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Desymmetrization of Aziridine with Malononitrile using Cinchona Alkaloid Amide/Zinc(II) Catalysts

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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The catalytic enantioselective desymmetrization of aziridines with malononitrile has been developed. Good yield and enantioselectivity were obtained by using cinchona alkaloid amide/Zn(II) and base catalysts. The obtained product can be converted to β-aminoester, β-aminoamide and triamide compounds.

Desymmetrization of aziridines with various nucleophiles is an effective strategy for the preparation of useful chiral 2-substituted amine compounds.[1] Therefore there are many reports on the catalytic desymmetrization of aziridines with various nucleophiles, such as nitrogen,[2] sulfur,[3] halogen,[4] and other nucleophiles.[5] In spite of these impressive advances, the desymmetrization of aziridines for carbon nucleophiles has not been too fruitful, except for the reaction with cyanides.[6] Müller and co-workers reported the first enantioselective ring-opening reaction with Grignard reagents as carbon nucleophiles using copper(II)-Schiff base catalysts to give products with high enantioselectivity.[7] Recently, the desymmetrization of aziridines with malonates using chiral hetero-dinuclear rare earth metal catalysts have been reported by Shibasaki and Matsunaga.[8] Since these milestone achievements, enantioselective ring-opening reactions with carbon nucleophiles have attracted considerable attention in organic chemistry, leading some research groups to report on the desymmetrization of aziridines with enolates and arene compounds as carbon nucleophiles.[9] However, there are no reports on the desymmetrization of aziridines with malononitriles as nucleophiles, in which the reaction gives highly functionalized chiral amines.[10] As a part of our ongoing studies on our original cinchona alkaloid catalysts, we recently reported the first highly enantioselective ring-opening reaction of aziridines with phosphorous nucleophiles[11] and nitro compounds[12] using chiral catalysts derived from cinchona alkaloids.[13] Furthermore, we recently reported various enantioselective reactions of the α-carbanion of nitrile compounds.[14] Herein, we report the first catalytic desymmetrization of aziridines with malononitrile using cinchona alkaloid picolinamide catalysts (Figure 1).

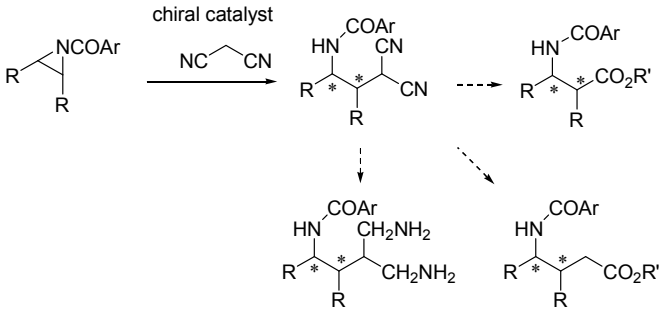

Fig. 1. Catalytic desymmetrization of aziridines with malononitrile using our original chiral catalysts derived from cinchona alkaloids

We first examined the asymmetric desymmetrization of aziridines **1** with malononitrile using a catalytic amount of diethylzinc and picolinamides **3** in various reaction conditions (Table 1). Although the ring-opening reaction of **1a** with malononitrile using **3a** derived from cinchonidine in toluene afforded product **2a** in moderate yield with low enantioselectivity, the reaction in THF afforded **2a** in 62% yield with 87% ee (entries 1 and 2). The reaction in other solvents such as CH_2Cl_2 or 1,2-dichloroethane gave **2a** in better yield but with slightly lower enantioselectivity than the reaction in THF (entries 3 and 4). The reaction using 5.0 equiv. of malononitrile improved the yield of product **2a** (entry 5). Next, we investigated the effect of protecting group of aziridines in order to improve enantioselectivity. We found that the reaction of aziridines **1b-d** having an imidazolecarbonyl group afforded products **2b-d** in good yield with high enantioselectivity (82-93% yield, 92-96% ee, entries 6-8). The reaction using aziridine **1b** showed higher reactivity than other aziridines, and the reaction of **1b** at lower temperature (0 °C) gave product **2b** in 89% yield with 97% ee (entry 9). The reaction using picolinamide **3b** derived from cinchonine gave **2b** having opposite stereochemistry in 74% yield with 94% ee (entry 10).

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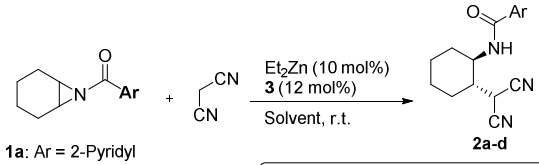
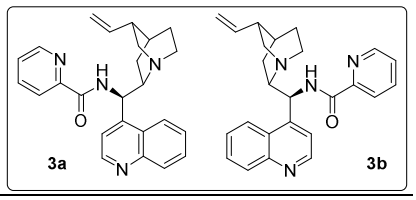
Table 1 Optimization of reaction conditions



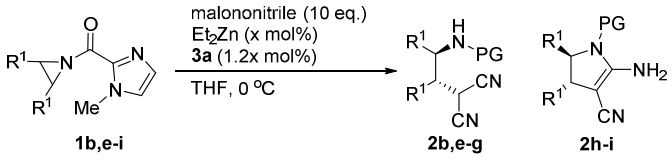


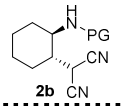
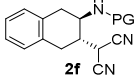
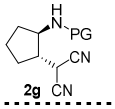
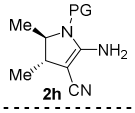
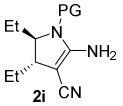
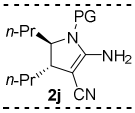
Entry	1	3	Solvent	Time (h)	Yield (%)	Ee (%)[b]
1	**1a**	**3a**	Toluene	48	51	15
2	**1a**	**3a**	THF	24	62	87
3	**1a**	**3a**	CH_2Cl_2	24	75	73
4	**1a**	**3a**	DCE	24	76	79
5[c]	**1a**	**3a**	THF	6	74	88
6[c]	**1b**	**3a**	THF	3	84	92
7[c]	**1c**	**3a**	THF	6	88	95
8[c]	**1d**	**3a**	THF	12	82	96
9[c,d]	**1b**	**3a**	THF	20	89	97
10[c,d]	**1b**	**3b**	THF	20	74	94[e]

DCE: 1,2-dichloroethane. a) Reaction conditions: aziridine **1** (0.1 mmol), malononitrile (1.5 equiv.), Et_2Zn (10 mol %), and **3** (12 mol %) in solvent (0.2 M) were used. b) Ee was determined by HPLC analysis using a chiral column. c) Malononitrile (5.0 equiv.) was used. d) At 0 °C. e) Opposite enantiomer was obtained.

Having established the optimized reaction conditions for the desymmetrization of aziridines, the reaction of various aziridines **1b**, **e-i** with malononitrile was carried out (Table 2). The reaction of aziridines **1b**,**e** having six-membered ring structure afforded products **2b**,**e** with high enantioselectivities, but aziridine **1f** having a bulky substituent showed low reactivity with moderate enantioselectivity. (entries 1-3). The reaction of aziridine **1g** bearing a five-membered ring afforded product **2g** in moderate yield (61%) with high enantioselectivity (95% ee, entry 4). Interestingly, the reaction of acyclic aziridines **1h-j** with malononitrile using the **3a**-Zn catalyst gave 2,3-dihydro-1H-pyrrole compounds **2h-j** which were formed by the intramolecular nucleophilic addition of amide nitrogen to the cyano group, in moderate yield with good enantioselectivity (entries 5-7).[15,16]

Table 2 Catalytic enantioselective desymmetrization of various aziridines with malononitrile[a]

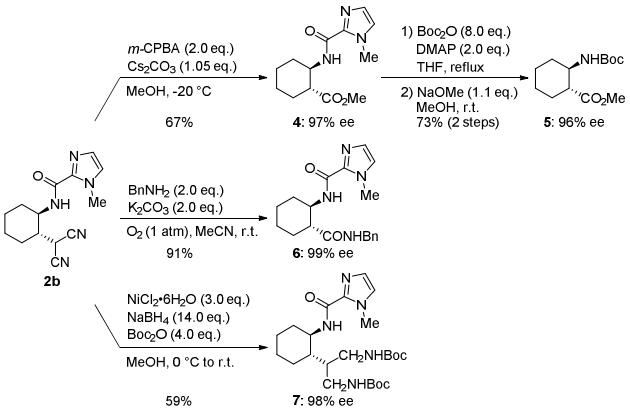


Entry	3a (x mol%)	Time (h)	2	Yield (%)	Ee (%)[b]
1[c]	10	20	 **2b**	89	97
2	20	36	 **2e**	71	94
3[c,d,e]	20	48	 **2f**	21	73
4	20	48	 **2g**	61	95
5[e]	20	10	 **2h**	64	90
6[e]	20	14	 **2i**	75	94
7[e]	20	20	 **2j**	69	94

a) Reaction conditions: aziridine **1** (0.1 mmol), malononitrile (10 equiv.), Et_2Zn (10-20 mol %), **4** (12 mol %) in solvent (0.2 M) were used. b) Ee was determined by HPLC analysis using a chiral column. c) Malononitrile (5 equiv.) was used. d) 1,2-Dichloroethane was used as the solvent. e) At r.t.

Next, the transformation of product **2b** to an ester or amides, and deprotection of the imidazole carbonyl group were examined (Scheme 1).

Scheme 1 Transformation of **2b** to β-aminoester **5**, β-aminoamide **6** and triamine **7**



The reaction of **2b** with *m*-CPBA and Cs_2CO_3 in methanol gave β-aminoester **4** in 67% yield.[17] Deprotection of the Boc group on the amide group of **4** was carried out using sodium methoxide in methanol to give *N*-Boc-β-aminoester **5** in 73% yield (two steps). The absolute configuration of **5** was determined as (1*R*,2*S*), based on the value of the specific rotation for previous paper (see supporting information).[18] We

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also succeeded to prepare β-aminoamide **6** from the reaction of **2b** with benzylamine, and potassium carbonate under an oxygen atmosphere in 91% yield with 99% ee.[19] Furthermore, **2b** could be transformed to triamide **7** in 59% yield with 98% ee by the reduction of the cyano group in **2b** using $NaBH_4$ and $NiCl_2 \cdot 6H_2O$ followed by Boc protection. These derivatives could be synthesized without the loss of enantiopurity.

The assumed catalytic cycle for the reaction of aziridine **1b** with malononitrile is shown in Figure 2. First, Et_2Zn reacts with picolinamide ligand **3a** to give complex **A**. Malononitrile then reacts with complex **A** to afford complex **B**, which coordinates to aziridine **1b** to give complex **C**, and the ring-opening reaction between aziridine **1b** and activated malononitrile gives complex **E**. Finally, the ligand exchange reaction of complex **E** with malononitrile proceeds to give product **2b** and complex **B**. In order to clarify the proposed reaction cycle, we conducted an ESI-mass spectroscopic analysis. We observed complex **C** for the reaction mixture of **1b**, malononitrile, Et_2Zn, and **3a** (cation mode, calcd for $C_{36}H_{40}N_7O_2Zn^+$ as complex **C**-$(CN)_2CH^-$: 666.2, found: 666.2). This signal supports our proposed reaction mechanism.

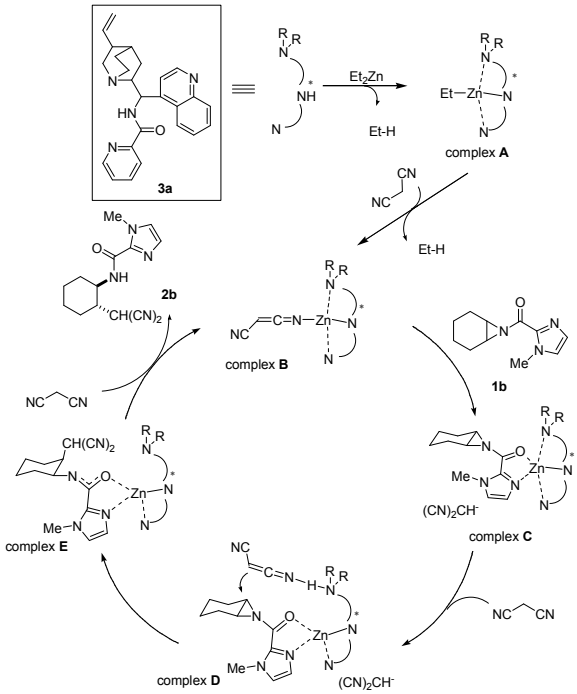

Fig. 2 Proposed reaction cycle for the desymmetrization of **1** with malononitrile using **3a** and Et_2Zn.

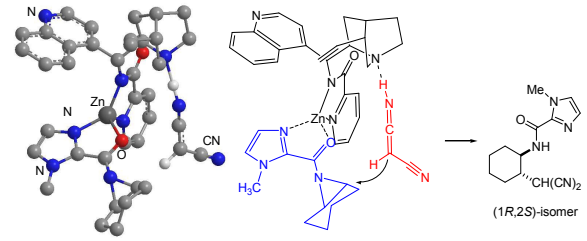

Fig. 3 Assumed transition state for the reaction of malononitrile with aziridine **1b** using **3a**.

From the absolute stereochemistry of products and the assumed reaction cycle, the proposed transition state for the desymmetrization of aziridine 1b with malononitrile is shown in Figure 3. Pyridine nitrogen and carbonyl oxygen in the imidazolyl group coordinates to the zinc cation in a tetrahedral form, and the quinuclidine moiety in the catalyst forms a hydrogen bond with malononitrile. Malononitrile then attacks aziridine on the zinc cation.

Conclusions

We developed the enantioselective desymmetrization of aziridines with malononitrile using cinchona alkaloid amide/zinc(II) catalysts. The reaction was screened for various aziridines. Both enantiomers of the product could be synthesized by using pseudoenantiomeric chiral catalysts. Additional studies are in progress to investigate the potential of these chiral catalysts for other synthetic processes.

This work was partially supported by Grants-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT (26105727) and the Uehara Memorial Foundation.

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