Organic LETTERS

Letter

pubs.acs.org/OrgLett

Desymmetrization of *meso*-Aziridines with TMSNCS Using Metal Salts of Novel Chiral Imidazoline–Phosphoric Acid Catalysts

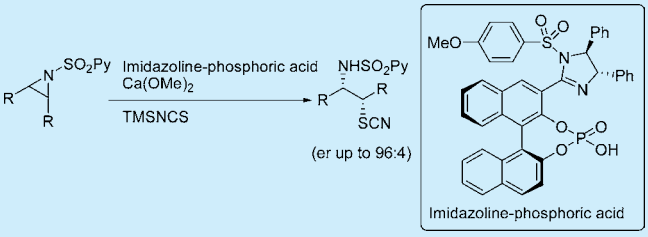
Shuichi Nakamura,*[,†] Mutsuyo Ohara,[†] Madoka Koyari,[†] Masashi Hayashi,[†] Kengo Hyodo,[†] Nadaf Rashid Nabisaheb,[†] and Yasuhiro Funahashi[‡]

[†]Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

[‡]Department of Chemistry, Graduate School of Science, Osaka University, 1-1 Machikaneyama, Toyonaka, Osaka 560-0043, Japan

Supporting Information

ABSTRACT: Highly enantioselective desymmetrization of aziridines with TMSNCS has been developed. Good yield and enantioselectivity were observed by using novel chiral imidazoline–phosphoric acid catalysts. The obtained product can be converted to a chiral β-aminothiol and a β-aminosulfonic acid.



The development of asymmetric catalysts has been extensively studied over the past decade. In this context, chiral phosphoric acid catalysts, developed by Akiyama and Terada, are among the most powerful chiral catalysts for asymmetric C–C, C–H, and C–heteroatom bond formation reactions.[1] Despite the impressive progress achieved in various enantioselective reactions using chiral phosphoric acid catalysts, the development of novel catalyst designs for chiral phosphoric acids still remains a major challenge. We recently developed chiral imidazoline catalysts as Brønsted acid–base catalysts and Lewis acid–Brønsted base catalysts.[2] Herein we would like to explore novel chiral catalysts having both an imidazoline and a phosphoric acid moiety. These novel asymmetric catalysts would control the reactivity and enantioselectivity by intramolecular H-bonding or chelation with metal species between the imidazoline and phosphoric acid moieties (Figure 1).[3]

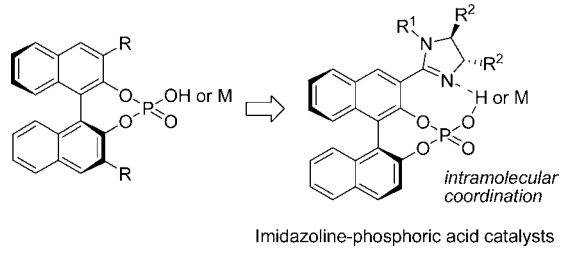


Figure 1. Design for novel imidazoline–phosphoric acid catalysts.

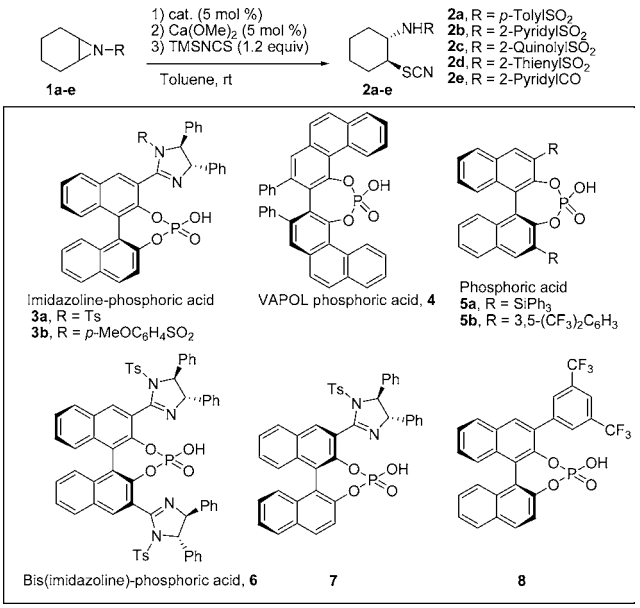
In order to evaluate the ability of novel catalysts, the desymmetrization of aziridines with TMSNCS was chosen as a benchmark reaction. The obtained β-aminothiocyanates are precursors for the synthesis of β-aminothiols and β-aminosulfonic acids, which are very important compounds for use as stereoselective catalysts[4] and biologically active compounds. For example, β-aminosulfonic acids are known as taurine derivatives,[5] which include biologically active compounds such as flavocristamide A and B,[6] halicylindramides,[7] and sulfobacin B.[8] Although there are many reports on the catalytic desymmetrization of *meso*-aziridines with various nucleophiles,[9] the catalytic desymmetrization of *meso*-aziridines using sulfur nucleophiles with high enantioselectivity is rare.[10] Efficient methods for this type of reaction were independently reported by Antilla and Della Sala, in which an enantioselective desymmetrization of aziridines with arenethiols or trimethylsilyl aryl sulfides using a chiral VAPOL phosphoric acid gave products with high enantioselectivity.[11] Although impressive progress have been achieved in this type of reaction, attempts to desymmetrize *meso*-aziridines using alkane- or arenethiols as sulfur nucleophiles afforded chiral β-aminoalkyl sulfides, which cannot be easily converted to chiral β-aminothiols or β-aminosulfonic acids. Recently, Tang et al. reported an interesting approach for the desymmetrization of aziridines using CS_2 and dibenzylamine in the presence of chiral guanidine catalysts giving products that could be converted to β-aminosulfonic acids after a three-step transformation.[12] On the other hand, TMSNCS as a sulfur nucleophile is a very attractive candidate as a thiol or sulfonic acid equivalent; however, the desymmetrization of aziridines with TMSNCS is rare. During the preparation of this manuscript, Della Sala's[11c] and RajanBabu's[13] groups independently reported the desymmetrization of aziridines with TMSNCS as a sulfur nucleophile to give a product with moderate enantioselectivity. Herein, we report the desymmetrization of aziridines with TMSNCS using novel chiral catalysts.

Received: July 9, 2014
Published: August 8, 2014

dx.doi.org/10.1021/ol501990t | *Org. Lett.* 2014, 16, 4452–4455

First we examined the desymmetrization of *meso*-*N*-(arenesulfonyl)aziridines **1a**−**e** with TMSNCS by using catalytic amounts of chiral imidazoline−phosphoric acids **3**. The results are shown in Table 1. Recent studies indicated that phosphoric

Table 1. Desymmetrization of Aziridines 1a−e with TMSNCS in the Presence of Various Chiral Phosphoric Acid Catalysts 3−8[a]



entry	1	catalyst	2	time (h)	yield (%)	er (%)[b]
1[c]	**1a**	**3a**	**2a**	120	30	41:59
2	**1a**	**3a**	**2a**	120	81	64:36
3	**1b**	**3a**	**2b**	12	95	88:12
4	**1c**	**3a**	**2c**	72	73	58:42
5	**1d**	**3a**	**2d**	120	94	55:45
6	**1e**	**3a**	**2e**	120	87	59:41
7	**1b**	**3b**	**2b**	4	96	89:11
8	**1b**	**4**	**2e**	120	99	68:32
9	**1b**	**5a**	**2b**	72	95	49:51
10	**1b**	**5b**	**2b**	18	99	50:50
11	**1b**	**6**	**2b**	48	99	58:42
12	**1b**	**7**	**2b**	24	83	50:50
13	**1b**	**8**	**2b**	24	85	51:49
14[d]	**1b**	**3b**	**2b**	2	94	89:11
15[d,e]	**1b**	**3b**	**2b**	72	99	94:6
16[f]	**1b**	**3b**	**2b**	12	99	14:86

[a]Catalyst (5 mol %) and TMSNCS (1.2 equiv) were used. [b]Enantiomer ratio was determined by HPLC analysis using chiral columns. [c]Without $Ca(OMe)_2$. [d]MS 4 Å was added. [e]At −20 °C. [f]Magnesium salt of **3b** was prepared using $Mg(OEt)_2$.

acids obtained after purification using column chromatography may contain metallic phosphate impurities.[14] Therefore, catalysts were used after purification by column chromatography and washing by aqueous HCl. The reaction of *N*-(*p*-toluenesulfonyl)aziridine **1a** with TMSNCS using chiral imidazoline−phosphoric acid catalyst **3a** afforded product **2a** with 18% ee (Table 1, entry 1). In order to improve the stereoselectivity of the reaction, we used the calcium phosphate salt of **3a**, which was prepared by the reaction of **3a** with calcium methoxide, to give product **2a** with slightly better enantioselectivity (Table 1, entry 2). Recently, we reported that heteroarenesulfonyl- or heteroarenecarbonyl groups were effective stereoselective activating groups for the ring-opening reaction of aziridines.[15] Therefore, we next tried the reaction of heteroarenesulfonylated or heteroarenecarbonylated aziridines using **3a**−$Ca(OMe)_2$. Although the reaction of *N*-(2-quinolinesulfonyl)-, *N*-(2-thiophenesulfonyl)-, and *N*-(picolyl)aziridine, **1c,d,e** using **3a**-$Ca(OMe)_2$ afforded products **2c,d,e** with low enantioselectivities, the reaction of *N*-(2-pyridinesulfonyl)-aziridine **1b** gave the product **2b** in high yield with high enantioselectivity (Table 1, entries 3−6).[16] These results provide evidence for the clear superiority of the 2-pyridinesulfonyl group as a stereocontrolling auxiliary for aziridines. Optimization experiments for the fine-tuning of the imidazoline substituent were carried out to improve the enantioselectivity of (1*S*,2*S*)-**2b**. Changing the substituent on the nitrogen from a tosyl group to the *p*-methoxybenzenesulfonyl group showed slightly higher enantioselectivity (Table 1, entry 7). On the other hand, the reaction using VAPOL−phosphoric acid **4**−$Ca(OMe)_2$ afforded the product **2b** in high yield but with low enantioselectivity (Table 1, entry 8). We also examined chiral phosphoric acids **5a,b** and bis(imidazoline)−phosphoric acid **6**; however, the reaction gave the product **2b** with low enantioselectivity (Table 1, entries 9−11). Interestingly, the reaction using either chiral imidazoline−phosphoric acid catalyst **7** having different stereochemistry on the binaphthyl group compared to **3a** or 3,5-trifluoromethylphenyl-substituted chiral phosphoric acid catalyst **8** afforded **2b** as an almost racemic product (Table 1, entries 12 and 13). The addition of 4 Å molecular sieves enhanced the reactivity of the reaction without a loss in enantioselectivity (Table 1, entry 14). When the reaction was carried out at lower temperature, the enantioselectivity was improved (Table 1, entry 15). Interestingly, the reaction using **3b** with magnesium ethoxide afforded the product **2b** having a stereochemistry opposite that obtained in the reaction using **3b**−$Ca(OMe)_2$ (Table 1, entry 16). The absolute configuration of product **2b** was determined to be (1*S*,2*S*) by X-ray crystallographic analysis.

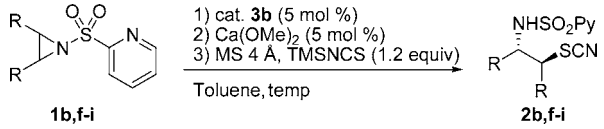
Having established the reaction conditions, the scope and limitations of the desymmetrization using TMSNCS with a variety of aziridines were investigated. The results are summarized in Table 2. The ring-opening reaction of aziridines having 5-, 6-, or 7-membered ring structures **1b,f**−**i** also afforded products **2b,f**−**i** in high yields with good enantioselectivities (Table 2, entries 1−5).[17]

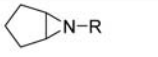
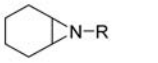
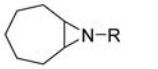
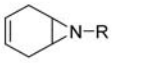
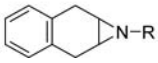
We also examined the desymmetrization of aziridines with other nucleophiles using catalyst **3b**. The reaction of aziridine **1f** with thiobenzoic acid afforded product **9** in high yield with high enantioselectivity (Scheme 1). To our knowledge, this result is the first successful example of the desymmetrization of an aziridine with thiocarboxylic acids.[18]

We next examined the transformation of the product **2b** into *β*-aminothiol and *β*-aminosulfonic acid. The thiocyano group can be reduced to a thiol using $LiAlH_4$ to give the *β*-aminothiol (Scheme 2). Since the obtained *β*-aminothiol dimerized to form a disulfide, the reaction was performed with benzyl bromide in situ to afford benzyl thioether **10** without loss of enantiopurity. We also attempted the oxidation of product **2b** to the *β*-aminosulfonic acid. The 2-pyridinesulfonyl group can be removed by magnesium in MeOH to give the *β*-aminothiocyanate. Oxidation of the thiocyano group in the *β*-aminothiocyanate to a sulfonic acid using H_2O_2 gave the chiral *β*-aminosulfonic acid **11** in high yield (Scheme 2). Based on the

dx.doi.org/10.1021/ol501990t | *Org. Lett.* 2014, 16, 4452−4455

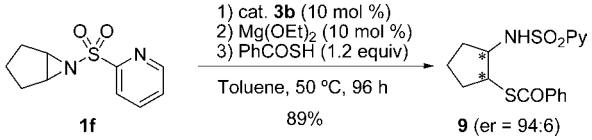
Table 2. Desymmetrization of *N*-(Heteroarenesulfonyl)aziridines 1b,f–i with TMSNCS in the Presence of 3b



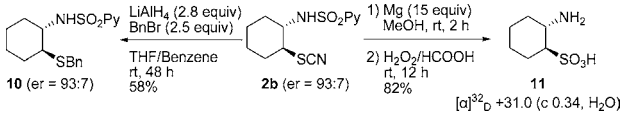
entry	substrate (R = 2-PySO$_2$)	2	temp (°C)	time (h)	yield (%)	er (%)
1[a]		2f	0	42	99	96:4
2		2b	-20	72	99	94:6
3[a]		2g	rt	48	52	82:18
4		2h	0	72	99	91:9
5[a]		2i	rt	24	79	83:17

[a] **3b** (10 mol %) and Ca(OMe)$_2$ (10 mol %) were used.

Scheme 1. Desymmetrization of *N*-(2-Pyridinesulfonyl)aziridine 1f with Thiobenzoic Acid in the Presence of 3b–Mg(OEt)$_2$



Scheme 2. Reduction of Thiocyano Group in 2b to *β*-Aminothiol 10 and Preparation of *β*-Aminosulfonic Acid 11 from 2b



value of the specific rotation reported in the literature,[12] the product can be obtained without loss of enantiopurity.

On the basis of the obtained results, we envisioned that catalyst **3** could act in a bifunctional fashion. We also checked the reaction using various ratios of **3** and Ca(OMe)$_2$ (1:2 to 2:1). The best enantioselectivity was obtained from the reaction using a 1:1 ratio of **3** and Ca(OMe)$_2$. Therefore, the reaction must be activated by a 1:1 complex of **3** and Ca(OMe)$_2$. The proposed catalytic cycle is shown in Figure 2. The catalyst **3** reacts with calcium methoxide to give the calcium salt (complex **A**) by coordination of the imidazoline nitrogen with the calcium cation. TMSNCS then reacts with complex **A** to give complex **B**. Coordination of the *N*-(2-pyridinesulfonyl)aziridine to the calcium cation in complex **B** affords complex **C**, which includes an octahedral Ca(II) cation. The SCN group in complex **C** reacts with the aziridine to give complex **D**. Finally, the reaction of complex **D** with TMSNCS affords the product and regenerates complex **B**.[19]

In conclusion, we have developed novel imidazoline–phosphoric acid catalysts. The desymmetrization of *N*-(2-pyridinesulfonyl)aziridines with TMSNCS in the presence of these new chiral imidazoline–phosphoric acid catalysts **3** gives chiral *β*-aminothiocyanates with good enantioselectivities. Both enantiomers of the product can be obtained by changing the metal salt. A range of aziridines are tolerated in the process. The 2-pyridinesulfonyl group works as an efficient stereocontrolling group for the ring-opening reaction of aziridine. These results present a novel method to synthesize optically active *β*-aminothiols and *β*-aminosulfonic acids. Further experiments are in progress to study the scope of this process and the potential applications of imidazoline–phosphoric acid catalysts to other reactions.

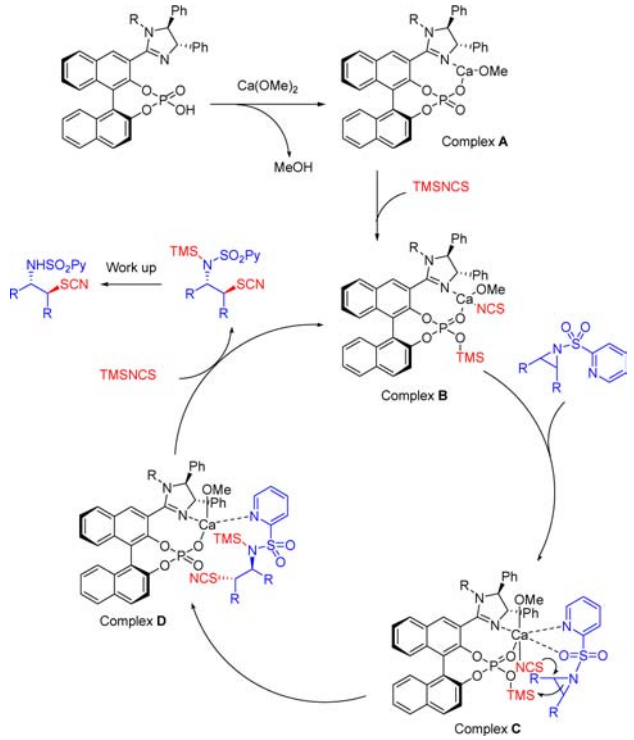


Figure 2. Proposed catalytic cycle for the desymmetrization of aziridines with TMSNCS using **3**.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: snakamur@nitech.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partly supported by Grants-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT (26105727), A-Step (AS251Z00922M) from JST, the Kurata Memorial Hitachi Science and Technology Foundation, and The Naito Foundation.

REFERENCES

(1) Reviews for chiral phosphoric acid catalysts: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Chem. Commun.* **2008**, 4097. (c) Terada, M. *Synthesis* **2010**, 1929 and references therein.

(2) (a) Nakamura, S.; Hyodo, K.; Nakamura, Y.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1443. (b) Nakamura, S.; Ohara, M.; Nakamura, Y.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2010**, *16*, 2360. (c) Ohara, M.; Nakamura, S.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 3285. (d) Hyodo, K.; Nakamura, S.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 10337. (e) Hyodo, K.; Kondo, M.; Funahashi, Y.; Nakamura, S. *Chem.—Eur. J.* **2013**, *19*, 4128. (f) Nakamura, S.; Hyodo, K.; Nakamura, M.; Nakane, D.; Masuda, H. *Chem.—Eur. J.* **2013**, *19*, 7304. (g) Ohara, M.; Hara, Y.; Ohnuki, T.; Nakamura, S. *Chem.—Eur. J.* **2014**, *20*, 8848.

(3) Recently, we developed dual-activation chiral catalysts including intramolecular H-bonding or complexation with metal species; see: (a) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2008**, *14*, 8079. (b) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2009**, *15*, 6790. (c) Nakamura, S.; Shibata, N.; Toru, T. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1017. (d) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2010**, *352*, 1621. (e) Hara, N.; Tamura, R.; Funahashi, Y.; Nakamura, S. *Org. Lett.* **2011**, *13*, 1662. (f) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem.—Eur. J.* **2012**, *18*, 9276. (g) Hayashi, M.; Shiomi, N.; Funahashi, Y.; Nakamura, S. *J. Am. Chem. Soc.* **2012**, *134*, 19366. (h) Hayashi, M.; Sano, M.; Funahashi, Y.; Nakamura, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5557.

(4) (a) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 1297.

(5) Page, M. I. *Acc. Chem. Res.* **2004**, *37*, 297.

(6) (a) Kobayashi, J.; Mikami, S.; Shigemori, H.; Takao, T.; Shimonishi, Y.; Izuta, S.; Yoshida, S. *Tetrahedron* **1995**, *51*, 10487. (b) Shioiri, T.; Irako, N. *Tetrahedron* **2000**, *56*, 9129.

(7) (a) Li, H. Y.; Matsunaga, S.; Fusetani, N. *J. Med. Chem.* **1995**, *38*, 338. (b) Seo, H.; Lim, D. *J. Org. Chem.* **2009**, *74*, 906.

(8) (a) Kamiyama, T.; Umino, T.; Satoh, T.; Sawairi, S.; Shirane, M.; Ohshima, S.; Yokose, K. *J. Antibiot.* **1995**, *48*, 924. (b) Takikawa, H.; Nozawa, D.; Kayo, A.; Muto, S.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2467.

(9) For reviews of enantioselective desymmetrization of aziridines, see: (a) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979. (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (c) Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2082. (d) Wang, P.-A. *Beilstein J. Org. Chem.* **2013**, *9*, 1677.

(10) (a) Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1994**, 2699. (b) Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *Tetrahedron* **1996**, *52*, 7817. (c) Luo, Z.-B.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **2007**, *18*, 443. (d) Wang, Z.; Sun, X.; Ye, S.; Wang, W.; Wang, B.; Wu, J. *Tetrahedron: Asymmetry* **2008**, *19*, 964. (e) Lattanzi, A.; Della Sala, G. *Eur. J. Org. Chem.* **2009**, 1845. (f) Cao, Y.-M.; Zhang, F.-T.; Shen, F.-F.; Wang, R. *Chem.—Eur. J.* **2013**, *19*, 9476.

(11) (a) Della Sala, G.; Lattanzi, A. *Org. Lett.* **2009**, *11*, 3330. (b) Larson, S. E.; Baso, J. C.; Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 5186. (c) Della Sala, G. *Tetrahedron* **2013**, *69*, 50. For the desymmetrization of aziridines with $TMSN_3$ using VAPOL phosphoric acids, see: (d) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084. For the desymmetrization of aziridines with $PhSeSiMe_3$ using VAPOL phosphoric acids, see: (e) Senatore, M.; Lattanzi, A.; Santoro, S.; Santi, C.; Della Sala, G. *Org. Biomol. Chem.* **2011**, *9*, 6205. For desymmetrization of aziridines with carboxylic acids using chiral phosphoric acids, see: (f) Monaco, M. R.; Poladura, B.; Bernardos, M. D. L.; Leutzsch, M.; Goddard, R.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7063.

(12) Zhang, Y.; Kee, C. W.; Lee, R.; Fu, X.; Soh, J. Y.-T.; Loh, E. M. F.; Huang, K.-W.; Tan, C.-H. *Chem. Commun.* **2011**, 3897.

(13) Wu, B.; Gallucci, J. C.; Parquette, J. R.; RajanBabu, T. V. *Chem. Sci.* **2014**, *5*, 1102.

(14) For selected examples of an enantioselective reaction using alkali or alkaline earth salts of phosphoric acids, see: (a) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776. (b) Shen, K.; Liu, X.; Cai, Y.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 6008. (c) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823. (d) Hatano, M.; Ishihara, K. *Synthesis* **2010**, 3785. (e) Drouet, F.; Lalli, C.; Liu, H.; Masson, G.; Zhu, J. *Org. Lett.* **2011**, *13*, 94. (f) Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1135. (g) Rueping, M.; Bootwicha, T.; Sugiono, E. *Synlett* **2011**, 323. (h) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860. (i) Terada, M.; Kanomata, K. *Synlett* **2011**, 1255. (j) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339. (k) Ingle, G. K.; Liang, Y.; Mormino, M. G.; Li, G.; Fronczek, F. R.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2054. (l) Larson, S. E.; Li, G.; Rowland, G. B.; Junge, D.; Huang, R.; Woodcock, H. L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2188. For a review on metal phosphates, see: (m) Parra, A.; Reboredo, S.; Castro, A. M. M.; Alemán, J. *Org. Biomol. Chem.* **2012**, *10*, 5001.

(15) Although we recently reported that the desymmetrization of *N*-(2-pyridinesulfonyl)aziridine catalyzed by bis(oxazoline)−Mg(II) as a Lewis acid catalyst gave products with high enantioselectivity, the reaction of *N*-(2-pyridinesulfonyl)aziridine with TMSNCS using bis(oxazoline)−Mg(II) afforded the product with low enantioselectivity; see: Nakamura, S.; Hayashi, M.; Kamada, Y.; Sasaki, R.; Hiramatsu, Y.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2010**, *51*, 3820.

(16) Review for alkaline earth metal catalysts: Yamashita, Y.; Tsubogo, T.; Kobayashi, S. *Chem. Sci.* **2012**, *3*, 967.

(17) We also examined the reaction of acyclic and heterocyclic aziridines; however, the reaction afforded products in low yield or with low enantioselectivity.

(18) We also examined the reaction of aziridine **1f** using catalyst **3b** and $Ca(OMe)_2$; however, the product can be obtained as the opposite enantiomer with low enantioselectivity.

(19) We examined the ESI-mass spectrum or X-ray crystal analysis for the complexes **A**−**D**; however, we could not observe these complexes.

dx.doi.org/10.1021/ol501990t | *Org. Lett.* 2014, 16, 4452−4455