## Asymmetric Catalysis

## Effecient Kinetic Resolution of Racemic Amino Aldehydes by Oxidation with N-Iodosuccinimide\*\*

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Amino acids are very useful as synthetic building blocks for various biologically active compounds.<sup>[1]</sup> Recently, several pseudopeptides containing natural or non-natural amino acids have been developed because they have pharmacologically important characteristics.<sup>[2]</sup> Although natural amino acids are prepared by biochemical techniques such as fermentation, there is scant information on the preparation of non-natural amino acids by using this approach.<sup>[3]</sup> Among the asymmetric catalytic methods for the synthesis of natural and non-natural amino acids,[4-6] the kinetic resolution of amino acid derivatives is frequently used.<sup>[7]</sup> However, there are few examples applicable to the synthesis of various optically active amino acids, including cyclic amino acids, and to the best of our knowledge, there is no chemical oxidation method for their preparation. We report herein the first efficient kinetic resolution of racemic amino aldehydes by oxidation.

Recently, we accomplished the oxidative kinetic resolution of 1,2-diols, which was based on their recognition by a copper(II)/(R,R)-Ph-BOX complex (see Scheme 2 for structure),<sup>[8]</sup> to afford optically active  $\alpha$ -ketoalcohols.<sup>[9a]</sup> Moreover, we have reported the asymmetric electrochemical oxidation of N-protected 1,2-amino aldehydes to afford optically active amino acid methyl esters in low yield, but with good enantioselectivity.<sup>[9b]</sup> In line with our previous work, we investigated the reaction conditions for oxidative kinetic resolution of racemic amino aldehydes to improve the yields and enantioselectivities of the optically active amino acids. To our delight, we found a simple method for a highly efficient kinetic resolution of racemic N-protected amino aldehydes. The use of a chiral copper catalyzed oxidation procedue with N-iodosuccinimide (NIS) afforded optically active amino acid methyl esters, including cyclic and acyclic compounds, with high enantioselectivity (Scheme 1). Additionally, instead of recovering the starting material, the corresponding optically active aminoaldehyde dimethyl acetals were preferentially obtained.

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**Scheme 1.** Oxidative kinetic resolution of racemic aminoaldehydes. PG = protecting group.

First, we applied the previous reaction conditions for asymmetric oxidation of 1,2-diols using *N*-bromosuccinimide (NBS) in the presence of  $K_2CO_3^{[9a]}$  for the oxidative kinetic resolution of *rac-N*-benzoyl-2-piperidinecarboaldehyde (*rac*-**1a**; Table 1, entry 1). (*R*)-**2a**<sup>[10]</sup> was obtained with a high

**Table 1:** Oxidative kinetic resolution of racemic *N*-benzoyl-2-piperidinecarboaldehyde (**1** a).<sup>[a]</sup>

N <sup>-</sup> C Bz 1a	HO $\frac{Cu(OTf)}{(R,R)-Pt}$ NBS, 12 Base	$\begin{array}{c} 2\\ \begin{array}{c} 2\\ \hline \\ -BOX\\ \hline \\ RT\\ \hline \\ \\ h \end{array} \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	$CO_2Me + N_Bz = (S)-1a$	CHO + N Bz (S)-3	OMe OMe a
Entry	Base	(R)- <b>2</b> a	(S)- <b>1 a</b>	(S)- <b>3 a</b>	s <sup>[c]</sup>
1	K <sub>2</sub> CO <sub>3</sub>	12% yield	51% yield	-	
		94% ee	4% ee <sup>[b]</sup>		
2	none	39% yield	-	46% yield	20
		85 % ee		50% ee	

[a] A mixture of **1a** (0.5 mmol), Cu(OTf)<sub>2</sub> (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), and NBS (0.25 mmol) in MeOH (2 mL) in the presence or absence of K<sub>2</sub>CO<sub>3</sub> (0.25 mmol) was stirred at RT for 12 h. [b] Determined after its reduction to the corresponding amino alcohol. [c] s=stereose-lectivity factor for kinetic resolution.<sup>[12]</sup> Bz=benzoyl, Tf=triflate.

enantiomeric excess, but the yield was low; the enantiomeric excess of recovered **1a** was also very low. On the other hand, the absence of a base drastically changed the reaction (Table 1, entry 2) such that the yield of (R)-**2a** was significantly increased and the optically active aminoaldehyde dimethyl acetal (S)- $(3a)^{[11]}$  was obtained in an acceptable yield with good enantioselectivity (s = 20).

Next, we sought to improve the reaction conditions by varying the amount and type of cationic halogen species (Table 2). Increasing the amount of NBS from 0.5 equivalents to 0.75 equivalents had no effect on the yield or the selectivity (Table 2, entry 1), and the use of other bromo cationic species (NBPI, DBDMH, Br<sub>2</sub>) led to a lower *s* value than that obtained with NBS (Table 2, entries 2–4). *N*-Chlorosuccinimide (NCS) did not oxidize **1a** to afford methyl ester **2a**, but transformed it into acetal **3a** in racemic form (Table 2, entry 5). In contrast, the use of NIS led to a higher *s* value than that obtained with NBS (Table 2, entries 6–8). The



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Table 2:Effect of the oxidant on the oxidative kinetic resolution of la.<sup>[a]</sup>1a $\frac{Cu(OTf)_{2'}(R,R)-Ph-BOX}{Oxidant, MeOH, RT}$ (R)-2a + (S)-1a + (S)-3a

Entry	Oxidant (equiv)	Yield [%] (ee [%])			
		(R)- <b>2</b> a	(S)- <b>1 a</b>	(S)- <b>3 a</b>	
1	NBS (0.75)	43 (79)	20	31 (77)	20
2	NBPI <sup>[d]</sup> (0.5)	28 (84)	17	51 (39)	17
3	DBDMH <sup>[e]</sup> (0.5)	60 (53)	-	31 (86)	7
4	Br <sub>2</sub> (0.5)	43 (45)	_	19 (17)	8
5 <sup>[b]</sup>	NCS (0.5)	_	-	48 (0)	
6 <sup>[b]</sup>	NIS (0.5)	22 (97)	_	65 (29)	87
7 <sup>[b]</sup>	NIS (0.75)	38 (97)	-	60 (51)	109
8 <sup>[b]</sup>	NIS (1.0)	43 (91)	-	51 (85)	57
<b>9</b> <sup>[b,c]</sup>	NIS (0.75)	16 (99)	63		
10 <sup>[b]</sup>	I <sub>2</sub> (0.5)	trace	-	92 (0)	
11 <sup>[b]</sup>	PhI(OAc) <sub>2</sub> (0.5)	-	42	20 (30)	

[a] A mixture of **1a** (0.5 mmol),  $Cu(OTf)_2$  (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), and oxidant (0.25, 0.375, or 0.50 mmol) in MeOH (2 mL) was stirred at RT for 12 h. [b] Reaction time of 24 h. [c] At 0°C. [d] *N*-Bromo phthalimide. [e] 1,3-Dibromo-5,5-dimethylhydantoin.

conversion was additioanlly improved as the amount of the NIS used was increased, and the *ee* value of acetal **3a** improved. The use of 0.75 equivalents of NIS led to the highest *s* value of 109 (Table 2, entry 7), whereas 1.0 equivalent of NIS slightly decreased the enantioselectivity of **2a** (Table 2, entry 8). Although at 0 °C **2a** was obtained in 99% *ee*, **3a** was not detected (Table 2, entry 9). Other iodo cationic species (I<sub>2</sub>, PhI(OAc)<sub>2</sub>) were not effective for the oxidation of **1a** (Table 2, entries 10 and 11).

To confirm the accelerating effect of the recognition of **1a** by the  $\text{Cu}^{II}/(R,R)$ -Ph-BOX complex on the oxidation with halogen cationic species (Table 3), we performed the reaction

Table 3: Accelerating effect based on recognition of 1a.[a]

Entry	Oxidant (equiv)	Condition <sup>[b]</sup>	Yield [%]		
			2 a	1a	3 a
1 <sup>[c]</sup>	NBS (0.5)	A	13	14	58
2 <sup>[c]</sup>	NBS (0.5)	В	22	12	62
3 <sup>[d]</sup>	NIS (0.75)	А	trace	42	45
4 <sup>[d]</sup>	NIS (0.75)	В	2	trace	81

[a] A mixture of **1a** (0.5 mmol),  $Cu(OTf)_2$  (0 or 0.05 mmol), (*R*,*R*)-Ph-BOX (0 or 0.05 mmol), and oxidant (0.25-0.375 mmol) in MeOH (2 mL) was stirred at RT. [b] Condition A: In the absence of  $Cu(OTf)_2$  and (*R*,*R*)-Ph-BOX. Condition B: In the absence of (*R*,*R*)-Ph-BOX. [c] Reaction time of 12 h. [d] Reaction time of 24 h.

in the absence of both  $Cu(OTf)_2$  and (R,R)-Ph-BOX (Condition A) and in the absence of (R,R)-Ph-BOX (Condition B). Similar tendencies were observed for both NBS and NIS reactions. Condition A gave a much lower yield of **2a** (Table 3, entries 1 and 3), whereas Condition B (Table 3, entries 2 and 4) led to a slight improvement in the yield compared to that obtained with Condition A. However, the reaction in the presence of  $Cu(OTf)_2$  and (R,R)-Ph-BOX afforded **2a** in a much higher yield, suggesting that **1a** is recognized by the  $Cu^{II}/(R,R)$ -Ph-BOX complex and thus activated. Although oxidation with NBS proceeded even

when there was no activation by the copper catalyst, oxidation of **1a** by NIS hardly proceeded in the absence of the  $\operatorname{Cu}^{II}/(R,R)$ -Ph-BOX complex. We believe that the difference in reactivity of the oxidants and the accelerating effect of the molecular recognition led to the high selectivity in the cases of oxidation with NIS.

Next, we screened various N-protecting groups on the 2-piperidinecarboaldehydes (Table 4).<sup>[13]</sup> Subtrates with acetyl groups and the alkoxycarbonyl groups (such as

**Table 4:** Effect of N-protecting groups on the oxidative kinetic resolution of 2-piperidinecarboaldehydes 1 b-e.<sup>[a]</sup>

N PG 1b-e	СНО	Cu(OTf) <sub>2</sub> ( <i>R</i> , <i>R</i> )-Ph-BOX MeOH, RT NIS, 24 h	N ''CO <sub>2</sub> Me PG ( <i>R</i> )- <b>2b-e</b>	+ NHCH PG (S)-1b-e	0 + N PG ( (S)-3b-6	OMe OMe
Entry	PG		Yield [%] (ee [%])			
			( <i>R</i> )- <b>2 b</b> –e	(S)- <b>1 b</b> —е	(S)- <b>3 b−e</b>	
1	16	Ac	39 (92)	-	47 (52)	40
2	1c	CO <sub>2</sub> Me	26 (95)	-	63 (25)	50
3	1 d	<sup>[b]</sup> Cbz	37 (95)	-	63 (29)	52
4	1e	Ts		81	19 (0)	

[a] A mixture of **1 b–e** (0.5 mmol),  $Cu(OTf)_2$  (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), and NIS (0.375 mmol) in MeOH (2 mL) was stirred at RT for 24 h. [b] Yield was determined by <sup>1</sup>H NMR analysis. Cbz = benzyloxy-carbonyl, Ts = 4-toluenesulfonyl.

 $CO_2Me$  and Cbz), which are generally used as protecting groups, led to desirable selectivities (Table 4, entries 1–3). Since these values are comparable to those substrates having a benzoyl group, these results might enhance the value of this oxidative kinetic resolution. In contrast, the reaction of *N*-tosylated amino aldehyde **1e** did not afford the corresponding methyl ester product **2e**.

The oxidation using NIS was applied to oxidative kinetic resolution of the various acyclic amino aldehydes **4a–f** (Table 5).<sup>[14,15]</sup> The kinetic resolution of **4a–e** proceeded smoothly and excellent *s* values, which are attractive for industrial applications, were attained. Particularly, the reaction of amino aldehydes possessing linear alkyl groups gave excellent selectivity (Table 5, entries 1–3 and 5). In the case of

**Table 5:** Oxidative kinetic resolution of acyclic aminoaldehydes  $4a-f^{[a]}$ 

R	R کی Bz <b>4a</b> -f	Ю	( <i>R,R</i> )-Ph MeOH, F NIS, 24	$ \stackrel{)_{2}}{\longrightarrow} \stackrel{R^{2}}{\longrightarrow} \stackrel{N}{\longrightarrow} N$	., '′CO₂Me + <sup>I</sup> ?)- <b>5a-f</b>	R <sup>2</sup> N Bz OMe (S)-6a-f	1e
Entry		R1	R <sup>2</sup>	Equiv of NI	S Yield [% ( <i>R</i> )- <b>5 a</b> –f	6] (ee [%]) (S)- <b>6 a</b> -f	s
1	4a	Me	Н	0.75	40 (97)	54 (65)	129
2	4b	Et	н	0.75	43 (99)	57 (64)	368
3	4c	<i>n</i> Pr	Н	0.75	42 (94)	52 (69)	67
4	4d	<i>i</i> Pr	н	0.75	43 (82)	56 (50)	17
5	4e	<i>n</i> Bu	Н	0.75	41 (96)	51 (71)	104
6	4 f	<i>i</i> Pr	Me	2.0	38 (55)	58 (25)	4

[a] A mixture of **4a-f** (0.5 mmol),  $Cu(OTf)_2$  (0.05 mmol), (*R*,*R*)-Ph-BOX (0.05 mmol), and NIS (0.375 or 1.0 mmol) in MeOH (2 mL) was stirred at RT for 24 h.

## Communications

branched amino aldehyde 4d, the selectivity was within an acceptable range (Table 5, entry 4) and the reaction of *N*,*N*-disubstituted amino aldehyde 4f required excess NIS because of reduced reactivity (Table 5, entry 6), and gave moderate selectivity.

A plausible reaction mechanism is shown in Scheme 2. We believe that the high selectivity was obtained because of the asymmetric oxidation of aminoaldehydes **1** and **4** associated with the chiral copper catalyst was considerably faster than that of the acid catalyzed acetalization of their noncoordinated counterparts. In our previous study on oxidative kinetic resolution,<sup>[9]</sup> bases performed an important role of neutralizing generated HX to accelerate the reaction. However, here



*Scheme 2.* Plausible reaction mechanism for the oxidative kinetic resolution of racemic N-protected aminoaldehydes.

the oxidative kinetic resolution without any base improved the yield of the methyl esters (2 and 5) and the HX generated acted as a catalyst for the transformation of noncoordinated amino aldehydes. Since this acetalization might proceed gradually, the *ee* values of acetals 3 and 6 are lower than those of the corresponding methyl esters 2 and 5. It seems to be reasonable that the Cu(OTf)<sub>2</sub> was not involved in this redox process by accepting one electron from the hemiacetal oxygen. This hypothesis is supported by an experimental result shown in Scheme 3, in which a chiral Zn(OTf)<sub>2</sub>/(*R*,*R*)-

rac- <b>1a</b>	$Zn(OTf)_2$ (0.1 equiv)			
		( <i>R</i> )- <b>2a</b>	+	(S)- <b>3a</b>
	NBS (0.5 equiv) MeOH, RT, 12 h	30% yield, 43% <i>ee</i>		57% yield, 14% <i>ee</i>

**Scheme 3.** Oxidative kinetic resolution of *rac*-1 **a** with a chiral Zn- $(OTf)_2/(R,R)$ -Ph-BOX complex.

Ph-BOX complex, lacking redox properties, catalyzed the oxidative kinetic resolution of 1a to afford (*R*)-2a and (*S*)-3a with moderate selectivity.

In conclusion, we have presented the first efficient method for the kinetic resolution of racemic N-protected amino aldehydes, which is based on the recognition by a copper(II) /(R,R)-Ph-BOX complex to afford optically active amino acid methyl esters with high enantiomeric excess. In

addition, optically active aminoaldehyde dimethyl acetals that are easy to handle were obtained. Additional mechanistic studies and synthetic applications are underway.

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- [14] The absolute stereoconfiguration of (*R*)-**5a** was determined by comparison with the specific rotation of an authentic sample. See reference [9b]
- [15] Absolute stereoconfigurations of (*R*)-**5b-f** and (*S*)-**6a-f** shown in Table 5 were deduced on the basis of that of (*R*)-**5a**.