JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Cinchona Alkaloid Amides/Dialkylzinc Catalyzed Enantioselective Desymmetrization of Aziridines with Phosphites

Masashi Hayashi, Noriyuki Shiomi, Yasuhiro Funahashi, and Shuichi Nakamura*

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

Supporting Information

ABSTRACT: The first highly enantioselective desymmetrization of aziridines with phosphites has been developed. Excellent yields and enantioselectivities were observed for the reaction with various aziridines using a new class of readily accessible chiral catalysts derived from 9-amino-9-deoxy-*epi*-cinchona alkaloids. In studies probing the reaction mechanism, we observed some complexes for the cinchona alkaloid amide-Zn(II) by ESI-MS analysis.

Optically active β-aminophosphonic acids and their derivatives are very important compounds because of their biological properties[1] and their catalytic ability as chiral ligands.[2] Therefore, the stereoselective synthesis of chiral β-aminophosphonic acids and their derivatives has received considerable attention. One of the most efficient and direct methods for the synthesis of chiral β-aminophosphonates is the enantioselective desymmetrization of aziridines with phosphites.[3] Although excellent methodologies have been developed in the enantioselective hydrophosphonylation with various electrophiles such as aldehydes, ketones, imines, α,β-unsaturated carbonyl compounds, and nitroolefins,[4] there is no report on the enantioselective desymmetrization of aziridines with phosphites due to their low reactivity.[5] Yet, we recently reported the first enantioselective hydrophosphonylation of ketimines using cinchona alkaloid derivatives and Na_2CO_3 as an activating reagent for phosphites.[6] We hypothesized that the activation of phosphites using some reagents would be effective for the ring-opening reaction of less reactive aziridines. Herein, our ongoing interest was extended to the enantioselective desymmetrization of aziridines with phosphites using the combination of novel cinchona alkaloid catalysts and dialkylzinc (Figure 1).

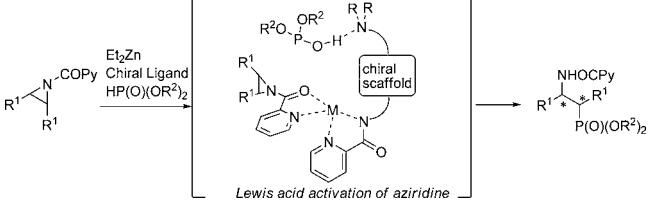
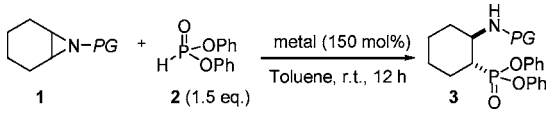


Figure 1. Catalytic enantioselective desymmetrization of aziridines with phosphites.

Initially, we examined the ring-opening reaction of aziridines having various protecting groups on nitrogen using a stoichiometric amount of Et_2Zn (Table 1).

Table 1. Screening of Protecting Groups on Aziridines[a]



entry	PG	1	metal	3	yield (%)
1	Ts	**1a**	Et_2Zn	**3a**	–
2	Bz	**1b**	Et_2Zn	**3b**	–
3	SO_2Py	**1c**	Et_2Zn	**3c**	17
4	COPy	**1d**	Et_2Zn	**3d**	68
5	3,5-$(CF_3)_2$Bz	**1e**	Et_2Zn	**3e**	–
6	3,5-$(NO_2)_2$Bz	**1f**	Et_2Zn	**3f**	–
7	4-OMeBz	**1g**	Et_2Zn	**3g**	–
8	COPy	**1d**	*n*BuLi	**3d**	–
9	COPy	**1d**	Bu_2Mg	**3d**	<30[b]
10	COPy	**1d**	Et_3Al	**3d**	trace[b]
11	COPy	**1d**	$Zn(OTf)_2$	**3d**	–

[a]Reaction conditions: aziridine **1** (0.2 mmol), metal (0.30 mmol), diphenyl phosphite **2** (0.3 mmol), and toluene (1.5 mL) were used. [b]Determined by ^1H and ^{31}P NMR.

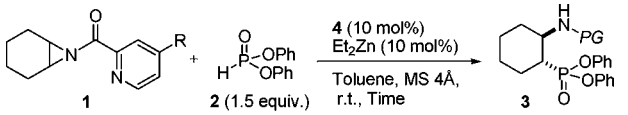
Although the reaction of *N*-tosylated or *N*-benzoylated aziridines **1a,b** did not afford products (entries 1 and 2), the reaction of *N*-(2-pyridinesulfonyl)- or *N*-(2-picolinoyl)-aziridines **1c,d** did (entries 3 and 4). The reaction with various aziridines (**1c–f**) having other benzoyl groups, such as 3,5-bis(trifluoromethyl)benzoyl, 3,5-dinitrobenzoyl, or 4-methoxybenzoyl groups, failed to afford products (entries 5–7). The reaction using other bases such as *n*BuLi, Bu_2Mg, and Et_3Al, or $Zn(OTf)_2$ as a Lewis acid, also did not afford products (entries 8–11). We next examined the catalytic desymmetrization of *N*-(2-picolinoyl)aziridines with phosphites using Et_2Zn as an activating reagent for phosphites. The desymmetrization of aziridines with diphenyl phosphite **2** was carried out in the presence of 10 mol % of cinchona alkaloid derivatives/Et_2Zn at rt (Table 2).[7]

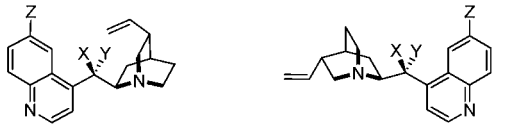
The reaction using cinchona alkaloid catalysts, such as cinchonine, cinchonidine, quinidine, and quinine (**4a–d**), gave the product **3d** in moderate yield but with low enantiose-

Received: October 9, 2012
Published: November 12, 2012

   dx.doi.org/10.1021/ja309963w | J. Am. Chem. Soc. 2012, 134, 19366–19369

Table 2. Enantioselective Desymmetrization of Aziridines 1d,h–j with Diphenyl Phosphite 2[a]





4a: X=H, Y=OH, Z=H
4c: X=H, Y=OH, Z=OMe
4e: X=NHBz, Y=H, Z=H
4f: X=NHSO$_2$Py, Y=H, Z=H
4g: X=NHCOPy, Y=H, Z=H
4i: X=NHCOPy, Y=H, Z=OMe

4b: X=H, Y=OH, Z=H
4d: X=H, Y=OH, Z=OMe
4h: X=NHCOPy, Y=H, Z=H
4j: X=NHCOPy, Y=H, Z=OMe

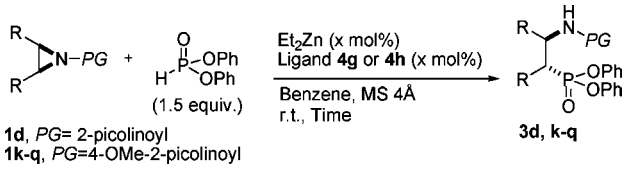
entry	R (1)	3	4	time (h)	yield (%)	ee (%)[b]
1	H (**1d**)	**3d**	**4a**	3	57	3 (*S,S*)
2	H (**1d**)	**3d**	**4b**	3	50	3 (*S,S*)
3	H (**1d**)	**3d**	**4c**	3	48	5 (*S,S*)
4	H (**1d**)	**3d**	**4d**	3	48	1 (*S,S*)
5	H (**1d**)	**3d**	**4e**	3	36	3 (*S,S*)
6	H (**1d**)	**3d**	**4f**	3	32	38 (*R,R*)
7	H (**1d**)	**3d**	**4g**	3	84	99 (*R,R*)
8	H (**1d**)	**3d**	**4h**	3	70	94 (*S,S*)
9	H (**1d**)	**3d**	**4i**	3	37	33 (*R,R*)
10	H (**1d**)	**3d**	**4j**	3	31	35 (*S,S*)
11[c]	H (**1d**)	**3d**	**4h**	3	80	98 (*S,S*)
12[c]	Cl (**1h**)	**3h**	**4g**	3	94	99 (*R,R*)
13[c]	NO_2 (**1i**)	**3i**	**4g**	3	6	54 (*R,R*)
14[c]	OMe (**1j**)	**3j**	**4g**	1	91	96 (*R,R*)

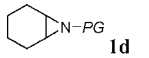
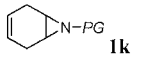
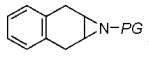
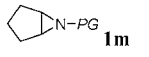
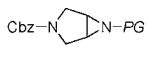
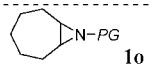
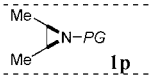
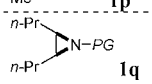
[a]Reaction conditions: aziridine **1** (0.2 mmol), Et_2Zn (0.02 mmol), **4** (0.02 mmol), diphenyl phosphite **2** (0.3 mmol), MS 4 Å (40 mg), and toluene (1.5 mL) were used. [b]The absolute configuration of **3** is provided in parentheses. [c]Benzene was use as a solvent.

lectivity (entries 1–4).[8,9] Although the reaction using *N*-benzoyl-9-amino-9-deoxy-*epi*-cinchonine **4e** also afforded **3d** with low enantioselectivity, 2-pyridinesulfonamide **4f** derived from cinchonine gave **3d** with 38% ee (entries 5–6). To our delight, excellent enantioselectivity could be obtained in the reaction using *N*-(2-picolinoyl)-9-amino-9-deoxy-*epi*-cinchonine **4g** (entry 7).[10,11] The reaction using *N*-(2-picolinoyl)-9-amino-9-deoxy-*epi*-cinchonidine **4h** gave **3d** having a stereochemistry opposite that obtained in the reaction using **4g** (entry 8). Moderate enantioselectivity was obtained in the presence of picolinoylamides **4i,j** derived from quinidine and quinine (entries 9–10). After optimization of the solvent, the reaction in benzene afforded the best enantioselectivity (entry 11). In order to improve the reactivity, we optimized the structure of aziridine to add the substituent on the 4-position of the pyridine ring, which can control the Lewis basicity of a nitorgen atom. The reaction of a 4-chloro-2-picolinoyl derivative **1h** gave product **3h** in good yield with excellent enantioselectivity; however, 4-nitro derivative **1i** gave **3i** in low yield (entries 12–13). The reactivity could be improved by the reaction using electron-donating 4-methoxy-2-picolinoyl derivative **1j** with high enantioselectivity (entry 14). The absolute configuration of product **3d** was determined to be (1*R*,2*R*) by X-ray crystallographic analysis (entry 7).

Having established the optimized reaction conditions for the desymmetrization of aziridines, we next examined the reaction of various aziridines with diphenyl phosphite. The results are summarized in Table 3. Catalyst loading could be reduced to 5 mol % without decreasing the yield and enantioselectivity

Table 3. Enantioselective Desymmetrization of Various Aziridines 1d,k–q with Diphenyl Phosphite 2[a]



entry	aziridine **1**	4 (x mol%)	time (h)	yield (%)	ee[b] (%)
1[c]		**4g** (10)	3	84	99 (*R,R*)
2	 **1d**	**4g** (5)	5	90	98 (*R,R*)
3[d]		**4g** (2)	24	75	97 (*R,R*)
4		**4h** (10)	3	80	98 (*S,S*)
5[d]	 **1k**	**4g** (10)	12	81	99 (*R,R*)
6[d]		**4h** (15)	12	81	97 (*S,S*)
7[d]	 **1l**	**4g** (20)	16	81	98 (*R,R*)
8[d]		**4h** (25)	16	76	98 (*S,S*)
9[d]	 **1m**	**4g** (15)	24	78	97 (*R,R*)
10[d]		**4h** (20)	24	85	96 (*S,S*)
11[d]	 **1n**	**4g** (20)	64	64[e]	97 (*R,R*)
12[d]		**4h** (30)	42	65[e]	95 (*S,S*)
13[d]	 **1o**	**4g** (20)	84	19[e]	90 (*R,R*)
14[d]	 **1p**	**4g** (10)	10	90	99 (*R,R*)
15[d]		**4h** (15)	8	80	97 (*S,S*)
16[d]	 **1q**	**4g** (20)	48	80	95 (*R,R*)
17[d]		**4h** (30)	24	83	95 (*S,S*)

[a]Reaction conditions: aziridine **1** (0.2 mmol), Et_2Zn (0.02 mmol), **4** (0.02 mmol), MS 4 Å (40 mg), and benzene (1.5 mL) were used. [b]The absolute configuration of **3** is provided in parentheses. [c]Toluene was used as a solvent. [d]MS 5 Å was used instead of MS 4 Å, and Na_2CO_3 (1.5 equiv) was added. [e]Undesired phospha-Brook rearrangement product was obtained.

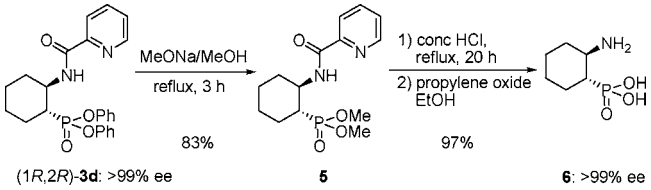
(entry 2). In the case of the reaction using 2 mol % of catalyst, changing the molecular sieves from 4 to 5 Å and the addition of sodium carbonate were effective for improving reactivity (entry 3). The catalytic desymmetrization of other six-membered aziridines **1k** and **1l** using **4g** or **4h** afforded both enantiomers of products **3k** and **3l** with excellent enantioselectivity (entries 5–8). The reaction of five-membered aziridines **1m** and **1n** afforded products **3m** and **3n** in moderate yield with high enantioselectivity (entries 9–12). In the case of the reaction of seven-membered aziridine **1o**, the reaction hardly proceeded, even with a high catalyst loading (entry 13). In the case of the low reactive aziridines **1n,o**, an undesired phospha-Brook rearrangement product was obtained (entries 11–13). On the other hand, nonbicyclic aziridines **1p,q** were also good substrates with respect to enantioselectivity and chemical yield (entries 14–17). To the best of our knowledge, this result is the first example of the enantioselective desymmetrization of aziridines with phosphorus nucleophiles.

We next examined the transformation of product **3d** to an optically active β-aminophosphonic acid **6**. After the transesterification of optically active diphenyl β-amino phosphonate **3d** to dimethyl phosphonate **5** using MeONa/MeOH, hydrolysis under acidic conditions afforded the corresponding

dx.doi.org/10.1021/ja309963w | J. Am. Chem. Soc. 2012, 134, 19366–19369

β-aminophosphonic acid **6** in 97% yield without loss in enantiopurity (Scheme 1).

Scheme 1. Synthesis of the Optically Active β-Aminophosphonic Acid 6



The enantioselective desymmetrization using *N*-(2-picolinoyl)-9-amino-*epi*-9-deoxy-cinchonine **4g** gave products **3** in high yield with high enantioselectivity, although *N*-benzoyl-9-amino-9-deoxy-*epi*-cinchonine **4e** afforded an almost racemic product (Table 2, entry 5 vs 7). On the other hand, the reaction of *N*-benzoyl aziridine with diphenyl phosphite **2** did not afford product **3** (Table 1, entry 2). These results imply that the pyridyl groups in both aziridines and catalysts are nessesary to give products in high yield with high stereoselectivity. The proposed catalytic cycle for the enantioselective desymmetrization of aziridine is shown in Figure 2. The picolinoylamide

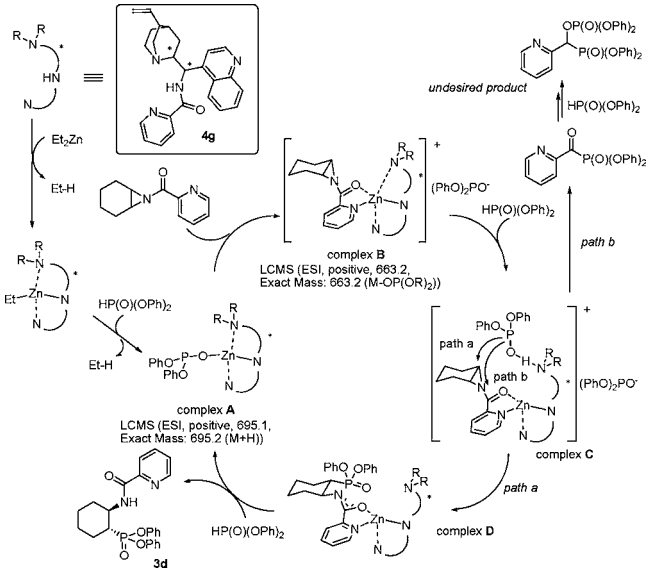


Figure 2. Assumed reaction mechanism for the desymmetrization of aziridines **1d** with diphenyl phosphite **2**.

catalyst **4g** reacts with Et_2Zn and diphenyl phosphite **2** to afford **4g**-Zn(II)-phosphite (complex **A**).[12] Picolinoyl aziridine **1d** coordinates to the zinc cation by *N*,*O*-bidantate chelation to give complex **B**. Subsequently, diphenyl phosphite coordinates to the quinuclidine moiety in complex **B** by H-bonding (complex **C**). Therefore, the reactivities for aziridine **1b** and diphenyl phosphite are effectively enhanced by **4g**-Zn(II) catalysts.[13] Phosphite attacks the aziridine carbon to give complex **D** (path a), which affords product **3d** by a proton exchange reaction with diphenyl phosphite. Yet, in the case of the reaction with less reactive aziridines such as **1n,o**, the phosphite attacks the picolinoyl carbon, which was also activated by **4g**-Zn(II) catalysts, to give α-ketophosphonates (path b). Further nucleophilic addition of diphenyl phosphite affords the phospha-Brook rearangement product as an undesired product. In order to clarify the assumed reaction mechanism, we conducted some spectroscopic analyses. The ESI-MS analysis of the mixture of **4g**, Et_2Zn, and diphenyl phosphite in a 1:1:1 ratio in toluene showed complex **A** (cation mode, calcd for $C_{37}H_{36}N_4O_4PZn$ as complex **A** + H^+: 695.2, found: 695.1; see Supporting Information). We also observed complex **B** in the case of the reaction using unreactive dimethyl phosphite (cation mode, calcd for $C_{37}H_{39}N_6O_2Zn$ as complex **B**− $OP(OR)_2^-$: 663.2, found: 663.2). These signals support our proposed reaction mechanism.[14]

From the above-mentioned consideration and absolute stereochemistry of the product, the assumed structure of the most reactive complex **C** is shown in Figure 3. Diphenyl

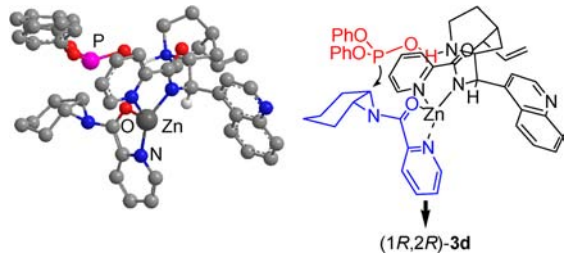


Figure 3. Proposed transition state for the reaction of **1d** with diphenyl phosphite **2** using **4g**. H-atoms have been omitted for clarity.

phosphite approaches aziridine by coordinating to the quinuclidine moiety in complex **C**; therefore the (1*R*,2*R*)-isomer is a preferable form. Further studies are required to fully elucidate the mechanistic details of the desymmetrization.

In conclusion, we have demonstrated the first enantioselective desymmetrization of aziridines with phosphites using a new class of readily accessible chiral catalysts derived from the 9-amino-9-deoxy-*epi*-cinchona alkaloid in combination with Et_2Zn. The catalytic desymmetrization of aziridines was screened for a broad range of aziridines. This approach gives us direct access to both enantiomers of optically active β-aminophosphonates in high yields with high enantioselectivities. Further studies are in progress to study the potential of these catalytic systems for other processes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure and characterization data including X-ray crystallography analysis of **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

snakamur@nitech.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partly supported by Commons from JST. We thank Prof. Norio Shibata at Nagoya Institute of Technology for unrestricted access to analytical facilities.

■ REFERENCES

(1) For reviews of the biological activity of β-amino phosphonic acids, see: (a) Hildebrand, R. L.; Henderson, T. O. In *The Role of Phosphonates in Living Systems*; Hildebrand, R. L., Eds.; CRC: Boca

Raton, FL, 1983; pp 5−29. (b) Horiguchi, M.; Kandatsu, M. *Nature* **1959**, *184*, 901−902. (c) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237−12273. (d) Kukhar, V. P.; Hudson, H. R., Eds. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Wiley: New York, NY, 2000. (e) Palacios, F.; Alonso, C.; de Los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899−931.

(2) (a) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497−537. (b) Amoroso, D.; Graham, T. W.; Guo, R.; Tsang, C.-W.; Abdur-Rashid, K. *Aldrichimica Acta* **2008**, *41*, 15−26 and references therein.

(3) For reviews on enantioselective desymmetrization of aziridines with various nucleophiles, see: (a) Pineschi, M. *Eur. J. Org. Chem.* **2006**, 4979−4988. (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743. (c) Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2082−2084.

(4) For reviews on enantioselective hydrophoshonylation, see: (a) Merino, P.; Marqués-López, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195−1208. (b) Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17−49. (c) Zhao, D.; Wang, R. *Chem. Soc. Rev.* **2012**, *41*, 2095−2108. For selected recent papers for enantioselective desymmetrization of aziridines, see: (d) Nakamura, S.; Hayashi, M.; Kamada, Y.; Sasaki, R.; Hiramatsu, Y.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2010**, *51*, 3820−3823. (e) Xu, Y.; Lin, L.; Kanai, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5791−5793. (f) Ohmatsu, K.; Hamajima, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 8794−8797.

(5) For the synthesis of β-amino phosphonates through the ring-opening reaction of aziridines with phosphites, see: (a) Duggan, M. E.; Karanewsky, D. S. *Tetrahedron Lett.* **1983**, *24*, 2935−2938. For the reaction of aziridines with phosphorus nucleophiles, see: (b) Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Uneyama, K. *J. Org. Chem.* **1999**, *64*, 7323−7329. (c) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597−2600.

(6) (a) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, *131*, 18240−18241. For related recent studies from our group, see: (b) Nakamura, S.; Nakashima, H.; Yamamura, A.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1209−1212. (c) Ohara, M.; Nakamura, S.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 3285−3289. (d) Hayashi, M.; Nakamura, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2249−2252.

(7) For the enantioselective hydrophosphonylation of α,β-unsaturated carbonyl compounds or nitroalkenes using phosphites and Et_2Zn, see: (a) Zhao, D.; Yuan, Y.; Chan, A. S. C.; Wang, R. *Chem.—Eur. J.* **2009**, *15*, 2738−2741. (b) Zhao, D.; Wang, Y.; Mao, L.; Wang, R. *Chem.—Eur. J.* **2009**, *15*, 10983−10987. For diastereoselective addition of phosphite to nitroalkenes using Et_2Zn, see: (c) Enders, D.; Tedeschi, L.; Bats, J. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 4605−4607. For enantioselective hydrophosphonylation of aldehydes using cinchona alkaloid−Lewis acid catalysts, see: (d) Yang, F.; Zhao, D.; Lan, J.; Xi, P.; Yang, L.; Xiang, S.; You, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5646−5649. For enantioselective hydrophosphonylation of aldehydes using a base, see: (e) Suyama, K.; Sakai, Y.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 797−799.

(8) The reaction without diethylzinc did not afford the product. We also examined the reaction with various phosphites such as diethyl phosphite, dibenzyl phosphite, and bis(2,2,2-trifluorethyl) phosphite; however the enantioselectivity or yield was not good (see Supporting Information).

(9) We also examined the desymmetrization of aziridines using Trost's dinuclear-Zn catalyst as a pioneering chiral zinc catalysts to give the product in moderate yield with enantioselectivity (see Supporting Information). For Trost's dinuclear-Zn catalyst, see selected examples: (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368. (c) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497−2500. (d) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338−339. (e) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023−2026. (f) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572−4573.

(10) For *N*-benzoyl 9-amino-9-deoxy-*epi*-cinchona alkaloid catalysts, see: (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832. (b) Brunner, H.; Schmidt, P. *Eur. J. Org. Chem.* **2000**, 2119−2133. (c) Brunner, H.; Schmidt, P.; Prommesberger, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1501−1512. (d) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635. (e) Rogers, L. M.-A.; Rouden, J.; Lecomte, L.; Lasne, M.-C. *Tetrahedron Lett.* **2003**, *44*, 3047−3050. (f) Brunner, H.; Baur, M. A. *Eur. J. Org. Chem.* **2003**, 2854−2862. (g) Baur, M. A.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron: Asymmetry* **2003**, *14*, 2755−2761. (h) Seitz, T.; Baudoux, J.; Bekolo, H.; Cahard, D.; Plaquevent, J.-C.; Lasne, M.-C.; Rouden, J. *Tetrahedron* **2006**, *62*, 6155−6165. (i) Cui, H.-L.; Peng, J.; Feng, X.; Du, W.; Jiang, K.; Chen, Y.-C. *Chem.—Eur. J.* **2009**, *15*, 1574−1577. (j) Xiong, X.-F.; Jia, Z.-J.; Du, W.; Jiang, K.; Liu, T.-Y.; Chen, T. Y.-C. *Chem. Commun.* **2009**, 6994−6996. (k) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, L. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664−3665. (l) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089−2091. (m) Sladojevich, F.; Trabocchi, A.; Guarna, A.; Dixon, D. J. *J. Am. Chem. Soc.* **2011**, *133*, 1710−1713.

(11) For selected examples of chiral catalysts having a 2-picolinoyl group, see: (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104−1105. (b) Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2004**, *69*, 4984−4990. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590−4591. (d) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751−3754. (e) Zheng, H.-J.; Chen, W.-B.; Wu, Z.-J.; Deng, J.-G.; Lin, W.-Q.; Yuan, W.-C.; Zhang, X.-M. *Chem.—Eur. J.* **2008**, *14*, 9864−9867. (f) Guizzetti, S.; Benaglia, M.; Celentano, G. *Eur. J. Org. Chem.* **2009**, 3683−3687.

(12) We also observed **4g**-ZnEt species by ^{1}H NMR analysis; see Supporting Information.

(13) For tridentate *N*-acyl 9-amino-9-deoxy-*epi*-cinchona alkaloids and metal salts, see a review: (a) Stegbauer, L.; Sladojevich, F.; Dixon, D. J. *Chem. Sci.* **2012**, *3*, 942−958. See also: (b) Casarotto, V.; Li, Z.; Boucau, J.; Lin, Y.-M. *Tetrahedron Lett.* **2007**, *48*, 5561−5564. (c) Lin, Y.-M.; Boucau, J.; Li, Z.; Casarotto, V.; Lin, J.; Nguyen, A. N.; Ehrmantraut, J. *Org. Lett.* **2007**, *9*, 567−570. (d) Lin, Y.-M.; Li, Z.; Boucau, J. *Tetrahedron Lett.* **2007**, *48*, 5275−5278. (e) Chidara, S.; Lin, Y.-M. *Synlett* **2009**, 1675−1679.

(14) Catalysts derived from **4i** and **4j** showed low reactivity and enantioselectivity (Table 1, entries 9 and 10). We assumed that the methoxy group in **4i** and **4j** enhanced the coordination ability of nitrogen in the quinoline ring. These nitrogens would cause the formation of a more complicated catalyst to give the product in low yield with low enantioselectivity.