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Short and Practical Synthesis of *O*-(*p*-Biphenoyl)-*N*-tosyl-*allo*-threonine-Derived Oxazaborolidinone Catalyst

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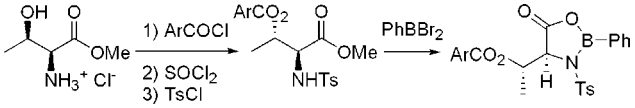
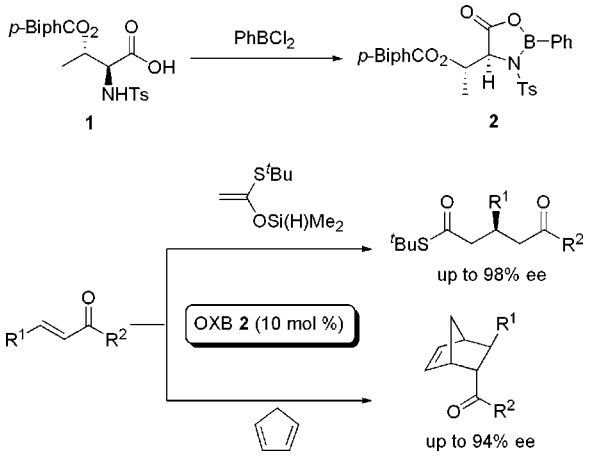


Ar = *p*-biphenyl

O-(*p*-Biphenoyl)-*N*-tosyl-(L)-*allo*-threonine methyl ester is synthesized in three steps (65% overall yield) starting from commercially available (L)-*allo*-threonine methyl ester hydrochloride by *N*-acylation followed by *N*,*O*-acyl migration with inversion of the β carbinol carbon and *N*-tosylation. Treatment of the methyl ester with dibromophenylborane gives oxazaborolidinone **1**, which can be used as a Lewis acid catalyst for the asymmetric Michael and Diels−Alder reactions.

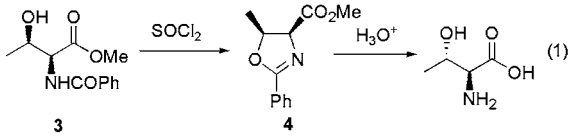
Asymmetric Lewis acid-catalyzed reactions of conjugated enones are challenging due to nonselective metal coordination of the sterically and electronically similar lone pairs of the carbonyl oxygen.[1] Recent reports from this laboratory have disclosed *allo*-threonine-derived oxazaborolidinone (OXB) **2** is an efficient Lewis acid catalyst for asymmetric reaction of simple acyclic enones (Scheme 1). In the presence of OXB **2** (10−20 mol %), the asymmetric Michael reaction[2] and Diels−Alder reaction[3] proceed with the high enantioface selection of the enones to give the products of high enantiopurity. While catalyst **2** can be prepared simply by mixing (L)-*allo*-threonine derivatives **1** with dichlorophenylborane, the preparation of ligand **1** required a multistep synthetic route. According to the method reported by Elliot,[4] (L)-*allo*-threonine is prepared in three steps by the inversion of the β carbinol carbon of (L)-threonine methyl ester hydrochloride (**5**). The amino acid is converted into **1** by an additional four-step sequence involving *N*-tosylation, protection of the carboxylic acid moiety as a benzyl ester, *O*-acylation, and final deprotection by hydrogenolysis.

SCHEME 1. OXB-Catalyzed Asymmetric Michael and Diels−Alder Reactions



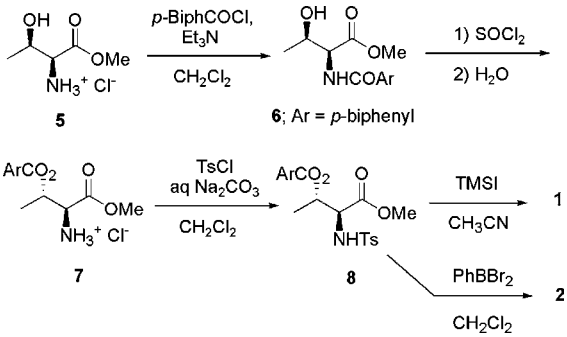
Herein, we wish to report a practical four-step synthesis of OXB **2** that provides an easy access to this useful Lewis acid catalyst.

The Elliot method involves thionyl chloride-mediated cyclization of benzamide derivative **3** with inversion of the carbinol carbon to oxazoline **4**, which is then fully hydrolyzed by treatment with hot aqueous HCl to give *allo*-threonine (eq 1).



If the selective C═N bond cleavage of **4** can be achieved under milder conditions, hydrolysis of **4** would afford the *O*-acyl derivative of *allo*-threonine methyl ester, realizing overall *N*,*O*-acyl group transfer with the inversion of the carbinol carbon. Such a possibility was examined for *N*-(*p*-biphenoyl) derivative **6** (Scheme 2).

SCHEME 2. Synthesis of OXB Catalyst 2



The reaction of hydrochloride **5** with *p*-biphenoyl chloride in the presence of triethylamine in CH_2Cl_2 at room temperature afforded *N*-acyl derivative **6** in 74% yield. After treatment of **6** with thionyl chloride (9 equiv) for 24 h, the concentrate of the mixture was dissolved in water and stood at room temperature for 4 days to give anticipated *N*,*O*-acyl migration product **7**.[5] The initial product of the reaction of **6** with thionyl chloride might be oxazoline hydrochloride **9**, which underwent hydrolysis

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(2) (a) Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A. *Org. Lett.* **2001**, *3*, 2101. (b) Wang, X.; Adachi, S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A.; Harada, T. *J. Org. Chem.* **2003**, *68*, 10046. (c) Harada, T.; Adachi, S.; Wang, X. *Org. Lett.* **2004**, *6*, 4877.

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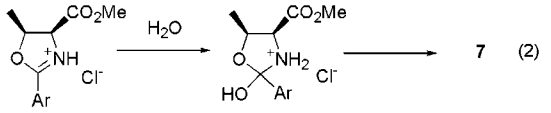
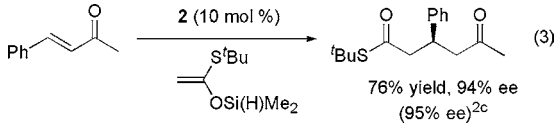
under weakly acidic conditions through tetrahedral intermediate **10** to produce **7** by selective $C-N^+$ bond cleavage (eq 2).



Although the product **7** can be isolated as a free base, the aqueous suspension of **7** obtained from **6** was subjected to the tosylation reaction under the Schotten-Baumann conditions. The product **8** was isolated by recrystallization from ethyl acetate and hexane in 88% overall yield from **6**. Although selective hydrolysis of the methyl ester moiety of **6** with aqueous LiOH failed owing to the competing reaction at the *p*-biphenylcarboxylate moiety, the conversion of **6** to ligand **2** could be achieved by demethylation with iodotrimethylsilane in 82% yield.[6] Thus, the preparation of chiral ligand **1** was achieved in four steps from commercially available hydrochloride **5** in 52% overall yield.

A more straightforward and convenient method for the preparation of OXB catalyst **2** would be the direct use of methyl ester **6** as a precursor. Indeed, when methyl ester **6** was treated with dichlorophenylborane in CH_2Cl_2 at room temperature, the formation of OXB **1** was detected by ^{1}H NMR analysis of the crude concentrate.[7] However, the full conversion of **6** was not attained even after prolonged reaction time. Gratifyingly, clean formation of **2** was observed by using dibromophenylborane instead. The activity of the catalyst prepared by the present method was confirmed in a representative asymmetric Michael reaction (eq 3).



In summary, a short and practical synthesis of OXB catalyst **2** has been developed from commercially available (L)-*allo*-threonine methyl ester hydrochloride by utilizing *N*,*O*-acyl transfer with inversion of the β carbinol carbon and demethylation/oxazaborolidinone-ring formation of ester **8** with dibromophenylborane. The present method provides an easy access to the efficient Lewis acid catalyst for asymmetric Michael and Diels−Alder reactions of acyclic enones.

Experimental Section

General. Dichloromethane and chloroform was dried and distilled over CaH_2 and P_2O_5, respectively. (L)-Threonine methyl ester hydrochloride was prepared from (L)-threonine by treatment with thionyl chloride in methanol.[8] Dibromophenylborane was prepared according to the literature procedure[9] and stored as a dichloromethane solution.

***N*-(*p*-Biphenoyl)-(L)-threonine Methyl Ester (6).** To a mixture of (L)-threonine methyl ester hydrochloride (4.6 g, 30 mmol) in $CHCl_3$ (20 mL) at room temperature was added dropwise triethylamine (9.9 mL, 71 mmol). To the resulting solution at 0 °C was added dropwise a suspension of 4-biphenylcarbonyl chloride (6.5 g, 30 mmol). The resulting mixture was stirred at room temperature for 3 h. The mixture was poured into water and extracted twice with $CHCl_3$. The organic layers were washed with water (2×), 1 N aqueous HCl, and 5% aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give **6** as a colorless solid, which was used in the next step without further purification (7.0 g, 74%): mp 181−183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (3H, d, J = 6.4 Hz), 2.32 (2H, br), 3.80 (3H, s), 4.48 (1H, dq, J = 2.4 and 6.4 Hz), 4.86 (1H, dd, J = 2.4 and 8.7 Hz), 7.04 (1H, br d, J = 8.7 Hz), 7.39 (1H, m), 7.46 (2H, m), 7.60 (2H, m), 7.65 (2H, d, J = 8.3 Hz), 7.92 (2H, d, J = 8.3 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 20.1, 52.7, 57.6, 68.3, 127.2, 127.3, 127.7, 128.0, 128.9, 132.3, 139.9, 144.7, 167.6, 171.6; IR (KBr disk) 1747, 1639, 1261, 1107, 743 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.98; H, 6.03; N, 4.54.

***O*-(*p*-Biphenoyl)-*N*-tosyl-(L)-*allo*-threonine Methyl Ester (8).** *N*-(*p*-Biphenoyl) derivative **6** (7.2 g, 23 mmol) was added portionwise to a stirred thionyl chloride (15 mL, 0.21 mol) cooled with an ice bath such that the temperature did not exceed 5 °C. After being stirred at room temperature for 24 h, the mixture was concentrated in vacuo. Dichloromethane (200 mL) and hexane (100 mL) were added to the residue and subsequently removed in vacuo. This was repeated again to remove excess thionyl chloride. The resulting solid was finely ground with a mortar, suspended in water (100 mL), and stirred vigorously for 4 days at room temperature to give the suspension of **7**. During this time, aliquots were removed to monitor the hydrolysis reaction by TLC (50% ethyl acetate in hexane) after treatment with 5% aqueous $NaHCO_3$ and extraction with CH_2Cl_2. Spectral data of *O*-(*p*-biphenoyl)-*allo*-threonine methyl ester (free base of **7**): mp 181−183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (3H, d, J = 6.4 Hz), 1.68 (2H, br), 3.78 (3H, s), 3.89 (1H, br), 5.39 (1H, m), 7.40 (1H, m), 7.47 (2H, m), 7.62 (2H, m), 7.66 (2H, d, J = 8.4 Hz), 8.10 (2H, d, J = 8.4 Hz).

Dichloromethane (46 mL) and Na_2CO_3 (12 g, 12 mmol) were added to the above suspension of **7**. To the resulting mixture at room temperature was added portionwise *p*-toluenesulfonyl chloride (5.3 g, 28 mL). After being stirred for 24 h, the mixture was extracted twice with CH_2Cl_2 (2 × 50 mL). Organic layers were washed with 1 N aqueous HCl followed by filtration of the precipitate formed. The filtrate was washed with 5% aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was recrystallized from ethyl acetate and hexane to give 8.2 g (88% yield) of **8**: mp 127−128 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (3H, d, J = 6.5 Hz), 2.36 (3H, s), 3.58 (3H, s), 4.31 (1H, dd, J = 4.3 and 9.6 Hz), 5.30 (1H, dq, J = 4.4 and 6.5 Hz), 5.44 (1H, br d, J = 9.6 Hz), 7.24 (2H, d, J = 8.2 Hz), 7.40 (1H, m), 7.47 (2H, m), 7.61−63 (4H, m), 7.71 (2H, d, J = 8.2 Hz), 8.03 (2H, J = 8.3 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 15.9, 21.5, 52.8, 58.9, 70.9, 127.0, 127.2, 128.2, 128.3, 128.9, 129.7, 130.3, 136.6,139.9, 143.8, 146.0, 165.4, 169.5, 174.8; IR (KBr disk) 1742, 1710, 1165, 1153, 748, 683 cm^{-1}. Anal. Calcd for $C_{25}H_{25}NO_6S$: C, 64.22; H, 5.39; N, 2.99. Found: C, 64.44; H, 5.24; N, 3.06.

***O*-(*p*-Biphenoyl)-*N*-tosyl-(L)-*allo*-threonine (1).** To a solution of **8** (2.00 g, 4.28 mmol) in dry chloroform (5 mL) was added iodotrimethylsilane (3.4 mL, 24 mmol). The resulting mixture was heated at 80 °C for 6 h. The resulting mixture was poured into water and extracted twice with ethyl acetate, washed successively with water (2×), aqueous 10% $Na_2S_2O_3$, and water, dried over Na_2SO_4, and concentrated in vacuo. The residue was recrystallized from benzene and hexane to give 1.60 g (82% yield) of **1**.[2a]

Oxazaborolidinone 2. To a solution of methyl ester **8** (0.14 g, 0.30 mmol) in CH_2Cl_2 (1.8 mL) under nitrogen atmosphere at room

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(9) Haubold, W.; Herdtle, J.; Gollinger, W.; Einholz, W. *J. Organomet. Chem.* **1986**, *315*, 1.

temperature was added a CH_2Cl_2 solution of dibromophenylborane (1.17 M, 0.256 mL, 0.30 mmol). After being stirred for 1 h, the mixture was concentrated in vacuo to give **2**, which was identified by ^{1}H NMR (see the Supporting Information). [2a]

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Supporting Information Available: ^{1}H NMR spectra of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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