ChemComm

This article was published as part of the

2009 'Catalysis in Organic Synthesis' web theme issue

Showcasing high quality research in organic chemistry

Please see our website
(http://www.rsc.org/chemcomm/organicwebtheme2009)
to access the other papers in this issue.

Asymmetric *meso*-aziridine ring-opening reactions using a chiral zirconium catalyst†‡

Kazutaka Seki, Rongmin Yu, Yumi Yamazaki, Yasuhiro Yamashita and Shū Kobayashi*

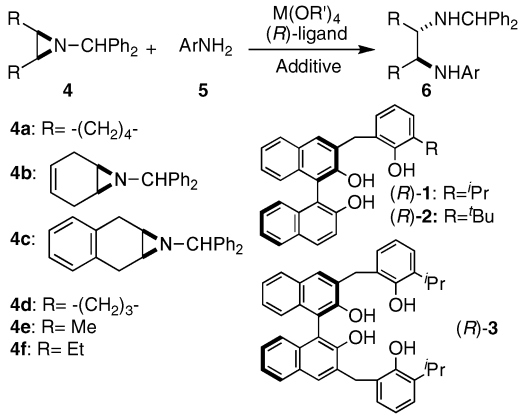
Received (in Cambridge, UK) 15th July 2009, Accepted 18th August 2009
First published as an Advance Article on the web 7th September 2009
DOI: 10.1039/b914271c

A chiral zirconium catalyst prepared from $Zr(O^tBu)_4$ and a chiral tridentate BINOL was found to be effective for asymmetric *meso*-aziridine ring-opening reactions with aniline derivatives. The *N*-benzhydryl group on the product obtained was easily cleaved to give the corresponding amine in high yield under reductive conditions.

Regioselective ring-opening reactions of *meso*-aziridines with amines are an efficient methodology for providing chiral 1,2-diamine derivatives, which are useful building blocks for the synthesis of natural products, as well as chiral organocatalysts and chiral ligands for enantioselective reactions.[1] While asymmetric *meso*-epoxide ring-opening reactions have been relatively well investigated,[2] the corresponding reactions with aziridines have been less progressed.[3] Recently, some successful examples using highly reactive nucleophiles such as TMSCN, MeMgBr and $TMSN_3$ have been reported.[4]

On the other hand, less reactive amine nucleophiles such as aniline derivatives have not been well studied. Our group has already disclosed that asymmetric ring-opening reactions of *meso*-aziridines with aniline derivatives proceeded smoothly using a chiral niobium catalyst, but that enantioselectivities were not satisfactory (up to 84% ee).[5] We also found that a chiral titanium catalyst promoted the ring-opening reactions of *meso*-aziridines with high enantioselectivities.[6] In both cases, *o*-methoxyphenyl group was employed as a *N*-protecting group, however successful removal of this group from the product in oxidative conditions was sometimes difficult. On the other hand, in the course of our investigations to develop more efficient catalysts for the activation of aziridines, we focused on possibilities of Zr and Hf.[7] Herein we report asymmetric ring-opening reactions of *meso*-*N*-benzhydryl aziridines with anilines catalyzed by a Zr-BINOLate complex (Scheme 1).

First, we conducted several ring-opening reactions using cyclohexene oxide-derived aziridines bearing *N*-tosyl and *N*-benzoyl groups in the presence of a chiral Nb or Ti catalyst. In these aziridines their basicities are lower, which might facilitate catalytic Lewis acid activations. However, unexpectedly, the reactions did not proceed at all in each case. Next, we turned our attention to aziridines bearing *N*-benzyl and related groups. While the aziridine bearing an *N*-benzyl group showed poor reactivity, the aziridine bearing an *N*-benzhydryl group gave the desired ring-opening product in good yield. We further surveyed the catalysts and finally found that zirconium-BINOLate complexes were promising, and a high yield and moderate enantioselectivity were obtained when a catalyst prepared from $Zr(O^iPr)_4$ and (*R*)-tridentate BINOL **1** was employed (Table 1, entry 1).



Scheme 1 Asymmetric *meso*-aziridine ring-opening reaction of aniline.

Table 1 Asymmetric *meso*-aziridine ring-opening reaction of aniline[a]

Entry	$M(OR')_4$	L[b]	Additives/mol%	Temp./°C	Yield (%)	ee (%)
1	$Zr(O^iPr)_4$	**1**	—	rt	70	50
2	$Zr(O^tBu)_4$	**1**	—	rt	54	29
3	$Zr(O^nPr)_4$	**1**	—	rt	73	69
4	$Zr(O^nPr)_4$	**1**	—	0	76	73
5	$Zr(O^tBu)_4$	**1**	EtOH (100)	0	83	73
6	$Zr(O^tBu)_4$	**1**	$^nC_5H_{11}OH$ (100)	0	82	75
7	$Zr(O^tBu)_4$	**2**	$^nC_5H_{11}OH$ (100)	rt	58	29
8	$Zr(O^tBu)_4$	**3**	$^nC_5H_{11}OH$ (100)	rt	69	9
9[c]	$Zr(O^tBu)_4$	**1**	$^nC_5H_{11}OH$ (50)	0	quant	73
10[c]	$Zr(O^tBu)_4$	**1**	$^nC_5H_{11}OH$ (50)	−20	54	77
11	$Hf(O^tBu)_4$	**1**	—	rt	96	20
12	$Hf(O^tBu)_4$	**1**	$^nC_5H_{11}OH$ (100)	rt	86	62
13[d]	$Hf(O^tBu)_4$	**1**	EtOH (50)	0	83	71

[a] The reaction was performed using aziridine **4a** and aniline **5a** (1.2 equiv.) in toluene (0.1 M) at 0 °C for 48 h in the presence of a chiral catalyst prepared from $M(OR')_4$ (20 mol%), (*R*)-ligand (22 mol%) and an additive unless otherwise noted. The absolute configuration of the product has not been determined yet. [b] (*R*)-Ligand. [c] Catalyst loading was 10 mol%, and concentration was 0.3 M. [d] Catalyst loading was 10 mol%, and concentration was 0.5 M.

Department of Chemistry, School of Science and Graduate School of Pharmaceutical Sciences, The University of Tokyo, The HFRE Division, ERATO, Japan Science Technology Agency (JST), HongoBunkyo-ku, Tokyo 113-0033, Japan.
E-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp

† This article is part of a ChemComm 'Catalysis in Organic Synthesis' web-theme issue showcasing high quality research in organic chemistry. Please see our website (http://www.rsc.org/chemcomm/organicwebtheme2009) to access the other papers in this issue.

‡ Electronic supplementary information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/b914271c

We then optimized the reaction conditions using the aziridine **4a** derived from cyclohexene oxide and aniline (**5a**) as models. It was found that the alkoxide part of the Zr catalyst influenced the reactivity and selectivity significantly. While a complex of zirconium *tert*-butoxide and chiral ligand **1** showed poor enantioselectivity, the complex prepared from zirconium primary alkoxide gave a higher selectivity (entries 2 and 3). Furthermore, the length of the alkoxide moiety was investigated, and finally the zirconium complex prepared from *n*-pentanol *via* exchange of the remaining *tert*-butoxy part was found to be the best (entries 4–6). We also employed tridentate BINOL **2** and tetradentate BINOL **3**; however, the selectivities were not satisfactory (entries 7 and 8). While the reaction at lower temperature showed higher selectivities, and good enantioselectivities were obtained (73 and 77% ee), the yields were also moderate to high, even in the presence of 10 mol% of the catalyst (entries 9 and 10). On the other hand, $Hf(O^tBu)_4$ was investigated instead of $Zr(O^tBu)_4$, and a similar tendency was observed as a result, except that the Hf catalyst was less stable and showed a higher selectivity when using ethanol as an alcohol additive (entries 11–13).

Next, we investigated the substrate scope of the aziridine ring opening reaction, and the results are summarized in Table 2. It was found that aniline derivatives bearing electron-withdrawing groups such as halogen atoms on the benzene ring showed high yields and high enantioselectivities, regardless of their less nucleophilic nature. When 3-halogen and 3,4-dihalogen substituted aniline derivatives were used, high enantioselectivities of over 80% ee were obtained (entries 2–5). Other aniline derivatives containing electron-withdrawing groups were also examined, and anilines bearing cyano, nitro and ester groups gave high enantioselectivities (entries 6–8). On the other hand, 3-methoxyaniline showed good selectivity in spite of its electron-donating nature (entry 9). However, selectivities slightly decreased when methylanilines were used, and 2-substituted aniline did not give a good result (entries 10–12). The trifluoromethyl group, a strong electron-withdrawing group, was also a promising substituent, and high enantioselectivities were obtained (entries 13 and 14). Notably, 92% ee was obtained when 3,5-bis(trifluoromethyl)aniline was used (entry 15).

We also examined the reactions with other *meso*-aziridines using 3,5-bis(trifluoromethyl)aniline as a nucleophile. Other aziridines containing 6-membered ring systems gave high yields and high enantioselectivities (entries 16 and 17). The aziridine containing a 5-membered ring system worked well to afford the desired diamine in high selectivity (entry 18). The monocyclic aziridines derived from *cis*-butene oxide and *cis*-hexene oxide also reacted with the aniline derivatives in moderate to high yields with high enantioselectivities (entries 19 and 20).

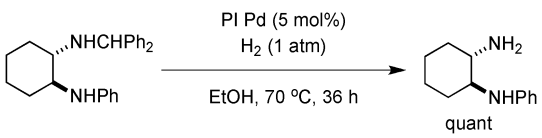
For cleavage of the benzhydryl group from the product, Pd/C-H_2 or Et_3SiH/TFA reduction[8] was found to be effective, and the desired monoamine-free diamine was obtained in high yield. In this reaction, recoverable and reusable polymer-incarcerated palladium catalyst (PI-Pd)[9] also worked well, and an excellent yield was obtained (Scheme 2), which was successfully employed in hydrogenation and Suzuki coupling reactions.

Finally, we investigated amplification of the optical yield to get information of structure of the Zr catalyst (Fig. 1). First, we conducted the ring-opening reaction of **4a** with **5a** using (*R*)-**1** with low optical purity (op) that was prepared by mixing

Table 2 Substrate scope[a]

Entry	4	Ar	Yield (%)	ee (%)
1[b]	**4a**	Ph (**5a**)	quant	73
2[b]	**4a**	3-ClC_6H_4 (**5b**)	80	86
3[b]	**4a**	3-BrC_6H_4 (**5c**)	80	83
4[b]	**4a**	3-IC_6H_4 (**5d**)	75	83
5	**4a**	3,4-$Cl_2C_6H_3$ (**5e**)	90	85
6	**4a**	3-NCC_6H_4 (**5f**)	86	80
7	**4a**	3-$O_2NC_6H_4$ (**5g**)	55	84
8	**4a**	3-(EtOCO)C_6H_4 (**5h**)	94	80
9	**4a**	3-$MeOC_6H_4$ (**5i**)	92	80
10	**4a**	4-MeC_6H_4 (**5j**)	86	73
11	**4a**	3-MeC_6H_4 (**5k**)	72	76
12	**4a**	2-MeC_6H_4 (**5l**)	54	65
13[b]	**4a**	4-$CF_3C_6H_4$ (**5m**)	77	83
14	**4a**	3-$CF_3C_6H_4$ (**5n**)	73	86
15[c]	**4a**	3,5-$(CF_3)_2C_6H_3$ (**5o**)	81	92
16[de]	**4b**	3,5-$(CF_3)_2C_6H_3$ (**5o**)	96	93
17[de]	**4c**	3,5-$(CF_3)_2C_6H_3$ (**5o**)	93	92
18[cd]	**4d**	3,5-$(CF_3)_2C_6H_3$ (**5o**)	51	86
19[d]	**4e**	3,5-$(CF_3)_2C_6H_3$ (**5o**)	77	93
20[f]	**4f**	3-ClC_6H_4 (**5b**)	56	80

[a] The reaction was performed using aziridine **4** and aniline derivative **5** in toluene (0.3 M) at 0 °C for 48 h in the presence of the chiral Zr catalyst prepared from $Zr(O^tBu)_4$ (10 mol%), (*R*)-**1** (11 mol%) and *n*-pentanol (50 mol%) unless otherwise noted. The absolute configurations of the products have not been determined yet. [b] Reaction runs for 24 h. [c] 3.0 equiv. of aniline derivatives were used. Reaction time was 68 h. [d] Reaction runs at −10 °C. [e] Concentration was 0.5 M. [f] 20 mol% catalyst was used. Concentration was 1.0 M.



Scheme 2 Cleavage of the *N*-protecting group.

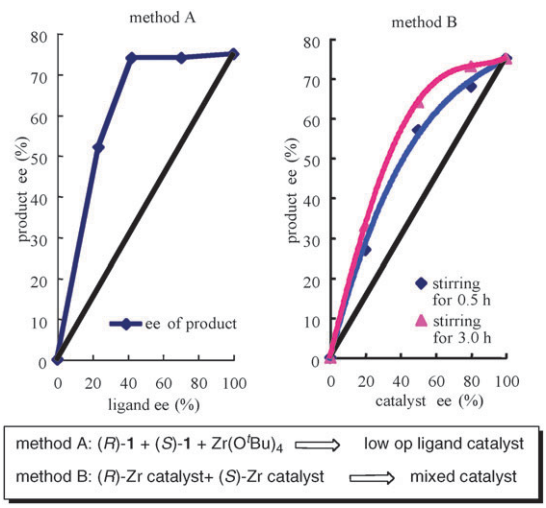


Fig. 1 Non-linear effect on the product ee.

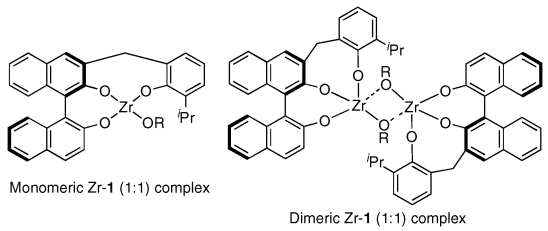


Fig. 2 Assumed structures of the chiral zirconium complex.

optically pure (*R*)-**1** ligand and (*S*)-**1** ligand in proper ratio (method A).

In this case, higher ees were nevertheless observed the less optically pure ligands were used. This significant positive non-linear effect (NLE) on the product ee could be explained based on an assumption that some catalytically inactive species containing an equal amount of *R* and *S* ligands formed in the reaction system. Next, we conducted the reaction using "mixed catalyst" prepared by mixing two optically pure zirconium catalysts ((*R*)-catalyst and (*S*)-catalyst) that were already prepared (method B). In method B, we performed two types of experiments; the difference between the experiments was only the "catalyst mixing time". One reaction was conducted using the mixed catalyst, which was prepared by 30 min mixing of (*R*)-catalyst and (*S*)-catalyst (method B-1) and the other was conducted using the catalyst prepared by 3 h mixing (method B-2). In each case, while a significant NLE on the product ee was observed, the degree of the NLE was a little different; the NLE of B-2 was stronger than that of B-1. These results indicated that the (*R*)- and (*S*)-Zr catalyst prepared from each optically pure **1** could also form the inactive species containing an equal amount of *R* and *S* ligands, easily. We have already reported that the Zr catalyst prepared from $Zr(O^tBu)_4$, ligand **1** and *N*-methylimidazole was efficient for an asymmetric Mannich-type reaction, and elucidated that the proposed structure of this catalyst was a monomeric form according to DFT calculations, and NLE and NMR studies.[10] Based on those experiments, we firstly assumed that the Zr catalyst consisted of a 1 : 1 complex of Zr and ligand **1**, and that it mainly existed as a monomer. However, the NLE experiments of method A, method B-1 and B-2 showed different curves on the graphs, which meant that the inactive *RS* dimer or oligomer complex gradually generated. Considering those results, the current Zr complex could form a dimer or oligomer structure in the solution state. The main difference from the complex for the Mannich-type reaction is absence of *N*-methylimidazole, a coordinative Lewis base, which could control the whole aggregation structure. The assumed structures of the Zr complexes are shown in Fig. 2, although, it is still unclear whether the real active species as a catalyst is monomeric, or a dimeric or oligomeric form of the complex.

In conclusion, we have found that the chiral Zr-tridentate BINOL complex was successfully employed for *meso*-aziridine ring-opening reactions with a variety of aniline derivatives in good yields with high enantioselectivities. The *N*-benzhydryl group on the product obtained was easily cleaved in high yield under reductive conditions. Furthermore, it was revealed that the zirconium complex could exist mainly in dimer or oligomer form according to investigations of the relationship between optical purity of the BINOL and the ee of the product. Further investigation of structure of the active species is now in progress.

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS) and Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering), The University of Tokyo, MEXT, Japan.

Notes and references

1 For example of non-chiral aziridine ring-opening reaction with aniline see: (*a*) S. Peruncheralathan, M. Henze and C. Schneider, *Synlett*, 2007, 2289; (*b*) J. Wu, X. Sun and W. Sun, *Org. Biomol. Chem.*, 2006, **4**, 4231; (*c*) J. Wu, X. Sun and Y. Li, *Eur. J. Org. Chem.*, 2005, **46**, 4271; (*d*) U. K. Nadir and A. Singh, *Tetrahedron Lett.*, 2005, **46**, 2083; (*e*) S. Chandrasekhar, S. J. Prakash and T. Shyamsunder, *Synth. Commun.*, 2004, **34**, 3865; (*f*) J. S. Yadav, B. V. S. Reddy and K. Premalatha, *Adv. Synth. Catal.*, 2003, **345**, 948; (*g*) J.-Y. Goujon, D. Gueyrard, P. Compani, O. R. Martin and N. Asano, *Tetrahedron: Asymmetry*, 2003, **14**, 1969; (*h*) I. D. G. Watson and A. K. Yudin, *J. Org. Chem.*, 2003, **68**, 5160; (*i*) N. R. Swamy and Y. Venkateswarlu, *Synth. Commun.*, 2003, **33**, 547; (*j*) R.-H. Fan and X.-L. Hou, *J. Org. Chem.*, 2003, **68**, 726; (*k*) R. V. Anand, G. Pandey and V. K. Singh, *Tetrahedron Lett.*, 2002, **43**, 3975; (*l*) J. S. Yadav, B. V. S. Reddy, B. Jyothirmai and M. S. R. Murty, *Synlett*, 2002, 53; (*m*) G. Sekar and V. K. Singh, *J. Org. Chem.*, 1999, **64**, 2537; (*n*) M. Meguro, N. Asao and Y. Yamamoto, *Tetrahedron Lett.*, 1994, **35**, 7395.

2 Review for ring-opening reaction of epoxide: (*a*) C. Schneider, *Synthesis*, 2006, 3919; (*b*) I. M. Pastor and M. Yus, *Curr. Org. Chem.*, 2005, **9**, 1; (*c*) E. N. Jacobsen and M. H. Wu, *Comprehensive Asymmetric Catalyst*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999, vol. 2, p. 649.

3 (*a*) C. Schneider, *Angew. Chem., Int. Ed.*, 2009, **48**, 2082; (*b*) *Aziridines and Epoxides in Organic Synthesis*, ed. A. K. Yudin, Wiley-VCH, Weiheim, 2006; (*c*) M. Pineschi, *Eur. J. Org. Chem.*, 2006, 4979; (*d*) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (*e*) W. McCoull and F. A. Davis, *Synthesis*, 2000, 1347.

4 Review for ring opening reaction of aziridine: (*a*) Z. Wang, X. Sun, S. Ye, W. Wang, B. Wang and J. Wu, *Tetrahedron: Asymmetry*, 2008, **19**, 964; (*b*) E. B. Rowland, G. B. Rowland, E. Rivera-Otero and J. C. Antilla, *J. Am. Chem. Soc.*, 2007, **129**, 12084; (*c*) I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, S. Furusho, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 16438; (*d*) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 6312; (*e*) Z. Li, M. Fermandez and E. N. Jacobsen, *Org. Lett.*, 1999, **1**, 1611; (*f*) P. Müller and P. Nury, *Org. Lett.*, 1999, **1**, 439.

5 K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2007, **129**, 8103.

6 (*a*) R. Yu, Y. Yamashita and S. Kobayashi, *Adv. Synth. Catal.*, 2009, **351**, 147; recently, Schneider *et al.* also reported a chiral Ti-catalyzed *meso*-aziridine ring opening reactions with aromatic amines, see: (*b*) S. Peruncheralathan, H. Teller and C. Schneider, *Angew. Chem., Int. Ed.*, 2009, **48**, 4849.

7 For examples of asymmetric Zr-catalyzed reactions, see: (*a*) S. Kobayashi, M. Ueno, S. Saito, Y. Mizuki, H. Ishitani and Y. Yamashita, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5476; (*b*) S. Yamasaki, M. Kanai and M. Shibasaki, *Chem.–Eur. J.*, 2001, **7**, 4066; (*c*) E.-I. Negishi, *Pure Appl. Chem.*, 2001, **73**, 239; (*d*) S. Huo, J.-C. Shi and E.-I. Negishi, *Angew. Chem., Int. Ed.*, 2002, **41**, 2141; (*e*) T. Okachi, N. Murai and M. Onaka, *Org. Lett.*, 2003, **5**, 85.

8 T. W. Green and P. G. M. Wuts, in *Protective groups in organic synthesis*, John Wiley & Sons, Inc., New York, 4th edn, 2007, p. 824.

9 (*a*) K. Okamoto, R. Akiyama and S. Kobayashi, *J. Org. Chem.*, 2004, **69**, 2871; (*b*) R. Akiyama and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, **125**, 3412.

10 Y. Ihori, Y. Yamashita, H. Ishitani and S. Kobayashi, *J. Am. Chem. Soc.*, 2005, **127**, 15528.

