenylpropanal (**3**),[33,34] chiral NHC precursor **4a**,[35] 1,8-bis(dimethylamino)naphthalene (proton sponge), and 4-dimethylaminobenzoic acid (Scheme 1).[29] We believe that the acylation undergoes via formation of hydrogen bonded complex between the amides and in situ generated carboxylate anion, and thus attributed the better performance of thioamides to the stronger acidity of NH than that of amides, reinforcing the hydrogen bonding. We speculated that introduction of an electron-withdrawing group on the nitrogen atom of amide would increase the acidity of the amide proton to improve the performance in the kinetic resolution.



Scheme 1. Kinetic resolution of α-hydroxyamide vs α-hydroxythioamide.[29]

Results and Discussion

Hence, α-hydroxyamide **1c**, bearing electron-withdrawing group, was acylated in chloroform at 0 °C using 2-bromo-3-phenylpropanal (**3**; 0.6 equiv.) and proton sponge (1 equiv.) in the presence of the NHC precursor **4a** (0.5 mol%) and 4-dimethylaminobenzoic acid (10 mol%) as catalysts (Table 1, entry 3). As expected, the acylation underwent with slightly better selectivity (*s* = 10) than that of **1a** (*s* = 7; entry 2), and product *R*-**5c** was obtained in 80% enantiomeric excess (ee) and 16% conversion after 4 h, along with unreacted *S*-**3c** in 15% ee. On the contrary, the reaction with **1b**, bearing an electron-donating group proceeded in almost the same selectivity (*s* = 7; entry 1) as the reference reaction (entry 2).

Next, we tested fluoroalkyl groups as an electron-withdrawing group on the nitrogen atom. N-Trifluoroethylated amide **1d** underwent the acylation in higher selectivity (*s* = 13) than aryl substituted **1c**, and provide *R*-**5d** in 79% ee and 37% conversion after 18 h (entry 4). Although N-tetrafluoropropylated amide **1e**

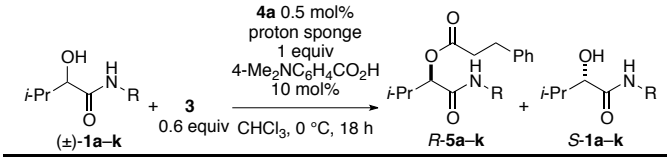
further improved the selectivity (*s* = 15; entry 5), contrary to our expectation, the selectivity decreased to *s* = 6 with N-pentafluoropropylated amide **1f** (entry 6). This indicates that too acidic amide NH likely results in loose hydrogen bonding.

To our surprise, *N*-ethyl amide **1g** was found to be more selective substrate to give *R*-**5g** in 89% ee and 24% conversion after 18 h (*s* = 23; entry 7). Although *N*-butyl amide **1h** performed similarly (*s* = 24; entry 8), *N*-isopropyl and *N*-*tert*-butyl amides **1i** and **1j** were acylated in improved selectivities of *s* = 34 and 76, respectively (entries 9 and 10). Therefore, it is likely steric factor that dominates the selectivity of this acylation reaction. However, to our disappointment, more bulky 1-(*p*-methoxypheyl)-1-methylethyl substituent[36] failed to further improve the selectivity; acylation of **1k** proceeded in decreased selectivity (*s* = 35; entry 11).

Because preliminary solvent screening indicated that halogenated solvent was suitable to the previous kinetic resolution,[35] we next tested other halogenated solvent in this kinetic resolution (Table 2). However, the use of dichloroethane, benzotrifuloride, or chlorobenzene as a solvent either failed to improve the reaction efficiency, resulting in decreased reaction rate (up to 5% conversion after 24 h) and selectivity (up to *s* =20; entries 1–4). While the use of benzoic acid in place of 4-dimethylaminobenzoic acid decreased the selectivity to *s* = 40 (entry 5), 9-julolidinecarboxylic acid provided better performance as an additive and the acylation of **1j** proceeded with *s* = 94 (entry 6).[29] The use of more electron deficient NHC precursor **4b**[29] was also beneficial to promote the kinetic resolution more selectively, giving *R*-**5j** in 96% ee and 45% conversion after 24 h, along with recovered *S*-**1j** in 80% ee (entry 7).

We next investigated the scope of the reaction (Table 3). Amides bearing secondary alkyl groups as α-substituents (**1j** and **1n**) provided as excellent selectivities (*s* = 121 and 128) as the corresponding thioamides (*s* = 142 and 131; entries 2 and 3, respectively). Amides **1m** and **1p** bearing primary and tertiary alkyl substituents, respectively, were also good substrates to undergo kinetic resolution with high selectivity (*s* = 24 and 12; entries 1 and 4, respectively). Unfortunately, amide **1q**, bearing phenyl group, gave poor selectivity (*s* = 2; entry 5). In the kinetic resolution of α-hydroxy amide with an oxygen functionality, the O-substituent significantly influenced the reaction rate and selectivity; amide **1r**, which possesses a benzyloxy group at theβ-position, was not a suitable substrate (*s* = 2; entry 6), while

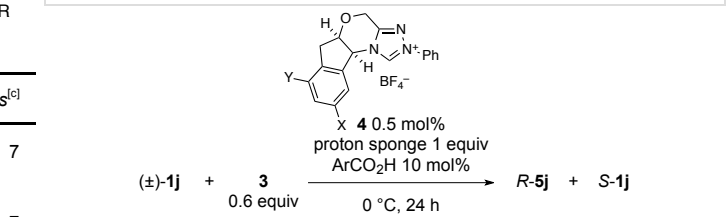
Table 1. Effect of the N-substituent in the NHC-catalyzed kinetic resolutions of α-hydroxyamides.



entry	**1**	R	**5**[a]	recovered **1**[a]	conv.[b]	*s*[c]
1[d]	**1b**	4-$MeOC_6H_4$	*R*-**5b** 75% ee	*S*-**1b** 5% ee	6%	7
2[d]	**1a**	Ph	*R*-**5a** 72% ee	*S*-**1a** 15% ee	17%	7
3[d]	**1c**	3,5-$(CF_3)_2C_6H_3$	*R*-**5c** 80% ee	*S*-**1c** 15% ee	16%	10
4	**1d**	CF_3CH_2	*R*-**5d** 79% ee	*S*-**1d** 46% ee	37%	13
5	**1e**	$CHF_2CF_2CH_2$	*R*-**5e** 83% ee	*S*-**1e** 36% ee	30%	15
6	**1f**	$CF_3CF_2CH_2$	*R*-**5f** 63% ee	*S*-**1f** 36% ee	36%	6
7	**1g**	Et	*R*-**5g** 89% ee	*S*-**1g** 28% ee	24%	23
8	**1h**	Bu	*R*-**5h** 90% ee	*S*-**1h** 22% ee	20%	24
9	**1i**	*i*-Pr	*R*-**5i** 90% ee	*S*-**1i** 58% ee	39%	34
10	**1j**	*t*-Bu	*R*-**5j** 96% ee	*S*-**1j** 44% ee	31%	76
11	**1k**	$PMP(Me)_2C$	*R*-**5k** 93% ee	*S*-**1k** 23% ee	20%	35

[a] Enantiomeric excess (ee) was determined by chiral HPLC. [b] The conversion *C* was calculated as follows: $C = ee_1/(ee_1 + ee_5)$. [c] The selectivity factor, *s* was calculated as follows: $s = \ln[(1 - C)(1 - ee_1)]/\ln[(1 - C)(1 + ee_1)]$. [d] The reaction time was 4 h.

Table 2. Further optimization of the NHC-catalyzed kinetic resolution of α-hydroxyamide.



entry	**4** X/Y	additive Ar	solvent	*R*-**5j**[a] % *ee*	*S*-**1j**[a] % *ee*	conv.[b] %	*s*[c]
1[d]	**4a** NO_2/H	Me_2N	$CHCl_3$	96	44	31	76
2	**4a** NO_2/H	Me_2N	$(CH_2Cl)_2$	90	4	5	20
3	**4a** NO_2/H	Me_2N	$PhCF_3$	89	2	2	18
4	**4a** NO_2/H	Me_2N	PhCl	87	<1	<1	-[e]
5	**4a** NO_2/H		$CHCl_3$	95	2	2	40
6	**4a** NO_2/H	N	$CHCl_3$	97	37	28	94
7	**4b** NO_2/Br	N	$CHCl_3$	96	80	45	121

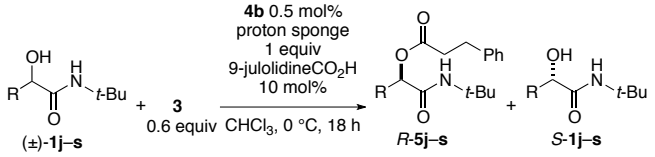
[a] Enantiomeric excess (ee) was determined by chiral HPLC. [b] The conversion, *C* was calculated as follows: $C = ee_{1j}/(ee_{1j} + ee_{5j})$. [c] The selectivity factor, *s* was calculated as follows: $s = \ln[(1 - C)(1 - ee_{1j})]/\ln[(1 - C)(1 + ee_{1j})]$. [d] Data from Table 1, entry 10 for comparison. [e] Not determined.

a bulky silyl protection of the oxygen functionality was found to be beneficial to recover the selectivity (*s* = 9; entry 7). The reaction rate and selectivity was slightly improved by using pivalic acid as a carboxylic acid additive (*s* = 10; entry 8).

Conclusion

We developed the kinetic resolutions of α-hydroxyamides catalyzed by the chiral bromo–nitro-substituent-bearing NHC and 9-julolidinecarboxylic acid. Moderately sterically hindered N- and α-substituents were beneficial for the selectivity of this acylation reaction. Although the ability of amides to form a hydrogen-bonded complex with the substrate is likely lower than that of thiomides, comparable selelctivity was observed in the kinetic resolution. Amide bearing an oxygen functionality was tested in the reaction, which revealed that the bulky silyl protective group improve the selectivity. The application to the asymmetric synthesis of biologically important α-hydroxy carboxylic acid derivatives are currently underway.

Table 3. Scope and limitations of the chiral NHC-catalyzed kinetic resolutions of α-hydroxyamides.



entry	**1**	R	*R*-**5**[a]	*S*-**1**[a]	conv.[b]	*s*[c]
1	**1m**	Et	*R*-**5m** 87% ee	*S*-**1m** 50% ee	37%	24
2[d]	**1j**	*i*-Pr	*R*-**5j** 96% ee	*S*-**1j** 80% ee	45%	121 (142)
3	**1n**	*c*-Hex	*R*-**5n** 98% ee	*S*-**1n** 26% ee	21%	128 (131)
4	**1p**	*t*-Bu	*R*-**5p** 84% ee	*S*-**1p** 4% ee	5%	12 (17)
5	**1q**	Ph	*R*-**5q** 31% ee	*S*-**1q** 19% ee	38%	2 (4)
6	**1r**	$BnOCH_2$	*R*-**5r** 27% ee	*S*-**1r** 16% ee	37%	2
7	**1s**	$TIPSOCH_2$	*R*-**5s** 79% ee	*S*-**1s** 6% ee	7%	9
8[e]	**1s**	$TIPSOCH_2$	*R*-**5s** 80% ee	*S*-**1s** 10% ee	11%	10

[a] Enantiomeric excess (ee) was determined by chiral HPLC. [b] The conversion, *C* was calculated as follows: $C = ee_1/(ee_1 + ee_5)$. [c] The selectivity factor, *s* was calculated as follows: $s = \ln[(1 - C)(1 - ee_1)]/\ln[(1 - C)(1 + ee_1)]$. Values in parentheses are *s* for the corresponding thioamides (see ref 29). [d] Data from Table 2, entry 7 for comparison. [e] Pivalic acid was used in place of 9-julolidinecarboxylic acid.

Experimental Section

Typical Procedure of the Catalytic Kinetic Resolution (Table 3, entry 1): A solution of **4b** (0.6 mg, 1 μmol), 9-julolidinecarboxylic acid (5 mg, 0.03 mmol), proton sponge (54 mg, 0.25 mmol), and (±)-**1m** (43 mg, 0.25 mmol) in $CHCl_3$ (2.5 mL) was stirred at rt for 10 min and cooled to 0 °C. To the mixture was added **3** (24 μL, 0.15 mmol), and the mixture was stirred at 0 °C for 18 h. The mixture was directly purified by column chromatography (hexane/EtOAc 9:1 to 2:1) to give *R*-**5m** with 87% ee (26 mg, 36% yield; $[\alpha]^{21}_D$ +16.4 (*c* 1.00, $CHCl_3$)) as yellow oil and recovered *S*-**1m** with 50% ee (26 mg, 60% yield; $[\alpha]^{21}_D$ −17 (*c* 0.64, $CHCl_3$)) as yellow solid.

Acknowledgements

This research was supported in part by JSPS KAKENHI Grant No. JP22H05569 from MEXT; the Sasakawa Scientific Research Grant; and a research program for the development of an intelligent Tokushima artificial exosome (iTEX) and the Research Clusters program No. 1802001 from Tokushima University.

Keywords: acylation • α-hydroxyamide • catalytic kinetic resolution • N-heterocyclic carbene • organocatalysis

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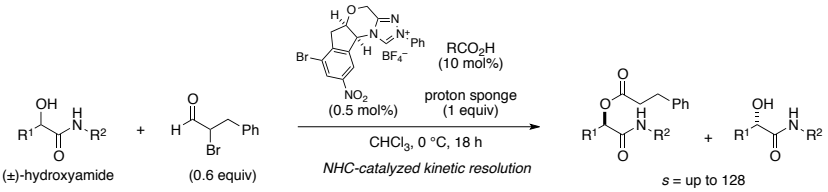

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