

# Enantioselective Oxidative Ring-Opening Reaction of Aziridines with $\alpha$ -Nitroesters Using Cinchona Alkaloid Amide/Nickel(II) Catalysts

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Supporting Information

**ABSTRACT:** The enantioselective oxidative ring-opening reaction of aziridines with  $\alpha$ -nitroacetates has been developed. Good yields and enantioselectivity were observed for the reaction of various aziridines using a novel cinchona alkaloid amide/NiBr<sub>2</sub> catalyst. Both enantiomers of products could be obtained by using pseudoenantiomeric chiral catalysts. This process offers an efficient route for the synthesis of  $\alpha$ -aminoketones.

An optically active  $\alpha$ -aminocarbonyl structure is an essential structural motif in many biologically active molecules and pharmaceuticals, such as cathinone, pyrovalerone, ketamine, ifenprodil, and keto-ACE, as well as in useful chiral ligand backbones (Figure 1).

Figure 1. Biologically active compounds for chiral  $\alpha$ -aminocarbonyl compounds.

The synthetic importance of these compounds has prompted considerable interest in developing asymmetric syntheses for  $\alpha$ -aminocarbonyl compounds. Therefore, excellent methodologies have been developed in asymmetric syntheses of  $\alpha$ -aminocarbonyl compounds, such as hydrogenation of  $\alpha$ -ketoketimines, cross coupling of aldehydes with imines, amination of enols, and other methods. On the other hand, one of the most efficient methods for the synthesis of optically active  $\alpha$ -aminocarbonyl compounds could be the oxidative desymmetrization of aziridines. Although there are many reports for the desymmetrization of aziridine using various nucleophiles and chiral catalysts to synthesize optically active amines, there are no reports on the enantioselective oxidative ring-opening

reaction of aziridines. <sup>13</sup> We recently reported the first catalytic desymmetrization of aziridines with phosphites using our original chiral catalysts derived from cinchona alkaloid. <sup>14,15</sup> Herein, we report the first catalytic enantioselective oxidative ring-opening reaction of aziridines with  $\alpha$ -nitroesters as a nucleophilic oxidant using our original chiral catalysts (Scheme 1)

Scheme 1. Catalytic Desymmetrization of Aziridines with  $\alpha$ -Nitroesters Using Chiral Catalysts Derived from Cinchona Alkaloids

$$\begin{array}{c|c} & \text{NCOAr} & \begin{array}{c} \text{chiral catalyst} \\ \hline R' & NO_2 \\ \hline CO_2 \text{Et} \end{array} & \begin{array}{c} \text{NHCOAr} \\ \hline R \end{array}$$

The enantioselective reaction of aziridine 1a with ethyl  $\alpha$ -nitroacetate 2a (2.0 equiv) was carried out in the presence of 10 mol % of picolinamide catalysts 4 derived from quinidine or quinine (Table 1).

The reaction of 1a with 2a using only N-picolinoyl-9-amino-9-deoxy-epi-quinidine 4a as organocatalyst did not give any products (Table 1, entry 1). The combined catalyst between 4a and metal species, especially Ni(OTf)<sub>2</sub>, gave product 3a in moderate yield but with low enantioselectivity (Table 1, entries 2–4). Optimization experiments by employing nickel salt were examined to improve the yield and stereoselectivity of the reaction, and as a result, NiBr<sub>2</sub> was found to be the most suitable Lewis acid (Table 1, entry 5). Next, we investigated the effect of

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Table 1. Enantioselective Oxidative Ring-Opening Reaction of Aziridines 1 with  $\alpha$ -Nitroesters 2 Using Various Metal Species and Picolinamide  $4^{\alpha}$ 

4a; R' 4b; R' 4c; R'	=OMe `N´ 🍑	OMe		N 4d	OMe MeC	N H N H N H N H N H N H N H N H N H N H	N N
entry	Lewis acid	$\mathbb{R}^1$	2	4	time (h)	yield (%)	ee <sup>b</sup> (%
1		Н	2a	4a	24	0	

entry	Lewis acid	$\mathbb{R}^1$	2	4	time (h)	yield (%)	ee <sup>b</sup> (%)
1		Н	2a	4a	24	0	
2	$Zn(OTf)_2$	Н	2a	4a	24	17	0
3	$Cu(OTf)_2$	Н	2a	4a	24	29	12
4	$Ni(OTf)_2$	Н	2a	4a	8	53	17
5	$NiBr_2$	Н	2a	4a	24	58	60
6	$NiBr_2$	Н	2b	4a	2	79	63
7	$NiBr_2$	Me	2b	4a	4	83	81
8	$NiBr_2$	Me	2b	4b	4	84	87
9	$NiBr_2$	Me	2b	4c	4	88	70
10	$NiBr_2$	Me	2b	4d	4	82	90
11 <sup>c</sup>	$NiBr_2$	Me	2b	4d	4	85	92
$12^{c,d}$	$NiBr_2$	Me	2b	4d	4	95	97
$13^{c,d}$	$NiBr_2$	Me	2b	4e	4	93	85 <sup>e</sup>

<sup>a</sup>Reaction conditions: aziridine 1 (0.1 mmol), 2 (0.2 mmol), metal species (10 mol %), and 4 (10 mol %) in toluene (0.1 M) were used. <sup>b</sup>The ee was determined by HPLC analysis using a chiral column. <sup>c</sup>Aziridines 1 (0.2 mmol) and 2 (0.1 mmol) were used. <sup>d</sup>Toluene/1,4-dioxane (0.1 M, v/v = 9/1) was used. <sup>e</sup>The opposite enantiomer was obtained.

the substituent on the nucleophile and protecting group of aziridine 1. We found that the reaction using  $\alpha$ -nitromalonate 2b, which has a highly acidic proton compared with  $\alpha$ -nitroacetate 2a, improved the reactivity of the reaction, and the enantioselectivity increased slightly (Table 1, entry 6). The reaction of aziridine 1b having a 6-methylpicolinoyl group afforded product 3b with good enantioselectivity (Table 1, entry 7). Furthermore, we examined various ligands to improve the enantioselectivity of the product. The reaction using 4b having an electron-donating group at the 4-position on the picolinamide group slightly improved enantioselectivity (Table 1, entry 8), but the electron-withdrawing group diminished enantioselectivity, probably due to the coordination ability of picolinamide group to Lewis acid catalysts (Table 1, entry 9). On the other hand, we expected that undesired coordination of the quinoline group to the Lewis acid would interfere in the highly enantioselective reaction pathway, so we introduced a tetrazolo[1,5-a]quinoline group to chiral catalysts. The reaction using 4d having a tetrazole group afforded  $\alpha$ -aminoketone 3b with higher enantioselectivity than that using catalysts 4a-c (90% ee, Table 1, entry 10). After optimization of the reaction conditions such as the ratio of the reagent and solvent, the enantioselectivity improved to 97% ee (Table 1, entries 11 and 12). An opposite enantiomer of **3b** could be obtained by the reaction using 4e derived from 9-amino-9deoxy-epi-quinine in high yield with good enantioselectivity (93%, 85% ee) (Table 1, entry 13).

Next, we examined the reaction of **2b** with various aziridines **1b**-**j** in the presence of **4d** and NiBr<sub>2</sub> (Table 2).

Table 2. Enantioselective Oxidative Ring-Opening Reaction of Aziridines 1b–j with  $\alpha$ -Nitromalonate  $2b^{\alpha}$ 

PG = 6-Me-picolinoyi							
entry	aziridine, 1		x	time (h)	yield (%)	ee <sup>b</sup> (%)	
1	N-PG	1b	10	4	95	97	
2	N-PG	1c	10	12	78	83	
3	N-PG	1d	10	12	81	70	
4	N-PG	1e	10	12	71	84	
5	N-PG	1f	20	72	54	96	
6	Me N-PG	1g	10	12	94	90	
7	Et N-PG	1h	20	12	76	92	
8	n-Pr n-Pr	1i	20	12	81	88	
9	Ph N-PG	1j	10	72	89	81	

<sup>a</sup>Reaction conditions: aziridine 1 (0.2 mmol), 2 (0.1 mmol), NiBr<sub>2</sub> (10 mol %), and 4d (10 mol %) in toluene:1,4-dioxane (0.1 M, v/v = 9/1) were used. <sup>b</sup>Ee was determined by HPLC analysis using a chiral column.

The reaction of aziridines 1c-e having a five- or six-membered ring also afforded products 3c-e with good enantioselectivities (Table 2, entries 2–4). Although the reaction of aziridine 1f bearing a seven-membered ring afforded product 3f in moderate yield (54%) due to the low reactivity of aziridine, the product was obtained with high enantioselectivity (96% ee) (Table 2, entry 5). The reaction with acyclic aziridines 1g-j showed that these were also good electrophiles in the oxidative ring-opening reaction, giving products 3g-j in 76-94% yield with 81-92% ee (Table 2, entries 6-9). These results are the first example of the enantioselective oxidative ring-opening reaction of aziridines.

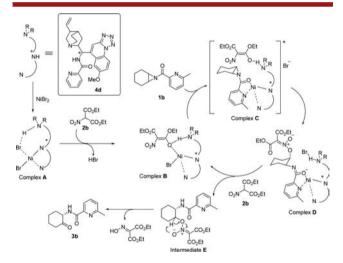
The obtained product 3b could be transformed to *trans*-1,2-amino alcohol 5 by the reduction of the carbonyl group using NaBH<sub>4</sub> (92%, dr = 81:19, ee = 97%) (Scheme 2). The absolute stereochemistry of product 3b was assigned as S in comparison with the value of the specific rotation of 5 prepared from commercially available (1S,2S)-*trans*-2-aminocyclohexanol (see the Supporting Information). Furthermore, we succeeded in the

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## Scheme 2. Transformation of 3b to Chiral 1,2-Amino Alcohols 5 and 6

preparation of 1,2-amino alcohol 6 having a tetrasubstituted chiral carbon center by using MeMgI as a nucleophile. The reaction afforded product 6 as a single diastereomer in good yield with 95% ee.

The proposed catalytic cycle for the ring-opening reaction of aziridine **1b** with  $\alpha$ -nitromalonate **2b** using ligand **4d** is shown in Figure 2. The coordination of nickel bromide to picolinamide



**Figure 2.** Assumed reaction cycle for the enantioselective desymmetrization of aziridines with  $\alpha$ -nitromalonates.

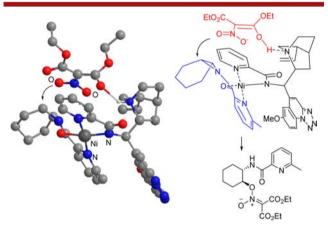
ligand 4d gives complex A, which reacts with nitromalonate 2b to form complex B. Then the coordination of pyridine nitrogen and carbonyl oxygen in aziridine 1b to complex B gives complex C, and the reaction between activated  $\alpha$ -nitromalonate 2b with aziridine 1b proceeds in the coordination sphere of nickel(II) to give a ring-opening product (complex D), which subsequently undergoes deprotonation and decomplexation to give intermediate E and regenerated complex B. Finally, the oxy-Copetype elimination of intermediate E leads to product 3b and oxime compound. 16,17 In order to clarify the assumed reaction mechanism, we conducted spectroscopic analyses. The ESI-MS analysis of the mixture of 1b, NiBr2, and 4d in a 1:1:1 ratio in toluene/1,4-dioxane (0.1 M, v/v = 9/1) showed complex C (cation mode, calcd for C<sub>39</sub>H<sub>42</sub>N<sub>9</sub>NiO<sub>3</sub> as complex C-2b-Br 742.2, found 742.2; see the Supporting Information). This signals support for our proposed reaction mechanism.

In order to clarify the structure of the chiral catalyst, we studied the X-ray crystallographic analysis of **4d** (Figure 3).



Figure 3. X-ray crystal structure of 4d.

In this structure, two nitrogens for pyridine and quinuclidine directed to the proton on picolinoyl amide. The distances between the amide proton and the two nitrogens are 2.32 and 2.63 Å, respectively. Considering the structure of 4d, the reaction mechanism of aziridines with  $\alpha$ -nitromalonates using a chiral catalyst derived from 4d and Ni(II) is shown in Figure 4.



**Figure 4.** Proposed transition state of the reaction of aziridine **1b** with  $\alpha$ -nitromalonate **2b** using **4d**-Ni(II). H atoms have been omitted for clarity.

Three nitrogens from ligand 4d and aziridine 1b and one oxygen from 1b coordinate to nickel(II) in a distorted square planar manner, and activated  $\alpha$ -nitromalonate 2b attacks aziridine. In general, the  $\alpha$ -nitroester generally acts as a C-nucleophile; however, in this reaction, the  $\alpha$ -nitroester reacted with aziridine by including oxygen in the nitro group. This result supports the assumption that the reaction proceeds in the coordination sphere of nickel(II). Because of the distance between nucleophilic oxygen in 2b and electrophilic aziridine, the (S)-isomer was formed. Further studies are required to fully elucidate the mechanistic detail of the reaction.

In conclusion, we developed the enantioselective oxidative ring-opening reaction of aziridines with  $\alpha$ -nitroesters using novel cinchona alkaloid catalysts having a tetrazole group and a 2-picolynoyl group. The reaction was screened for a broad range of aziridines, and this process offers an efficient route for the synthesis of  $\alpha$ -aminocarbonyl compounds in an optically active form. The obtained product can be converted to optically active 1,2-amino alcohols. This process provides stereodivergent access to optically active  $\alpha$ -aminocarbonyl compounds. Further studies are in progress to determine the potential of these catalytic systems to other processes.

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#### ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03346.

X-ray data for compound 4d (CIF)

<sup>1</sup>H and <sup>13</sup>C NMR spectra and experimental procedures for all new compounds (PDF)

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**Notes** 

The authors declare no competing financial interest.

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