ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Chiral magnesium(II)-catalyzed asymmetric ring-opening of *meso*-aziridines with primary alcohols†

Cite this: *Chem. Commun.*, 2014, 50, 6672

Received 25th March 2014,
Accepted 6th May 2014

DOI: 10.1039/c4cc02206h

www.rsc.org/chemcomm

Published on 14 May 2014. Downloaded by Temple University on 29/10/2014 23:16:41.

Jun Li, Yuting Liao, Yulong Zhang, Xiaohua Liu, Lili Lin and Xiaoming Feng*

The asymmetric ring-opening of *meso*-aziridines with primary alcohols is realized using an *N*,*N*′-dioxide–Mg(OTf)$_2$ complex as the catalyst. The desired vicinal *trans*-β-amino ethers are afforded in good yields and enantioselectivities. Aniline and water could also be used as the nucleophiles for the ring-opening in an identical catalyst system.

Nucleophilic ring-opening of aziridines is an effective strategy in modern synthetic chemistry.[1] Specifically, enantioselective desymmetrization of *meso*-aziridines has received a tremendous amount of attention, because it furnishes valuable 1,2-difunctionalized chiral molecules[2–4] with vicinal stereocenters in just one step. The pioneering work on the catalytic desymmetrization of *meso*-aziridines was initiated by the Jacobsen group in 1999 using $TMSN_3$ as the nucleophile.[5a] Then, versatile methodologies have been developed in the enantioselective desymmetrization of *meso*-aziridines with a number of nucleophiles such as $TMSN_3$,[5] TMSCN,[5e,6] amines,[7] thiols,[8] halogen,[9] *etc.*[10] In spite of these impressive advances, there are still few reports on the direct catalytic asymmetric ring-opening of *meso*-aziridines with the oxygen nucleophiles,[11] although the corresponding chiral vicinal amino ether is a vital structural subunit of a variety of biologically active compounds.[12] This reaction is a challenge possibly due to the weaker nucleophilicity of oxygen compared with nitrogen or carbon nucleophiles.[1a] In addition, the excessive oxygen nucleophiles used in the reaction, such as alcohols, would compete for the coordination of the chiral ligands and the reactant to the Lewis acid, hence deteriorate the effective activation and enantiotopic differentiation of the aziridine. In 2008, the Toste group devised a chiral anion-mediated asymmetric ring opening of *meso*-aziridinium ions generated from the ring closure of β-chloro tertiary amines.[13] Various alcohols are used as the nucleophile to give the *N*,*N*-disubstituted amino ethers with excellent enantioselectivities. Catalytic amounts of chiral binaphthol-phosphate and stoichiometric silver salt are necessary for the reaction to proceed. Herein, we accomplish a direct asymmetric nucleophilic ring opening of *meso*-aziridines with primary alcohols. The level of enantioselection is certainly good with the chiral *N*,*N*′-dioxide–Mg(OTf)$_2$ complex in the formation of vicinal amino ethers. The success with ring opening of alcohol can be extended to aniline and water.

At the outset, we explored the reaction of *meso*-aziridine **1a** with methanol as both the nucleophile and the solvent, using chiral *N*,*N*′-dioxide–metal complex catalysts established by our group.[14] We chose aziridine **1a** having a *N*-(2-picolinoyl)-protecting group as the substrate in view that it can bind to the metal center well in a bidentate manner.[10b] The incorporation of *N*,*N*′-dioxide **L1** with strong Lewis acid Sn(OTf)$_2$ gave almost quantitative yield but the product is racemic (Table 1, entry 1).[11a] Investigation of alkaline earth metals[15] showed that Mg(OTf)$_2$ gave the highest level of enantioselectivity (entries 2–5; 24% yield, 45% ee). The low yield resulted from the generation of the byproduct **4a** which formed easily in methanol (entries 2–5). Delightfully, when the amount of methanol was decreased to 5.0 equivalents and CH_2Cl_2 was used as the solvent, the desired product **3a** was obtained in 78% yield with 68% ee (entry 6). Focusing on Mg(OTf)$_2$-type catalysts, we then evaluated the performance of *N*,*N*′-dioxides with varied chiral backbones. It seemed that L-ramipril derived ligand **L3** was superior to these derived from L-proline and L-pipecolic acid (entry 8 *vs.* entries 6 and 7). Subsequently, the effect of solvent was surveyed.[15] The enantioselectivity increased to 92% ee when the reaction was run in *para*-xylene (entry 10). A survey of the protecting group of aziridine[15] showed that the substituent on the *N*-2-picolinoyl group of aziridine was harmful to the enantioselectivity, and the electron-donating one was also unfavorable in the yield (entries 11 and 12). *N*-Benzoyl aziridine failed in the reaction indicating that the binding of the 2-piconlinoyl group to the metal center accounts for the high yield and stereoselectivity achieved.[15]

With the optimized reaction conditions in hand (Table 1, entry 10), the generality of the protocol was explored (Table 2). Firstly, the reaction was extended to the use of other primary alcohols.[15,16] Ethanol, propan-1-ol and prop-2-enol can be

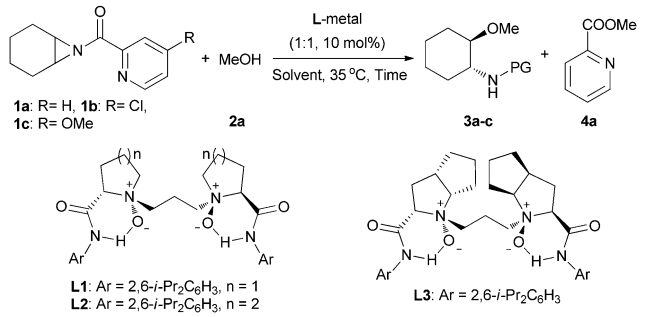
Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China.
E-mail: xmfeng@scu.edu.cn; Fax: +86 28 85418249; Tel: +86 28 85418249

† Electronic supplementary information (ESI) available: Additional experimental and spectroscopic data. CCDC 991793. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc02206h

This journal is © The Royal Society of Chemistry 2014

Published on 14 May 2014. Downloaded by Temple University on 29/10/2014 23:16:41.

Table 1 Optimization of the reaction conditions



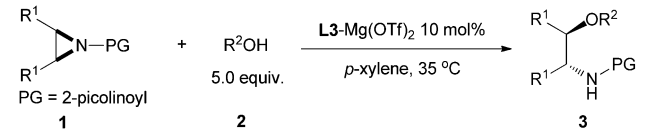
Entry[a]	L	Metal	Solvent	t (h)	Yield[b] (%)	ee[c] (%)
1[d]	**L1**	$Sn(OTf)_2$	—	20	90	0
2[d]	**L1**	$Mg(OTf)_2$	—	20	24	45
3[d]	**L1**	$Mg(ClO_4)_2$	—	20	34	35
4[d]	**L1**	$Ca(OTf)_2$	—	20	27	35
5[d]	**L1**	$Ba(OTf)_2$	—	20	9	0
6	**L1**	$Mg(OTf)_2$	CH_2Cl_2	20	78	68
7	**L2**	$Mg(OTf)_2$	CH_2Cl_2	20	64	56
8	**L3**	$Mg(OTf)_2$	CH_2Cl_2	20	88	78
9	**L3**	$Mg(OTf)_2$	*p*-Xylene	18	98	82
10[e]	**L3**	$Mg(OTf)_2$	*p*-Xylene	21	96	92
11[e,f]	**L3**	$Mg(OTf)_2$	*p*-Xylene	24	98	79 (1*R*,2*R*)
12[e,g]	**L3**	$Mg(OTf)_2$	*p*-Xylene	48	67	78

[a] Unless otherwise noted, all reactions were performed with **L**–metal (1 : 1, 10 mol%), **1a** (0.1 mmol), MeOH (0.5 mmol) in solvent (0.2 mL) under N_2 at 35 °C for the indicated time. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] MeOH (0.2 mL) and **1a** was completely consumed. [e] *p*-Xylene (0.5 mL). [f] **1b** was used instead of **1a**. The absolute configuration was determined by X-ray crystallography. [g] **1c** was used instead of **1a**.

employed as the nucleophile, giving the desired β-amino ethers with good yields and enantioselectivities (entries 2–4). The substrates range to other *meso*-aziridines formed from different cyclic olefins and acyclic *cis*-alkenes. Cyclopentene-derived aziridine **1m** behaved similarly as its analogue and furnished the product with 81% yield and 91% ee (entry 5). The catalytic desymmetrization of other aziridines **1n** and **1o** bearing a six-membered ring afforded the corresponding products **3n** and **3o** with good yields and enantioselectivities (entries 6 and 7). Aziridines containing a pyrrolidine ring or a tetrahydrofuran unit delivered the desired heterocyclic β-amino ethers **3p** and **3q** with 80% and 78% ee, respectively (entries 8 and 9). The addition of methanol to cycloheptene derived aziridine **1r** resulted in the formation of the ring-opened product **3r** in moderate yield and enantioselectivity (entry 10). Acyclic alkyl-substituted *meso*-aziridine **1s** was also a competent substrate, providing the β-amino ether **3s** as a single diastereomer in 88% yield and 84% ee (entry 11). *cis*-Diphenyl substituted aziridine **1t** underwent the reaction sluggishly, affording the ring-opening *trans*-product **3t** with moderate enantioselectivity, indicating a predominant S_N2-pathway in the catalytic process (entry 12).[9a]

It is noteworthy that this catalyst system was also successfully applied to the desymmetrization of the aziridine using aniline as the nucleophile, providing the corresponding 1,2-diamine[4] in 97% yields with 95% ee (Scheme 1a). We further found that the ring-opening of *meso*-aziridine **1a** was compatible with water, although the yield of the aminoalcohol[3] product was moderate (50% yield and 92% ee; Scheme 1b). In addition, the corresponding β-amino alcohol **3v** could be obtained from β-amino

Table 2 Substrate scope



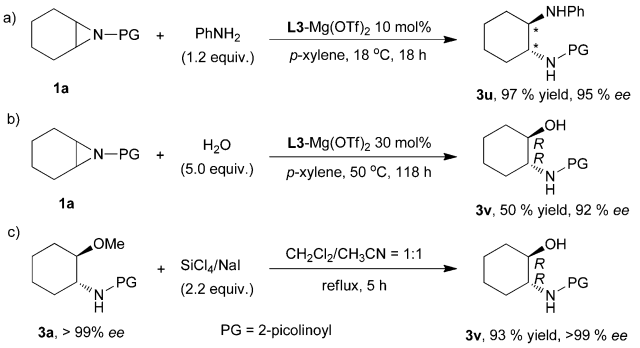
Entry[a]	Aziridines **1**	R^2	t (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	Me	21	96 (**3a**)	92 (*R*,*R*)
2		Et	24	87 (**3j**)	87 (*R*,*R*)
3		^{n}Pr	35	90 (**3k**)	88 (*R*,*R*)
4		Allyl	16	89 (**3l**)	92 (*R*,*R*)
5	**1m**	Me	48	81 (**3m**)	91
6[d]	**1n**	Me	75	88 (**3n**)	83 (*R*,*R*)
7[d]	**1o**	Me	93	86 (**3o**)	76 (*R*,*R*)
8[d,e]	**1p**	Me	49	75 (**3p**)	80
9[f]	**1q**	Me	118	66 (**3q**)	78
10[f]	**1r**	Me	118	62 (**3r**)	75
11[d]	**1s**	Me	65	88 (**3s**)	84
12[f,g]	**1t**	Me	118	68 (**3t**)	57

[a] Unless otherwise noted, all reactions were performed with **L3**–$Mg(OTf)_2$ (1 : 1, 10 mol%), **1** (0.1 mmol), alcohol (0.5 mmol) in *p*-xylene (0.5 mL) under N_2 at 35 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configurations of the products **3a,j–l,n,o** were determined by comparing the circular-dichroism spectra with that of **3b**. [d] 20 mol% catalyst loading, MeOH (1.0 mmol) in *p*-xylene (0.4 mL) at 50 °C. [e] MeOH (2.5 mmol). [f] 30 mol% catalyst loading, MeOH (2.5 mmol) in *p*-xylene (0.4 mL) at 50 °C. [g] 99 : 1 dr.

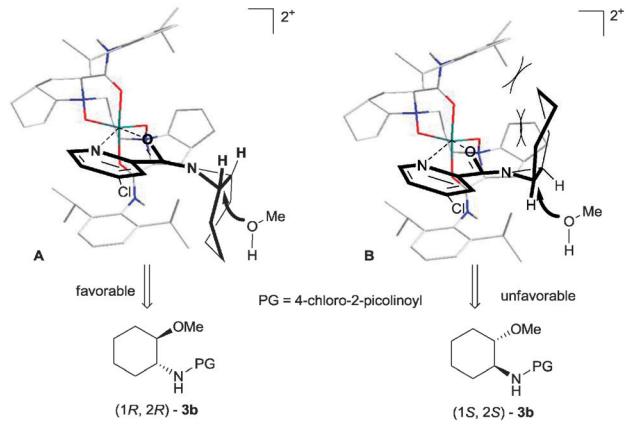
ether easily in high yield without loss of the diastereo- and enantioselectivity (Scheme 1c).[17] To show the synthetic utility of the catalyst system, the catalytic enantioselective ring-opening of aziridine **1a** was expanded to a gram-scale. The desired β-amino ether **3a** was obtained in 96% yield with 90% ee. No self-disproportionation of enantiomers was observed in the purification process *via* achiral chromatography.[18] Additionally, the optical pure product **3a** (> 99% ee) was obtained through single recrystallization.

The HRMS spectrum of the mixture of **L3**–$Mg(OTf)_2$ and aziridine **1a** reveals an ion at *m*/*z* 1075.5570, which corresponds to the intermediate $[Mg^{2+} + \mathbf{1a} + \mathbf{L3} + TfO^-]^+$. In light of the X-ray structure of the *N*,*N*′-dioxide–Mg(II) complex[14f] and the absolute configuration of the product **3b**,[19] the catalytic model for the desymmetrization reaction of the aziridine **1b** is proposed as shown in Scheme 2. The metal ion Mg(II) coordinates with four oxygens of the *N*,*N*′-dioxide ligand, and oxygen and nitrogen of the picolinoyl group on the aziridine **1b**.[10b] The catalytic model B is unfavorable due to the hindrance between the upward six-membered ring of the substrate and the right octahydrocyclopenta[*b*]pyrrole and the upward amide subunits of the chiral ligands. Therefore, the desired (1*R*,2*R*)-product **3b** can be produced *via* the favorable transition state A.

Published on 14 May 2014. Downloaded by Temple University on 29/10/2014 23:16:41.



Scheme 1 Asymmetric ring-opening of aniline/water and deprotection of the methyl ether **3a**.



Scheme 2 Proposed catalytic model.

In summary, we demonstrated the first direct enantioselective desymmetrization of *meso*-aziridines with primary alcohols. The chiral Mg(II)–*N*,*N*′-dioxide complex mediated the asymmetric ring-opening to generate a variety of optically active β-amino ethers in good yields (up to 96%) with excellent enantioselectivities (up to 92% ee). The catalytic system can also tolerate the nucleophilic ring-opening of *meso*-aziridine with aniline and water, giving 1,2-amino alcohols and 1,2-diamines in excellent enantioselectivities, respectively. The application of this catalytic protocol to other reactions is in progress.

We appreciate the National Natural Science Foundation of China (No. 21321061 and 21172151), and the Ministry of Education (No. 20110181130014) for financial support.

Notes and references

1 For selected reviews, see: (*a*) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (*b*) A. K. Yudin, *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2006.
2 C. Schneider, *Angew. Chem., Int. Ed.*, 2009, **48**, 2082.
3 For selected β-amino alcohols, see: (*a*) Y. Wang, S. Chackalamannil, Z. Hu, C. D. Boyle, C. M. Lankin, Y. Xia, R. Xu, T. Asberom, D. Pissarnitski, A. W. Stamford, W. J. Greenlee, J. Skell, S. Kurowski, S. Vemulapalli, J. Palamanda, M. Chintala, P. Wu, J. Myers and P. Wang, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3149; (*b*) J. Y.-T. Soh and C.-H. Tan, *J. Am. Chem. Soc.*, 2009, **131**, 6904.
4 For selected 1,2-diaimines: (*a*) A. Bisai, B. A. B. Prasad and V. K. Singh, *Tetrahedron Lett.*, 2005, **46**, 7935; (*b*) T. Nagata, T. Yoshino, N. Haginoya, K. Yoshikawa, Y. Isobe, T. Furugohri and H. Kanno, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4683.
5 (*a*) Z. Li, M. Fernandez and E. N. Jacobsen, *Org. Lett.*, 1999, **1**, 1611; (*b*) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 6312; (*c*) E. B. Rowland, G. B. Rowland, E. Rivera-Otero and J. C. Antilla, *J. Am. Chem. Soc.*, 2007, **129**, 12084; (*d*) S. Nakamura, M. Hayashi, Y. Kamada, R. Sasaki, Y. Hiramatsu, N. Shibata and T. Toru, *Tetrahedron Lett.*, 2010, **51**, 3820; (*e*) B. Wu, J. C. Gallucci, J. R. Parquette and T. V. RajanBabu, *Chem. Sci.*, 2014, **5**, 1102.
6 T. Mita, I. Fujimori, R. Wada, J. Wen, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 11252.
7 (*a*) K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2007, **129**, 8103; (*b*) K. Seki, R. Yu, Y. Yamazaki, Y. Yamashita and S. Kobayashi, *Chem. Commun.*, 2009, 5722; (*c*) S. Peruncheralathan, H. Teller and C. Schneider, *Angew. Chem., Int. Ed.*, 2009, **48**, 4849; (*d*) S. Peruncheralathan, S. Aurich, H. Teller and C. Schneider, *Org. Biomol. Chem.*, 2013, **11**, 2787.
8 (*a*) Z. Wang, X. Sun, S. Ye, W. Wang, B. Wang and J. Wu, *Tetrahedron: Asymmetry*, 2008, **19**, 964; (*b*) G. D. Sala and A. Lattanzi, *Org. Lett.*, 2009, **11**, 3330; (*c*) S. E. Larson, J. C. Baso, G. Li and J. C. Antilla, *Org. Lett.*, 2009, **11**, 5186; (*d*) Y. Zhang, C. W. Kee, R. Lee, X. Fu, J. Y.-T. Soh, E. M. F. Loh, K.-W. Huang and C.-H. Tan, *Chem. Commun.*, 2011, **47**, 3897.
9 (*a*) T. Mita and E. N. Jacobsen, *Synlett*, 2009, 1680; (*b*) K. Ohmatsu, Y. Hamajima and T. Ooi, *J. Am. Chem. Soc.*, 2012, **134**, 8794; (*c*) J. A. Kalow and A. G. Doyle, *Tetrahedron*, 2013, **69**, 5702.
10 (*a*) Y. Xu, L. Lin, M. Kanai, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2011, **133**, 5791; (*b*) M. Hayashi, N. Shiomi, Y. Funahashi and S. Nakamura, *J. Am. Chem. Soc.*, 2012, **134**, 19366; (*c*) Y.-M. Cao, F.-T. Zhang, F.-F. Shen and R. Wang, *Chem. – Eur. J.*, 2013, **19**, 9476.
11 For racemic reports: (*a*) B. A. B. Prasad, G. Sekar and V. K. Singh, *Tetrahedron Lett.*, 2000, **41**, 4677; (*b*) X.-L. Hou, R.-H. Fan and L.-X. Dai, *J. Org. Chem.*, 2002, **67**, 5295; (*c*) R.-H. Fan and X.-L. Hou, *J. Org. Chem.*, 2003, **68**, 726; (*d*) R.-H. Fan and X.-L. Hou, *Tetrahedron Lett.*, 2003, **44**, 4411.
12 For selected studies of biologically active compounds bearing a *trans*-β-aminoether motif, see: (*a*) B. Plouvier, G. N. Beatch, G. L. Jung, A. Zolotoy, T. Sheng, L. Clohs, T. D. Barrett, D. Fedida, W. Q. Wang, J. J. Zhu, Y. Liu, S. Abraham, L. Lynn, Y. Dong, R. A. Wall and M. J. A. Walker, *J. Med. Chem.*, 2007, **50**, 2818; (*b*) O. Rebollo, E. del Olmo, G. Ruiz, J. L. Lopez-Perez, A. Gimenez and A. San Feliciano, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 184.
13 G. L. Hamilton, T. Kanai and F. D. Toste, *J. Am. Chem. Soc.*, 2008, **130**, 14984.
14 For reviews and examples of *N*,*N*′-dioxide–metal complexes in asymmetric reactions, see: (*a*) X. H. Liu, L. L. Lin and X. M. Feng, *Acc. Chem. Res.*, 2011, **44**, 574; (*b*) X. H. Liu, L. L. Lin and X. M. Feng, *Org. Chem. Front.*, 2014, **1**, 298; (*c*) B. Gao, Y. H. Wen, Z. G. Yang, X. Huang, X. H. Liu and X. M. Feng, *Adv. Synth. Catal.*, 2008, **350**, 385; (*d*) X. L. Hu, B. Gao, Y. Y. Chu, W. Li, X. H. Liu, L. L. Lin and X. M. Feng, *Chem. – Eur. J.*, 2012, **18**, 3473; (*e*) B. Gao, M. S. Xie, A. M. Sun, X. L. Hu, X. Q. Ding, X. H. Liu, L. L. Lin and X. M. Feng, *Adv. Synth. Catal.*, 2012, **354**, 1509; (*f*) K. Zheng, C. K. Yin, X. H. Liu, L. L. Lin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2011, **50**, 2573; (*g*) K. Zheng, L. L. Lin and X. M. Feng, *Acta Chim. Sin.*, 2012, **70**, 1785; (*h*) M. S. Xie, X. X. Wu, G. Wang, L. L. Lin and X. M. Feng, *Acta Chim. Sin.*, 2014, **72**, DOI: 10.6023/A13121253.
15 See ESI† for details.
16 Moderate results (53% yield and 72% ee) were obtained using phenylmethanol. Phenol failed in the reaction.
17 M. V. Bhatt and S. S. El-Morey, *Synthesis*, 1982, 1048.
18 V. A. Soloshonok, C. Roussel, O. Kitagawa and A. E. Sorochinsky, *Chem. Soc. Rev.*, 2012, **41**, 4180.
19 CCDC 991793 (**3b**).

 This journal is © The Royal Society of Chemistry 2014