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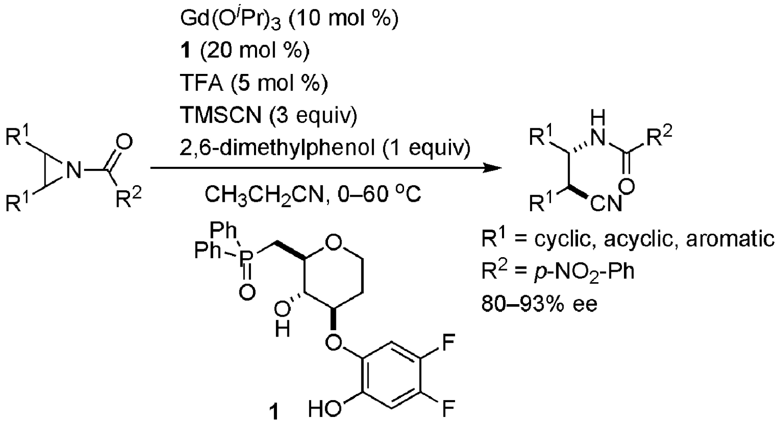

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Catalytic Enantioselective Desymmetrization of *meso*-*N*-Acylaziridines with TMSCN

Tsuyoshi Mita, Ikuo Fujimori, Reiko Wada, Jianfeng Wen, Motomu Kanai,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan

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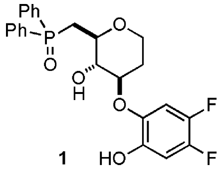
Chiral β-amino acids are important building blocks for natural products and pharmaceuticals.[1] Among them, chiral cyclic β-amino acids are currently of great interest due to the recent finding that peptides composed of these amino acids can act as foldamers with a well-defined secondary structure.[2] Despite the emerging importance, there are few enantioselective synthetic methods that produce chiral cyclic β-amino acids.[3] Specifically, there is no method available using an artificial enantioselective catalyst to access these compounds.[4] Here, we describe the first such method based on the catalytic enantioselective desymmetrization of *meso*-aziridines by cyanide.

Catalytic enantioselective ring-opening of *meso*-aziridines with carbon nucleophiles is a formidable challenge due to both the low reactivity of aziridines and the general difficulty in differentiation of enantiotopic centers.[5] The only example that begins to address these difficulties is a dimeric copper-catalyzed aziridine opening with MeMgBr.[6] Although enantioselectivity was excellent (91% ee) using 30 mol % of catalyst (i.e., 60 mol % of Cu), this reaction was applied to only one substrate, and the catalyst turned over less than twice (52% yield). A more sophisticated example in catalytic desymmetrization of aziridines was reported by Jacobsen using $TMSN_3$ as a nucleophile.[7,8] Regarding the nucleophile, TMSCN is currently the only carbon nucleophile that can be used for catalytic enantioselective desymmetrization reactions (epoxide opening).[9] Importantly, those reactions appear to be promoted via dual activation of an electrophile and a nucleophile by bifunctional asymmetric catalysts.[10]



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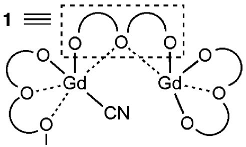
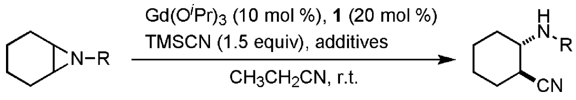


2

We developed several catalytic enantioselective cyanation reactions using Gd complexes derived from ligand **1**.[11] The active catalyst structure was proposed as a 2:3 complex of Gd and **1** (**2**; catalyst for Strecker reaction of ketoimines[11c] and conjugate addition of cyanide[11d]). These catalysts are thought to promote the reactions through a dual activation mechanism: one Gd atom acts as a Lewis acid to activate an electrophile, while the other Gd generates a reactive nucleophile via transmetalation. This mechanism and high cyanation activity of the catalyst prompted us to investigate an enantioselective *meso*-aziridine opening with TMSCN.

We initially screened substituents on the nitrogen atom using cyclohexene-derived aziridines as substrates, TMSCN as the nucleophile, and the Gd complex (10 mol %) as the catalyst (Table 1).[12] When *N*-benzyl and *N*-phosphinoyl aziridines were used, the ring-opening reaction did not proceed. On the other hand, *N*-sulfonyl aziridines and *N*-Boc aziridine produced the corresponding adducts in low to moderate yield with low enantioselectivity (entries 1−3). When *N*-*p*-nitrobenzoyl aziridine was used, the reaction was completed within 5 h with a significantly improved enantioselectivity of 72% ee (entry 4). Similar to the finding in the catalytic enantioselective Strecker reaction,[11c] enantioselectivity was further improved in the presence of 2,6-dimethylphenol (DMP, entry 5).[13] Other benzoyl derivatives gave comparable or less satisfactory results.[14]

Table 1. Optimization of Reaction Conditions



entry	R	additives	time (h)	yield (%)[a]	ee (%)[b]
1[c]	Ts		48	58	24
2	*p*-Ns		48	63	16
3	Boc		48	18	31[d]
4	*p*-NO_2-Bz		5	90	72
5[e]	*p*-NO_2-Bz	DMP[f]	3	>99	80
6[e]	*p*-NO_2-Bz	DMP[f] + TFA[g]	2	>99	83
7[e]	*p*-NO_2-Bz	DMP[f] + TFA[h]	26	67	83
8[e]	*p*-NO_2-Bz	TFA[g]	3	96	83
9[e,i]	*p*-NO_2-Bz	DMP[f] + TFA[g]	20	94	87
10[e,i]	*p*-NO_2-Bz	TFA[g]	43	92	86

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Toluene was used as solvent. [d] Determined by chiral GC. [e] TMSCN (3 equiv) was used. [f] DMP (1 equiv) was used. [g] TFA (5 mol %) was used. [h] TFA (10 mol %) was used. [i] Temperature = 0 °C.

To further improve the enantioselectivity, we next investigated the effects of additional strong acids aimed at the enhancement of the Lewis acidity of the Gd through conjugation to an acid (see complex **5**). Among the acids screened, the addition of 5 mol % (half the amount of Gd) of TFA (trifluoroacetic acid) improved enantioselectivity to 83% ee (Table 1, entry 6).[14] Although the improvement was not large, higher enantiomeric excess was generally and reproducibly obtained in the presence of TFA.[15] Catalyst activity decreased dramatically when more TFA was used (entry 7). Interestingly, high enantioselectivity was produced even in the absence of DMP if 5 mol % of TFA was present (entry 4 vs 8). In this case, however, the reaction rate was retarded (entry 6 vs 8, 9 vs 10). Finally, the optimum enantioselectivity (87% ee) was produced when the reaction was conducted at 0 °C in the presence of 5 mol % of TFA and 1 equiv of DMP (entry 9).

The optimized reaction conditions were applied to substrates with different ring size and acyclic aziridines (Table 2). Although the reaction temperature was dependent on the substrates, high enantioselectivity was generally obtained from a wide range of aziridines. The products were crystalline, and enantiomerically pure materials were obtained through recrystallization (entries 1, 4, and 5). Thus, this is the first example of catalytic enantioselective desymmetri-

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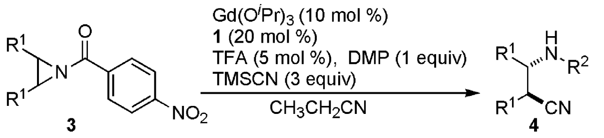
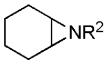
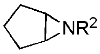
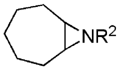
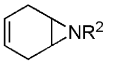
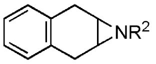
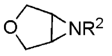
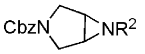
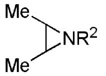
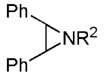
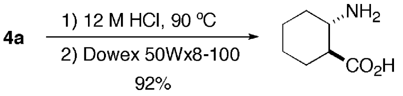
Table 2. Catalytic Enantioselective Desymmetrization of *meso*-*p*-Nitrobenzoylaziridines with TMSCN



entry	substrate (R^2 = *p*-NO_2-Bz)		temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1		**3a**	0	20	94 (79)[c]	87[d] (>99)[c]
2[e]		**3b**	r.t.	69	81	93[d]
3[e]		**3b**	40	14	98	91[d]
4[f]		**3c**	60	64	92 (58)[c]	80 (>99)[c]
5		**3d**	r.t.	95	85 (66)[c]	82 (>99)[c]
6[g]		**3e**	r.t.	42	91	83
7[e]		**3f**	60	96	92	88
8[e]		**3g**	60	23	89	84
9		**3h**	r.t	39	93	85[h]
10		**3i**	r.t.	96	81 (54 / 46)[i]	90/89

[a] Isolated yield. [b] Determined by chiral HPLC. [c] After recrystallization. Recrystallization yield and its ee are shown in parentheses. [d] Absolute configuration was determined to be (1*S*,2*S*). [e] With 20 mol % of Gd(O^{i}Pr)$_3$ and 40 mol % of **1**. [f] TFA (2.5 mol %) was used. [g] CH_3CH_2CN/CH_2Cl_2 = 1/2 was used as solvent. [h] Absolute configuration was determined to be (2*S*,3*S*). [i] Ratio of diastereomers determined by ^{1}H NMR analysis.

Scheme 1. Typical Conversion to Chiral *β*-Amino Acids



zation of *meso*-aziridines with TMSCN that produces synthetically useful catalyst activity and enantioselectivity. The resulting *β*-amino nitriles were easily converted to the corresponding *β*-amino acids via acid hydrolysis and purification through ion exchange chromatography (Scheme 1).[14]

To obtain insight into the origin of the beneficial additive TFA effect, catalyst composition was investigated using ESI-MS (Figure 1).[14] It was previously proposed that a 2:3 complex **2** is the active catalyst in the presence of excess TMSCN and DMP.[11c] The addition of 0.5 equiv of TFA to Gd generated a new 2:3 complex **5** possessing TFA (observed MW = 1949, calcd for $[M - CN]^+$ = 1949).[16] This incorporated TFA might bridge the two Gd atoms[17] of the catalyst, thus stabilizing the enantioselective 2:3 complex. In addition, enhancement of the Lewis acidity of Gd as well as fine-tuning of the relative positions of the two Gd atoms might also contribute to the improved enantioselectivity. Detailed structural studies of the catalyst are ongoing.

In conclusion, we developed an enantioselective desymmetrization reaction of *meso*-aziridines with TMSCN catalyzed by a new TFA-incorporated chiral Gd complex derived from **1**. The products can be efficiently transformed into chiral *β*-amino acids. This contribution provides a new strategy for the construction of this important group of chiral amino acids.

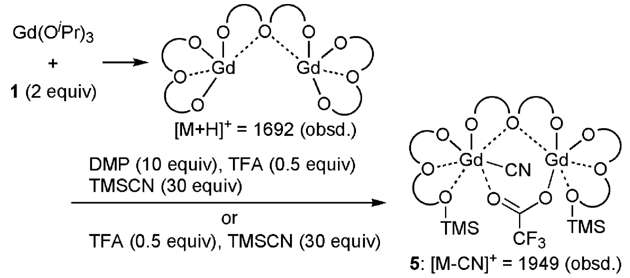


Figure 1. Proposed catalyst structure in the presence of TFA.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1. (c) Fülöp, F, *Chem Rev.* **2001**, *101*, 2181.

(2) (a) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 6206. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.

(3) Diastereoselective reactions using chiral amine derivatives are the main method. For selected examples, see: (a) Enders, D.; Wiedemann, J.; Bettray, W. *Synlett* **1995**, 369. (b) LePlae, P. R.; Umezawa, N.; Lee, H.-S.; Gellman, S. H. *J. Org. Chem.* **2001**, *66*, 5629.

(4) For enzymatic synthesis, see: Kanerva, L. T.; Csomós, P.; Sundholm, O.; Bernáth, G.; Fülöp, F. *Tetrahedron: Asymmetry* **1996**, *7*, 1705.

(5) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, Chapter 35.

(6) Muller, P.; Nury, P. *Org. Lett.* **1999**, *1*, 439.

(7) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611.

(8) For other catalytic enantioselective desymmetrizations of aziridines, see: (a) Zhang, Z. D.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 2602. (b) Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1994**, 2699.

(9) (a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668. (b) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704. (c) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.

(10) (a) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865. (b) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491.

(11) (a) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908. (b) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (c) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147. (d) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514.

(12) Other lanthanide metals gave less satisfactory results than Gd. In all entries, the isomeric isonitriles were produced in less than detectable amounts.

(13) Addition of HCN instead of DMP produced less satisfactory results (89% yield, 74% ee).

(14) See Supporting Information for details.

(15) For example, **4d** and **4h** were obtained with 78 and 82% ee in the absence of TFA (82 and 85% ee in the presence of TFA; see Table 2).

(16) The same MS peak was observed in the absence of DMP, which was consistent with the experimental results that DMP did not change the enantioselectivity.

(17) For example, see: Yang, X.; Jones, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 7686.

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