High facial selectivity observed in amine coordination to chiral oxazaborolidinones†

Toshiro Harada,* Yuuki Yamamoto and Takahiro Kusukawa

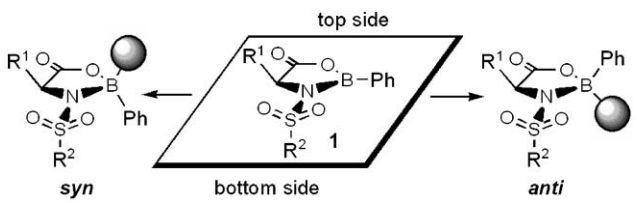
Received (in Cambridge, UK) 2nd September 2004, Accepted 8th November 2004
First published as an Advance Article on the web 16th December 2004
DOI: 10.1039/b413370f

A variety of 1,3,2-oxazaborolidin-5-ones (OXB) derived from *N*-sulfonyl amino acids exhibit a high top-face selectivity in complexation with pyridines under thermodynamically controlled conditions.

N-Sulfonyl 1,3,2-oxazaborolidin-5-ones (OXB **1**) stand for one of the most important and versatile classes of chiral Lewis acids.[1] The simplicity of their syntheses from natural and unnatural α-amino acids allows the OXB catalysts to be easily optimized to a variety of asymmetric transformations. Since the initial reports by Yamamoto[2a] and Helmchen,[2b] these catalysts have been applied successfully to enantiotopic face selective[1,2] and group selective reactions.[3]

Elucidation of the structure of an activated complex derived from a catalyst and a substrate is one of the central issues to understand the origin of enantioselectivities and improve its performance. The primary structural concern of the OXB activated complexes is whether the substrate coordinates from the top or bottom face of the OXB ring (Scheme 1).[4,5] ^{1}H NMR NOE study might afford information on the top *vs* bottom complexation.[6] Unfortunately, however, rapid reversible complexation of the carbonyl groups to the boron atom results in averaged spectra of both complexation modes, making NOEs, if observed,[6b] less informative for the structural elucidation.

In our recent study on asymmetric Michael reactions of acyclic enones catalyzed by *allo*-threonine-derived OXBs, we proposed an activated complex model involving the coordination of an enone to the top face of OXB (Fig. 1), based on the observed correlation between the catalyst structures and enantioselectivities.[7] Since attempts to obtain direct structural information by NMR analyses of an enone–OXB mixture failed, attention was then focused on the complexation by more basic amines. Herein, we wish to report that amines form *syn* and *anti* OXB-complexes discernible on the time scale of NMR analyses under equilibrating conditions. The study reveals a high top-face selectivity in coordination by OXBs.



Scheme 1 Top *vs* bottom coordination by OXB.

The ^{1}H NMR (500 MHz) spectrum of an equimolar mixture of phenylalanine-derived OXB **1a** and pyrrolidine (**2a**) at 23 °C in $CDCl_3$ showed the formation of two diastereomeric complexes *syn*-**1a**·**2a** and *anti*-**1a**·**2a** in the ratio of 1.9:1 (Scheme 2). The stereochemistries of the complexes were determined based on positive NOEs observed in a NOESY experiment (see ESI).† ^{1}H NMR analysis immediately after mixing the components revealed the preferential formation of *anti*-**1a**·**2a** (*syn*:*anti* = 1:2.0). The ratio was reversed within several hours to the constant value of 1.9:1. The observation indicates that the *syn* and the *anti* complex are in equilibrium, while the rate of equilibrium is relatively slow on the NMR time scale. Therefore, the observed *syn*:*anti* ratio is determined thermodynamically.[8]

In contrast to the behavior of pyrrolidine (**2a**), pyridine (**2b**) showed a high selectivity in complexation with **1a**. Thus, an equimolar mixture of **1a** and **2b** in $CDCl_3$ at 27 °C exhibited a single set of proton resonances of a complex, whose structure was determined to be *syn*-**1a**·**2a** by a NOESY analysis (Fig. 2). In the NMR titration experiments of **1a** with 0.5 and 2.0 equiv. of **2b**, the signals of the complex were not time-averaged and appeared independently with those of excess **1a** and **2b**, respectively, implying the relatively slow exchange rate of coordinated pyridine. It is unlikely that the observed set of resonances is the result of a rapid equilibrium between the *syn* and *anti* isomers.

The high top-face selectivity observed for a planar amine **2b** is of interest in connection with the structurally relevant R(R′)C=O–OXB complexes. Considering the structural resemblance of the pyridyl and the phenyl group both attached to the boron atom, the structures of *syn*-**1a**·**2b** and *anti*-**1a**·**2b** (not observed) are quite similar. The phenomenon cannot be rationalized by a simple steric effect. To gain insight into the origin of the top-face selectivity, complexation experiments were carried out with OXBs **1a–f** and amines **2a–f** (Table 1).

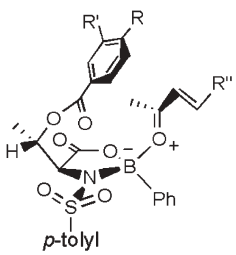
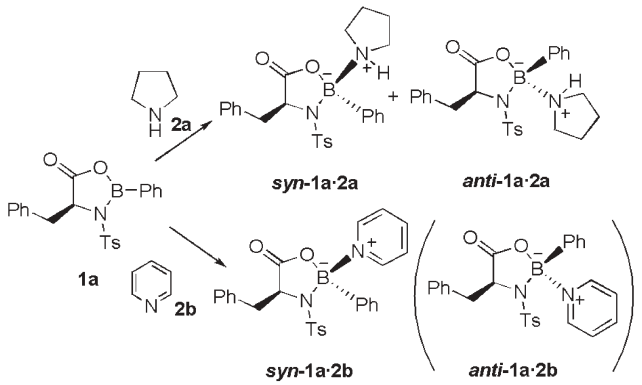


Fig. 1 Proposed activated complex for asymmetric Michael reaction catalyzed by *allo*-threonine-derived OXBs.

† Electronic Supplementary Information (ESI) available: experimental procedures and ^{1}H NMR and NOESY spectra for amine–OXB complexes. See http://www.rsc.org/suppdata/cc/b4/b413370f/

*harada@chem.kit.ac.jp



Scheme 2 Complex formation between OXB **1a** and pyrrolidine (**2a**) and pyridine (**2b**).

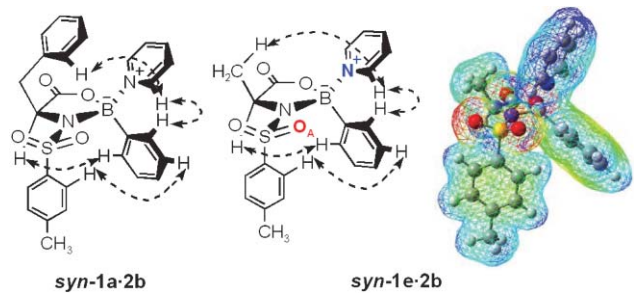


Fig. 2 NOEs observed for *syn*-**1a**·**2b** (left) and *syn*-**1e**·**2b** (middle), and electrostatic potential between −50 (red) and 50 (blue) kcal mol^{-1} on the van der Waals molecular surface of *syn*-**1e**·**2b** according to *ab initio* calculation in vacuum (right).

Complexation of pyridine by *N*-mesyl-OXB **1b** and *allo*-threonine-derived OXB **1c**[7] was also highly top-face selective (entries 4 and 5). NOEs observed for the pyridyl protons (see ESI†) suggested a face-to-face arrangement of the side-chain aromatic groups (R^1) and a top-face coordinated pyridyl group similar to that in *syn*-**1a**·**2b** (Fig. 2), implying a π–π interaction between these groups to be a major stabilizing factor. However, aliphatic amine **2c** also showed a high top-face selectivity in complexation with **1a** (entry 3). In addition, valine-derived OXB **1d** and alanine-derived OXB **1e** also exhibited top-face selectivity albeit with minor formation of the *anti* isomers (entries 6 and 7). In the NOESY spectra of these complexes, negative NOEs due to a chemical exchange were observed between the proton signals of the major *syn* isomer and the corresponding signals of the minor *anti* isomer in addition to the positive NOEs which are consistent with the top-face coordinating structure of the major isomers.

Ab initio calculations‡[9,10] of *syn*- and *anti*-**1e**·**2b** reproduced the observed top-face selectivity well. The calculated free energy difference (−4.10 and −1.42 kcal mol^{-1} in vacuum and in $CHCl_3$, respectively) is in agreement with the experimental value (−1.33 kcal mol^{-1}). The optimized conformation of the *syn* isomer (Fig. 2), in which the tosyl group locates at the bottom face *anti* to the ring methyl group with a perpendicular C_{ipso}–S–N–B dihedral angle (−90.0°), is in accord with the observed NOEs. The analysis of the electrostatic potential suggested that the attractive interaction between the negatively charged sulfonyl oxygen atom (O_A) and the positively charged pyridyl moiety is a stabilizing factor for the *syn* isomer.

Experimental support for the hypothesis was obtained from the complexation experiments with 4-substituted pyridines **2d–f**. The enhanced top-face selectivity of 17:1 was observed by the introduction of the electron-withdrawing trifluoromethyl group at the 4-position (entry 8). On the other hand, the electron-donating methyl and methoxy groups lowered the selectivity (entries 9 and 10).§ The nonselective complexation of pyridine observed for *N*-trifluoromethenesulfonyl OXB **1f** (entry 11) provides additional support. The observation can be rationalized by a stabilizing electrostatic interaction in the *anti* complex between the negatively polarized fluorine atoms and the positively charged pyridyl group at the bottom face.

The facial selectivity observed in the complexation of planar pyridines supports our activated complex model for asymmetric Michael additions involving top-face coordination of planar carbonyl compounds (Fig. 1).[7c] The enhanced selectivity for phenylalanine derived OXB **1a,b** and *allo*-threonine-derived OXB **1c** implies that the π–π interaction is an additional factor.[6] Electrostatic interaction for activated, electron-deficient substrates will be exploited in the structural design of chiral Lewis acid catalysts as a new guiding principle.¶

Table 1 Facial selectivity in complexation of amines by OXB **1a–f**[a]

Entry	OXB	Amine	*syn*:*anti*
1	**1a**; R^1 = $PhCH_2$, R^2 = *p*-tolyl	**2a**; pyrrolidine	1.9:1
2[b]	**1a**	**2b**; pyridine	>20:1
3[b,c]	**1a**	**2c**; butylamine	11:1
4[b,c]	**1b**; R^1 = $PhCH_2$, R^2 = Me	**2b**	>20:1
5[b,c]	**1c**; R^1 = (*S*)-2-naphthylCO_2CH(Me)–, R^2 = *p*-tolyl	**2b**	>20:1
6	**1d**; R^1 = *i*-Pr, R^2 = *p*-tolyl	**2b**	6.6:1
7	**1e**; R^1 = Me, R^2 = *p*-tolyl	**2b**	9.6:1
8	**1e**	**2d**; 4-CF_3-pyridine	17:1
9	**1e**	**2e**; 4-Me-pyridine	9.1:1
10	**1e**	**2f**; 4-MeO-pyridine	7.6:1
11	**1f**; R^1 = Me, R^2 = CF_3	**2b**	1.2:1

[a] Unless otherwise noted, ^{1}H NMR (500 MHz) spectra were measured in $CDCl_3$ (0.1 M) at 23 °C. [b] Measured at 27 °C. [c] C_6D_6 was used as a solvent.

Toshiro Harada,* Yuuki Yamamoto and Takahiro Kusukawa
Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan.
E-mail: harada@chem.kit.ac.jp

Notes and references

‡ Geometries were optimized at the HF/3-21G* level. The self-consistent reaction field (SCRF) method based on the Onsager model[9] implemented in the Gaussian 98 program[10] was used for the calculation in $CHCl_3$.
§ Calculated free energy differences (kcal mol^{-1}) in $CHCl_3$ and in vacuum (shown in parentheses) are as follows: **1e·2d**; −3.36 (−4.26); **1e·2e**; −1.81 (−4.00); **1e·2f**; −0.54 (−3.57).
¶ This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

1 (*a*) K. Ishihara, in *Lewis Acids in Organic Synthesis*; ed. H. Yamamoto, Wiley-VCH, Weinheim, Germany, 2000, p 135; (*b*) For leading references see; K. Ishihara, S. Kondo and H. Yamamoto, *J. Org. Chem.*, 2000, **65**, 9125; (*c*) L. Deloux and M. Srebnik, *Chem. Rev.*, 1993, **93**, 763.
2 (*a*) M. Takasu and H. Yamamoto, *Synlett*, 1990, 194; (*b*) D. Sartor, J. Saffrich and G. Helmchen, *Synlett*, 1990, 197; (*c*) E. J. Corey and T.-P. Loh, *J. Am. Chem. Soc.*, 1991, **113**, 8966; (*d*) S.-i. Kiyooka, Y. Kaneko, M. Komura, H. Matsuo and M. Nakano, *J. Org. Chem.*, 1991, **56**, 2276; (*e*) E. R. Parmee, O. Tempkin, S. Masamune and A. Abiko, *J. Am. Chem. Soc.*, 1991, **113**, 9365.
3 (*a*) M. Kinugasa, T. Harada and A. Oku, *J. Am. Chem. Soc.*, 1997, **119**, 9067; (*b*) T. Harada, T. Egusa, Y. Igarashi, M. Kinugasa and A. Oku, *J. Org. Chem.*, 2002, **67**, 7080 and references cited therein.
4 (*a*) D. Sartor, J. Saffrich, G. Helmchen, C. J. Richards and H. Lambert, *Tetrahedron: Asymmetry*, 1991, **2**, 639; (*b*) E. J. Corey and J. J. Rohde, *Tetrahedron Lett.*, 1997, **38**, 37; (*c*) E. J. Corey, D. Barnes-Seeman and T. W. Lee, *Tetrahedron Lett.*, 1997, **38**, 4361.
5 For theoretical approach, see; L. Salvatella and M. F. Ruiz-López, *J. Am. Chem. Soc.*, 1999, **121**, 10772 and references cited therein.
6 (*a*) E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara and M. C. Noe, *J. Am. Chem. Soc.*, 1992, **114**, 8290; (*b*) K. Ishihara, Q. Gao and H. Yamamoto, *J. Am. Chem. Soc.*, 1993, **115**, 10412.
7 (*a*) T. Harada, H. Iwai, H. Takatsuki, K. Fujita, M. Kubo and A. Oku, *Org. Lett.*, 2001, **3**, 2101; (*b*) X. Wang, T. Harada, H. Iwai and A. Oku, *Chirality*, 2003, **15**, 28; (*c*) X. Wang, S. Adachi, H. Iwai, H. Takatsuki, K. Fujita, M. Kubo, A. Oku and T. Harada, *J. Org. Chem.*, 2003, **68**, 10046.
8 For relevant study on the equilibrium behavior of OXB complexes, see: (*a*) E. Vedejs, E. S. C. Fields, S. Lin and M. R. Schrimpf, *J. Org. Chem.*, 1995, **60**, 3028; (*b*) E. Vedejs, R. W. Chapman, S. Lin, M. Müller and D. R. Powell, *J. Am. Chem. Soc.*, 2000, **122**, 3047.
9 (*a*) M. W. Wong, M. J. Frisch and K. B. Wiberg, *J. Am. Chem. Soc.*, 1990, **112**, 4776; (*b*) M. W. Wong, K. B. Wiberg and M. J. Frisch, *J. Chem. Phys.*, 1991, **95**, 8991.
10 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, *GAUSSIAN 98 (Revision A.7)*, Gaussian, Inc., Pittsburgh, PA, 1998.