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## LEWIS ACID-CATALYZED MICHAEL ADDITION REACTIONS OF *N*-BOC-2-SILYLOXYPYRROLES TO 3-ACRYLOYL-2- OXAZOLIDINONE

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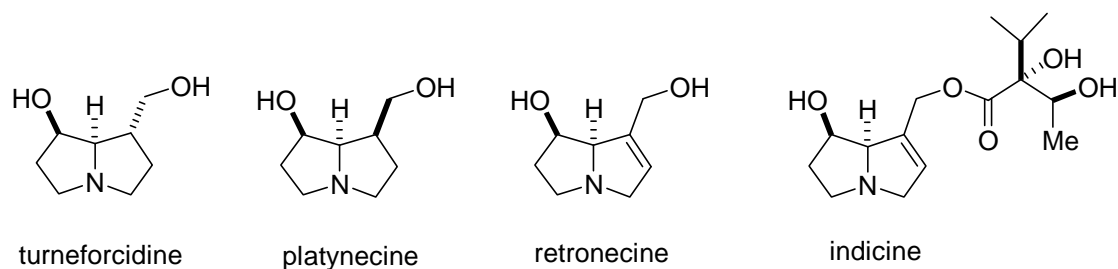
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**Abstract** – Among several Lewis acids examined, Sc(OTf)<sub>3</sub> (10 mol%) was found to be the most effective catalyst to promote a Michael addition reaction of *N*-Boc-2-(*tert*-butyldimethylsilyloxy)pyrrole to 3-acryloyl-2-oxazolidinone. A slow addition of the 2-silyloxy pyrrole in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol (5 equiv.) at –25 °C were needed to obtain good yield (77 – 80%). The asymmetric version of the reaction could be performed with good enantioselectivity (up to 82% ee) by using the chiral Sc(III) catalyst (10 mol%), which was prepared from 2,6-bis[(4*S*)-4-isopropyl-2-oxazolin-2-yl]pyridine and Sc(OTf)<sub>3</sub>, in reasonable yield (60 – 70%).

### INTRODUCTION

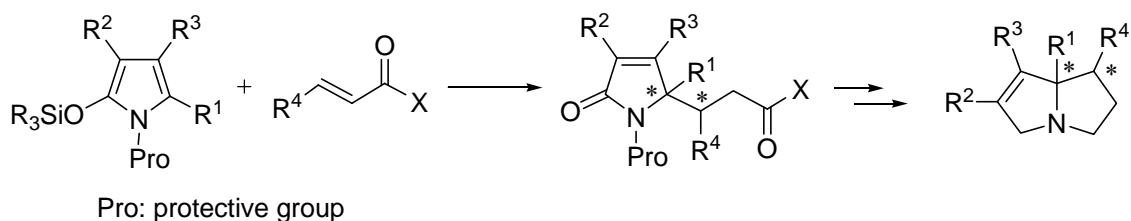
Silyloxy-substituted 5-membered aromatic heterocycles have been received a considerable attention from a synthetic point of view, because of potential reactivity toward electrophiles such as aldehydes, imines, acetals, and  $\alpha,\beta$ -unsaturated carbonyl compounds to form carbon-carbon bonds by using Lewis acids and Lewis bases as catalysts.<sup>1</sup> Actually, a great number of research works concerning stereoselectivity of the reactions and applications to biologically important natural product syntheses have been reported mainly for Mukaiyama aldol type reactions of 2-silyloxyfurans.<sup>1,2</sup> A catalytic asymmetric version of Michael addition reactions using 2-silyloxyfurans has been reported by use of chiral Lewis acids<sup>3</sup> and organocatalysts.<sup>4</sup> Diastereoselective Mukaiyama aldol and Mannich type reactions of 2-silyloxy pyrroles or 2-silyloxythiophenes with chiral aldehydes or imines were also explored and applied for asymmetric syntheses of several natural products.<sup>1,5</sup> For catalytic asymmetric Mukaiyama aldol reaction of a

2-silyloxypyrrole, the reaction with tridecanal using the catalyst prepared from  $\text{Ti}(\text{O}i\text{-Pr})_4$  and (*R*)-BINOL (1:2) was reported with moderate yield (52%) and enantioselectivity (68% ee).<sup>6</sup> However, Lewis acid-catalyzed Michael addition reactions of 2-silyloxypyrroles have not been well studied probably due to the complexity arose from the equilibrium between addition and retro processes and also from competing Friedel-Craft type process. Furthermore, to the best of our knowledge, there are no examples of enantioselective Michael addition reactions of 2-silyloxypyrroles catalyzed by a chiral Lewis acid. The enantioselective version of the Michael addition reactions of 2-silyloxypyrroles will open a novel route to asymmetric synthesis of biologically important pyrrolizidine derivatives such as pyrrolizidine alkaloides,<sup>7</sup> which are found as a number of natural products, for examples, turneforcidine, platynecine, retronecine, and indicine (Figure 1), by ring-closure of a side chain introduced by the Michael addition (Scheme 1).



**Figure 1.** Natural products containing pyrrolizidine skeletons

**Scheme 1.** A route to synthesis of pyrrolizidine skeletons via Michael additions of 2-silyloxypyrroles



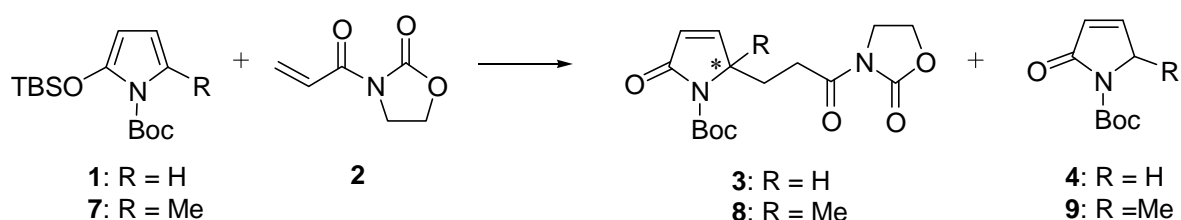
In this paper, we report that  $\text{Sc}(\text{OTf})_3$  (10 mol%) was found to be the most favorable Lewis acid among the Lewis acids tested in the Michael addition reactions of *N*-Boc-2-(*tert*-butyldimethylsilyloxy)pyrrole (**1**) to 3-acryloyl-2-oxazolidinone (**2**). For an asymmetric version of the reaction, the chiral Sc(III) catalyst (10 mol%), which was prepared from 2,6-bis[(4*S*)-4-isopropyl-2-oxazolin-2-yl]pyridine ((*S,S*)-Pybox-Pr') and  $\text{Sc}(\text{OTf})_3$ , was found to show good enantioselectivity (up to 82% ee).

## RESULTS AND DISCUSSION

A Michael addition reaction of *N*-Boc-2-silyloxypyrrole **1** to acryloyloxazolidinone **2** in the presence of

several achiral Lewis acids was first investigated by using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a protonating agent (Scheme 2, Table 1). The reaction was carried out by stirring silyloxypyrrole **1** (1.2 equiv) and oxazolidinone **2** in the presence of the corresponding Lewis acid (10 mol%) and HFIP (1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> at room temperature. Only 3% yield of Michael adduct **3** was obtained when Et<sub>2</sub>AlCl was used as a Lewis acid (entry 1). The use of Mg(OTf)<sub>2</sub> or Cu(OTf)<sub>2</sub> did not give any Michael adduct and resulted in a complex mixture (entries 3 and 4). The reaction utilizing 10 mol% of ZnCl<sub>2</sub> hardly proceeded and a stoichiometric amount of ZnCl<sub>2</sub> was needed to afford 47% yield of the desired adduct **3** (entry 2). Under the ZnCl<sub>2</sub>-catalyzed conditions, a significant amount of desilylated by-product **4** was also produced. Lanthanoid triflates seemed to show relatively good catalytic activity among the Lewis acids tested (entries 5, 7, and 8). However, the yield of **3** was modest with production of by-product **4**. In the case of using Sc(OTf)<sub>3</sub> as a catalyst, the conditions at lower temperature (–25 °C) rather exhibited better result in terms of yield (entries 9 vs 10). The amount of HFIP was investigated whether that influence the yields of adduct **3** and by-product **4** using Sc(OTf)<sub>3</sub> as a catalyst.<sup>9</sup> Surprisingly, in the absence of HFIP, the yield of desilylated by-product **4** was increased with decreasing the amount of Michael adduct **3** (entry 11). The yield of product **3** was improved when the amount of HFIP was increased from 1 equiv. to 2 – 3 equiv. (entries 10, 12 and 13). The reaction in the presence of 4 – 5 equiv. of HFIP showed almost similar yield of **3** (entries 14 and 15). Further increasing the amount of HFIP did not give better result in terms of yield. These results indicated that the Michael addition reaction is probably in equilibrium with its retro process, and smooth protonation and desilylation are needed to produce the desired adduct **3** efficiently (Scheme 3). By-product **4** may be produced not only from simple desilylation of silyloxypyrrole **1** but also from the retro process (Scheme 3). A slow addition of **1**, by which preventing direct desilylation of **1** and efficient protonation of the Michael adduct presumably occurred, was next examined to expect improvement of the yield. The slow addition of **1** in a period of over 1 h to oxazolidinone **2** greatly increased the yield up to 80% (entries 16 – 18).

**Scheme 2.** Michael addition reactions of 2-silyloxyfurans to 3-acryloyl-2-oxazolidinone (**2**)



**Table 1.** Michael addition reaction of silyloxypyrrole **1** to oxazolidinone **2** in the presence of achiral Lewis Acids<sup>a</sup>

Entry	Lewis acid	Temp.	HFIP (equiv)	Addition time (h) <sup>c</sup>	Time (h) <sup>b</sup>	Yield (%) <sup>d</sup>	
						<b>3</b>	<b>4</b>
1	Et <sub>2</sub> AlCl	rt	1	< 1 min <sup>f</sup>	24	3	6
2	ZnCl <sub>2</sub> <sup>g</sup>	rt	1	< 1 min <sup>f</sup>	6	47	22
3	Mg(OTf) <sub>2</sub>	rt	1	< 1 min <sup>f</sup>	60	0	0
4	Cu(OTf) <sub>2</sub>	rt	1	< 1 min <sup>f</sup>	60	0	0
5	Yb(OTf) <sub>3</sub>	rt	1	< 1 min <sup>f</sup>	3	36	16
6	Yb(OTf) <sub>3</sub>	-25	5	1	50	61	8
7	La(OTf) <sub>3</sub>	rt	1	< 1 min <sup>f</sup>	3	36	22
8	Sm(OTf) <sub>3</sub>	rt	1	< 1 min <sup>f</sup>	3	36	14
9	Sc(OTf) <sub>3</sub>	rt	1	< 1 min <sup>f</sup>	1	7	9
10	Sc(OTf) <sub>3</sub>	-25	1	< 1 min <sup>f</sup>	24	31	36
11	Sc(OTf) <sub>3</sub>	-25	0	< 1 min <sup>f</sup>	15	14	45
12	Sc(OTf) <sub>3</sub>	-25	2	< 1 min <sup>f</sup>	15	43	3
13	Sc(OTf) <sub>3</sub>	-25	3	< 1 min <sup>f</sup>	12	56	3
14	Sc(OTf) <sub>3</sub>	-25	4	< 1 min <sup>f</sup>	12	55	3
15	Sc(OTf) <sub>3</sub>	-25	5	< 1 min <sup>f</sup>	1	58	21
16	Sc(OTf) <sub>3</sub>	-25	5	1	1	77	11
17	Sc(OTf) <sub>3</sub>	-25	5	3	18	78	13
18	Sc(OTf) <sub>3</sub>	-25	5	6	12	80	9

<sup>a</sup> The reaction was carried out by adding a solution of silyloxypyrrole **1** (1.2 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> to a solution of Lewis acid (10 mol%), oxazolidinone **2**, and HFIP in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> Stirring time after addition of silyloxypyrrole **1**. <sup>c</sup> Addition time of silyloxypyrrole **1**. <sup>d</sup> Based on oxazolidinone **2**. <sup>e</sup> Based on silyloxypyrrole **1**. <sup>f</sup> A solution of silyloxypyrrole **1** in CH<sub>2</sub>Cl<sub>2</sub> was added without slow addition. <sup>g</sup> One equiv. of ZnCl<sub>2</sub> was used.

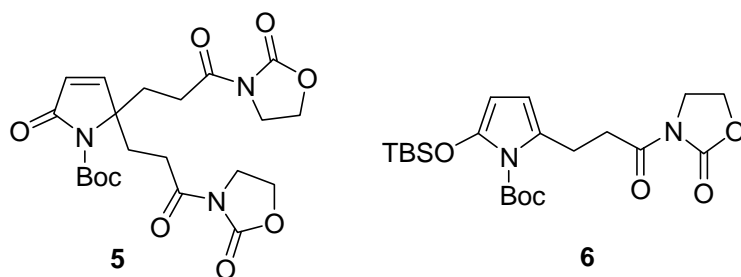
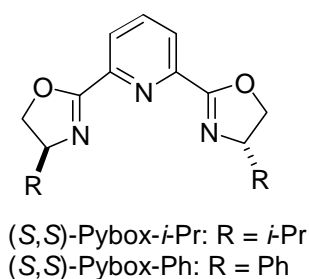
Subsequently, asymmetric induction in the reaction of silyloxyfuran **1** with oxazolidinone **2** was investigated by using the complexes of chiral Pyboxs (Figure 2) and Sc(OTf)<sub>3</sub> or Yb(OTf)<sub>3</sub> as chiral Lewis acid catalysts (Table 2). In the reaction using Yb(OTf)<sub>3</sub> as a metal triflate in conjunction with chiral (*S,S*)-Pybox-*i*-Pr or (*S,S*)-Pybox-Ph at -25 °C under the similar conditions described above, the

corresponding Michael adduct **3** was obtained in low yield with low to moderate enantioselectivity (entries 1 and 2). In the case of utilizing Sc(OTf)<sub>3</sub> as metal triflate in combination with both chiral Pybox-*i*-Pr or Pybox-Ph as catalysts under the similar conditions, Michael adduct **3** was afforded in moderate yield with much better or promising enantioselectivity, respectively (entries 3 and 8). To our surprise, when the reaction was quenched immediately after the addition of silyloxypyrrole **1** without continuous stirring both at -10 °C and -25 °C, the yield was considerably decreased (entries 4 and 5). It must be noted that decreased yield of desired Michael adduct **3** was caused not only by production of desilylated compound **4** (both 27% yield at -10 °C and -25 °C) but also by formation of another by-product **5** (54% yield at -10 °C and 66% yield at -25 °C) which was presumed to produce from pyrrole **1** and oxazolidinone **2** in a 1 : 2 ratio by an elemental analysis (Figure 3 and Scheme 3). The <sup>1</sup>H and <sup>13</sup>C NMR spectra showed that product **5** possessed one *N*-Boc pyrrolidinone moiety and two oxazolidinone moieties which were symmetrically arranged each other. From these analyses, compound **5** was determined to have a structure that two oxazolidinone moieties were connected with side chains at 5-position of pyrrolidinone. Under these conditions, the enantiomeric excess of Michael adduct **3** was also dramatically decreased compared with entry 8. However, under the conditions that the stirring was continued for 1 to 48 h after addition of silyloxypyrrole **1**, the yield of Michael adduct **3** was increased with relatively good to high enantioselectivity (72 – 82% ee), and also with considerably decreasing formation of by-product **5** (entries 6 – 9). The yield (5 – 14%) of desilylated product **4** was also minimized under these conditions. Extending addition time of silyloxypyrrole **1** to 6 h showed a similar result in terms of enantioselectivity (79% ee) with slightly decreased yield of the adduct **3**. A survey of reaction solvents (entries 11 – 14) resulted that dichloromethane (up to 82% ee) and toluene (80% ee) were favorable in terms of enantioselectivity. Among examinations under several other conditions, a small amount of silyloxypyrrole derivative **6** (Figure 3) was also obtained in the cases such as in the presence of 8 equiv of HFIP. Pyrrole **6** was only characterized by <sup>1</sup>H NMR and immediately decomposed on standing to give Michael adduct **3** as a racemate. Considering from these results, the Michael addition step is still reversible under above conditions, in spite of adding silyloxypyrrole **1** over a period of 1 h. Under the influence of the (*S,S*)-Pybox-Pr<sup>*i*</sup>-Sc(III) complex in the presence of HFIP, the reaction mixture probably achieved in equilibrium, and the Michael adduct **3** was obtained in 60 – 70% yield with about 80% ee. By-product **6** was presumably produced by aromatization to pyrrole without desilylation after Michael addition of silyloxypyrrole **1** to oxazolidinone **2** (Scheme 3).

**Table 2.** Asymmetric Michael addition reaction of silyloxypyrrole **1** to oxazolidinone **2** catalyzed by Pybox-rare earth metal triflate<sup>a</sup>

entry	Pybox	M(OTf) <sub>3</sub>	Solvent	temp (°C)	Addition time (h)	time (h) <sup>b</sup>	Yield (%)	ee (%) <sup>c</sup>
1	Pybox-Ph	Yb(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	1	24	13 (ND <sup>e</sup> ) <sup>d</sup>	-45
2	Pybox- <i>i</i> -Pr	Yb(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	1	24	30 (ND <sup>e</sup> ) <sup>d</sup>	27
3	Pybox-Ph	Sc(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	1	24	69 (ND <sup>e</sup> ) <sup>d</sup>	64
4	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-10	1	0	12 (54) <sup>d</sup>	0
5	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	1	0	25 (66) <sup>d</sup>	38
6	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	1	1	68 (10) <sup>d</sup>	72
7	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	1	3	70 (5) <sup>d</sup>	82
8	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	1	24	61 (9) <sup>d</sup>	80
9	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	1	48	60 (6) <sup>d</sup>	78
10	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	-25	6	60	42 (ND <sup>e</sup> ) <sup>d</sup>	79
11	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	CHCl <sub>3</sub>	-25	1	12	39 (62) <sup>d</sup>	68
12	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	Toluene	-25	1	15	66 (15) <sup>d</sup>	80
13	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	THF	-25	1	90	4 (13) <sup>d</sup>	ND
14	Pybox- <i>i</i> -Pr	Sc(OTf) <sub>3</sub>	MeCN	-25	1	90	44 (5) <sup>d</sup>	46

<sup>a</sup> The reaction was carried out by adding a solution of silyloxypyrrole **1** in CH<sub>2</sub>Cl<sub>2</sub> over a period of the time cited in the table to a suspension of the Pybox-Sc(OTf)<sub>3</sub> complex (10 mol %), oxazolidinone **2**, HFIP (5 equiv), and 4Å molecular sieves in CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup> Stirring time after addition of silyloxypyrrole **1**. <sup>c</sup> Determined by HPLC analysis (Daicel Chiralpak AD-H). <sup>d</sup> Yield of adduct **5** was shown in a parenthesis. <sup>e</sup> Not determined.

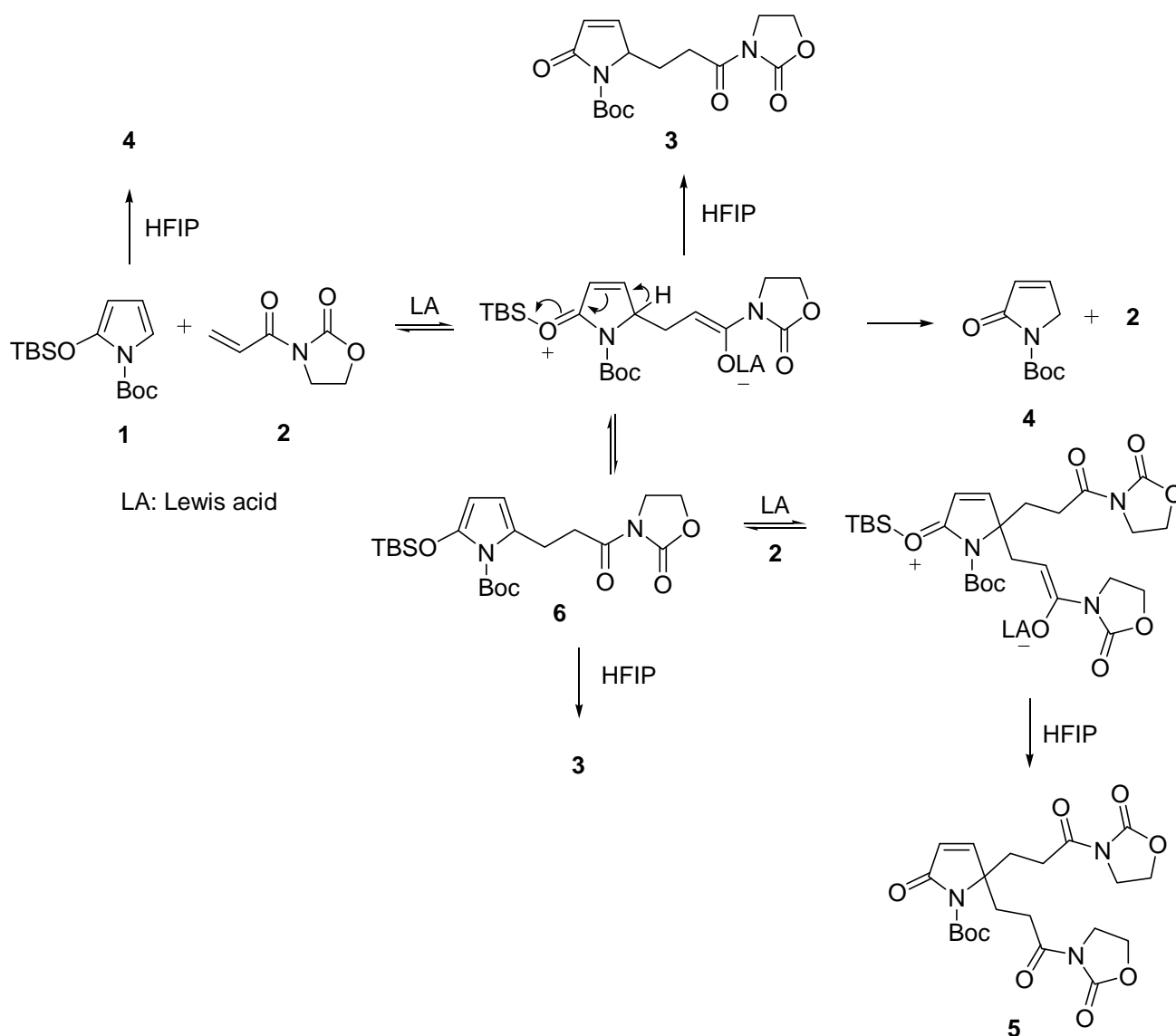


**Figure 2.** Structures of Pyboxs

**Figure 3.** Structures of by-products **5** and **6**

To obtain more mechanistic informations for production of 1 : 2 adduct, a reaction of *N*-Boc-2-(*tert*-butyldimethylsilyloxy)-5-methylpyrrole (**7**) with oxazolidinone **2** was investigated under the similar conditions using (*S,S*)-Pybox-*i*-Pr-Sc(OTf)<sub>3</sub> complex as a catalyst. In this case, reacting at room temperature for 24 h after stirring at -10 °C for 15 h was needed to complete the reaction. The desired Michael adduct **8** was obtained in 73% yield with moderate enantioselectivity (40% ee) along with **9** (35% yield based on **7**) (Scheme 2). In contrast to the reaction of silyloxypyrrole **7**, in the case of using silyloxypyrrole **1** without a substituent at 5-position, by-product **5** was probably obtained from pyrrole **6**, which underwent Michael addition reaction with oxazolidinone **2** (Scheme 3).

**Scheme 3.** Proposed mechanism for the formation of compounds **3**, **4**, **5** and **6**



In conclusion, we have found that Sc(OTf)<sub>3</sub> is an efficient catalyst for promoting Michael addition reaction of *N*-Boc-2-(*tert*-butyldimethylsilyloxy)pyrrole (**1**) to 3-acryloyl-2-oxazolidinone (**2**), after a

survey of several Lewis acids. The conditions with slow addition of silyloxypyrrole **1** in the presence of HFIP (5 equiv.) at  $-25\text{ }^{\circ}\text{C}$  were desirable to obtain good yield (77 – 80%), probably due to a competing retro Michael addition process. A relatively good level of asymmetric induction (up to 82 % ee) was also observed when the Michael addition reaction was carried out by using the chiral Sc(III) catalyst (10 mol%), which was prepared from (*S,S*)-Pybox-*i*-Pr and Sc(OTf)<sub>3</sub>, in reasonable yield (60 – 70%).

## EXPERIMENTAL

Melting points are uncorrected. IR spectra were taken with FT/IR spectrophotometer. <sup>1</sup>H NMR spectra were run at 400 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. <sup>13</sup>C NMR spectra were recorded at 100 MHz using broadband proton decoupling. Chemical shifts are expressed in parts per million downfield from tetramethylsilane, using the middle resonance of CDCl<sub>3</sub> (77.0 ppm) as an internal standard. For preparative column chromatography, Wakogel C-300HG was employed. Medium-pressure liquid chromatography was carried out using a column packed with Wakogel C-300HG. All reactions were carried out under an argon atmosphere in dried glassware.

Rare earth metal triflates utilized for the reaction were individually dried in a schlenk tube at 200 °C in vacuo for 12 h before use. Powdered 4Å molecular sieves was commercially available and dried in vacuo at 250 °C for 12 h before use. Dichloromethane was purified by distillation first from CaCl<sub>2</sub> and then CaH<sub>2</sub> under argon. Toluene and THF were freshly distilled from a sodium benzophenone still under argon. Acetonitrile (anhydrous) was commercially available, and used without further purification. Silyloxypyrroles **1** and **7** were prepared according to the procedure reported by Cashiraghi.<sup>1a</sup> 3-Acryloyl-2-oxazolidinone (**2**) was prepared according to the procedure in the literature.<sup>8</sup>

### **General procedure in the presence of an achiral Lewis acid was exemplified by the reaction of silyloxypyrrole 1 with oxazolidinone 2 using Sc(OTf)<sub>3</sub>.**

To a solution of Sc(OTf)<sub>3</sub> (24.6 mg, 0.05 mmol), 3-acryloyl-2-oxazolidinone (**2**) (70.0 mg, 0.50 mmol), and HFIP (0.25 mL, 2.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at  $-25\text{ }^{\circ}\text{C}$ , was added a solution of *N*-Boc-2-(*t*-butyldimethylsilyl)oxypyrrole (**1**) (178 mg, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) over a period of 6 h. Stirring was continued at  $-25\text{ }^{\circ}\text{C}$  for 12 h, and then the mixture was quenched with water (5 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL x 3), and then the combined organic layer was dried over MgSO<sub>4</sub>. After evaporation of solvent, the residue was chromatographed over silica gel with hexane-EtOAc (3 : 2, vol/vol) as eluent to give adduct **3** (130 mg, 80%).

### **General procedure in the presence of a chiral Lewis acid was exemplified by the reaction of silyloxypyrrole 1 with oxazolidinone 2 using (*S,S*)-Pybox-*i*-Pr-Sc(OTf)<sub>3</sub> complex.**



A solution of 2,6-bis[(4*S*)-(-)-4-isopropyl-2-oxazolin-2-yl]pyridine (15.1 mg, 0.05 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added to a suspension of Sc(OTf)<sub>3</sub> (24.6 mg, 0.05 mmol) and powdered 4 Å molecular sieves (MS 4A, 0.50 g) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL). After stirring the mixture for 2 h, a solution of oxazolidinone **2** (70.0 mg, 0.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and HFIP (0.25 mL, 2.50 mmol) were successively added. The mixture was cooled to -25 °C, and then a solution of pyrrole **1** (178 mg, 0.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added over a period of 1 h. The stirring was continued at same temperature for 3 h and water (5 mL) was added to the mixture. After removal of MS 4A through celite, the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL x 3). The combined extracts were dried over MgSO<sub>4</sub> and the solvent was removed in vacuo. The residue was chromatographed over silica gel with hexane-EtOAc (3 : 2, vol/vol) as eluent to give adduct **3** (113 mg, 70%). The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane-2-PrOH (2 : 1 vol/vol), detector: UV 254 nm, Flow rate = 0.5 mL/min, 35 °C).  $t_{major} = 14.4$  min,  $t_{minor} = 18.4$  min.

#### ***N*-Boc-5-[(2-oxazolidinoyl)-1-propanoyl]pyrrolin-2-one (3)**

Colorless needles, mp 144-146 °C (CH<sub>2</sub>Cl<sub>2</sub>-hexane);  $[\alpha]_D^{26} +145.5$  ° (*c* 1.0, CHCl<sub>3</sub>, 83% ee); IR (KBr) 2982, 2934, 1763, 1697, 1477, 1460, 1365, 1331, 1300, 1197, 1167, 1118, 1039, 1020, 989, 962, 844, 808, 783, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.56 (9H, s), 2.33 (2H, m), 2.75-3.01 (2H, m), 4.03 (2H, m), 4.42 (2H, m), 5.30 (1H, m), 6.12 (1H, dd, *J* = 1.7, 6.1 Hz), 7.16 (1H, dd, *J* = 2.0, 6.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 26.0 (CH<sub>2</sub>), 28.0 (CH<sub>3</sub>), 29.3 (CH<sub>2</sub>), 42.5 (CH<sub>2</sub>), 62.1 (CH), 62.2 (CH<sub>2</sub>), 82.9 (C), 126.7 (CH), 148.9 (C), 149.5 (CH), 149.5 (C), 153.1 (C), 171.7 (C); HRMS (EI) Calcd for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub> (M<sup>+</sup>): 324.1320. Found: 324.1322. Anal. Calcd for C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>: C, 55.55; H, 6.22; N, 8.64 %. Found: C, 55.73; H, 6.29; N, 8.39 %.

#### ***N*-Boc-5,5-bis[(2-oxazolidinoyl)-1-propanoyl]pyrrolin-2-one (5)**

The chromatography was carried out over silica gel with EtOAc as eluent. Colorless prisms, mp 153-155 °C (CH<sub>2</sub>Cl<sub>2</sub>-hexane); IR (KBr) 4415, 3530, 3364, 3099, 2982, 2932, 1778, 1689, 1612, 1477, 1435, 1392, 1367, 1323, 1292, 1255, 1230, 1205, 1157, 1107, 1039, 960, 841, 808, 792, 752, 704, 636, 603, 576, 461, 407 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.59 (9H, s), 2.07-2.25 (2H, m), 2.62-2.82 (6H, m), 3.89-4.86 (4H, m), 4.32-4.50 (4H, m), 6.12 (1H, d, *J* = 6.1 Hz), 6.96 (1H, d, *J* = 6.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 28.2 (CH<sub>3</sub>), 29.2 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 42.6 (CH<sub>2</sub>), 62.1 (CH<sub>2</sub>), 70.2 (C), 83.5 (C), 126.2 (CH), 148.8 (C), 153.0 (C), 153.5 (CH), 168.9 (C), 171.8 (C). Anal. Calcd for C<sub>21</sub>H<sub>27</sub>N<sub>3</sub>O<sub>9</sub>: C, 54.19; H, 5.85; N, 9.03%. Found: C, 54.28; H, 5.91; N, 8.88%.

#### ***N*-Boc-2-(*t*-Butyldimethylsilyloxy)-5-[(2-oxazolidinoyl)-1-propanoyl]pyrrole (6)**

The chromatography was carried out over silica gel with hexane-EtOAc (4 : 1, vol/vol) as eluent. Pale

yellow oil,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.22 (6H, s), 0.97 (9H, s), 1.58 (9H, s), 2.95-3.28 (4H, m), 4.01 (2H, t,  $J = 7.8$  Hz), 4.40 (2H, t,  $J = 7.8$  Hz), 5.10 (1H, d,  $J = 3.4$  Hz), 5.69 (1H, d,  $J = 3.4$  Hz).

#### ***N*-Boc-5-[(2-oxazolidinoyl)-1-propanoyl]-5-methylpyrrolin-2-one (8)**

The chromatography was carried out over silica gel with EtOAc as eluent. Colorless powder, mp 117-119 °C ( $\text{CH}_2\text{Cl}_2$ -hexane);  $[\alpha]_{\text{D}}^{25} = +24.4^\circ$  ( $c$  0.27,  $\text{CHCl}_3$ , 40%ee); IR (KBr) 3520, 3383, 3092, 2978, 2935, 2876, 1772, 1699, 1493, 1460, 1433, 1392, 1367, 1325, 1288, 1255, 1228, 1201, 1157, 1107, 1039, 966, 837, 763, 756, 721, 700, 634  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.57 (3H, s), 1.58 (9H, s), 2.05-2.18 (1H, m), 2.60-2.77 (3H, m), 3.92-4.04 (2H, m), 4.33-4.47 (2H, m), 6.05 (1H, d,  $J = 5.9$  Hz), 7.00 (1H, d,  $J = 5.9$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.99 ( $\text{CH}_3$ ), 29.62 ( $\text{CH}_2$ ), 28.24 ( $\text{CH}_3$ ), 30.87 ( $\text{CH}_2$ ), 42.61 ( $\text{CH}_2$ ), 62.07 ( $\text{CH}_2$ ), 67.69 (C), 83.06 (C), 124.7 (CH), 149.05 (C), 153.03 (CH), 155.7 (C), 168.93 (C), 171.91 (C); HRMS (EI) Calcd for  $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_6$  ( $\text{M}^+$ ): 338.1476. Found: 338.1504. Anal. Calcd for  $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_6$ : C, 56.80; H, 6.55; N, 8.28%. Found: C, 57.34; H, 6.75; N, 7.54%.

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#### **REFERENCES**

1. For a review, see: (a) G. Casiraghi and G. Rassu, *Synthesis*, 1995, 607. (b) G. Casiraghi and F. Zanardi, *Chem. Rev.*, 2000, **100**, 1929.
2. (a) D. A. Evans, C. S. Burgey, M. C. Kozlowski, and S. W. Tregay, *J. Am. Chem. Soc.*, 1999, **121**, 686. (b) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, and R. J. Staples, *J. Am. Chem. Soc.*, 1999, **121**, 669. (c) M. Szlosek, X. Franck, B. Figadère, and A. Cavé, *J. Org. Chem.*, 1998, **63**, 5169. (d) M. Szlosek and B. Figadère, *Angew. Chem. Int. Ed.*, 2000, **39**, 1799. (e) Y. Matsuoka, R. Irie, and T. Katsuki, *Chem. Lett.*, 2003, **32**, 584. (f) S. Onitsuka, Y. Matsuoka, R. Irie, and T. Katsuki, *Chem. Lett.*, 2003, **32**, 974.
3. (a) H. Kitajima and T. Katsuki, *Synlett*, 1997, 568. (b) H. Kitajima, K. Ito, and T. Katsuki, *Tetrahedron*, 1997, **53**, 17015. (c) G. Desimoni, G. Faita, S. Filippone, M. Mella, M. G. Zampori, and M. Zema, *Tetrahedron*, 2001, **57**, 10203. (d) H. Suga, T. Kitamura, A. Kakehi, and T. Baba, *Chem. Commun.*, 2004, 1414.
4. S. P. Brown, N. C. Goodwin, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 1192.
5. (a) F. Zanardi, L. Battistini, G. Rassu, M. Cornia, and G. Casiraghi, *J. Chem. Soc., Perkin Trans. 1*, 1995, **19**, 2471. (b) P. Spanu, G. Rassu, F. Ulgheri, F. Zanardi, L. Battistini, and G. Casiraghi, *Tetrahedron*, 1996, **52**, 4829. (c) F. Zanardi, L. Battistini, M. Nespi, G. Rassu, P. Spanu, M. Cornia,

- and G. Casiraghi, *Tetrahedron: Asymmetry*, 1996, **7**, 1167. (d) P. Soro, G. Rasso, P. Spanu, L. Pinna, F. Zanardi, and G. Casiraghi, *J. Org. Chem.*, 1996, **61**, 5172. (e) G. Rasso, L. Pinna, P. Spanu, F. Zanardi, L. Battistini, and G. Casiraghi, *J. Org. Chem.*, 1997, **62**, 4513. (f) P. Spanu, G. Rasso, L. Pinna, L. Battistini, and G. Casiraghi, *Tetrahedron: Asymmetry*, 1997, **8**, 3237. (g) G. Rasso, P. Carta, L. Pinna, L. Battistini, F. Zanardi, D. Acquotti, and G. Casiraghi, *Eur. J. Org. Chem.*, 1999, **6**, 1395. (h) H. Uno, Y. Nishihara, N. Mizobe, and N. Ono, *Bull. Chem. Soc. Jpn.*, 1999, **72**, 1533. (i) G. Rasso, L. Auzzas, L. Pinna, F. Zanardi, L. Battistini, and G. Casiraghi, *Org. Lett.*, 1999, **1**, 1213. (j) G. Rasso, L. Auzzas, L. Pinna, L. Battistini, F. Zanardi, L. Marzocchi, D. Acquotti, and G. Casiraghi, *J. Org. Chem.*, 2000, **65**, 6307. (k) D. A. DeGoey, H.-J. Chen, W. J. Flosi, D. J. Grampovnik, C. M. Yeung, L. L. Klein, and D. J. Kempf, *J. Org. Chem.*, 2002, **67**, 5445. (l) D. M. Barnes, M. A. McLaughlin, T. Oie, M. W. Rasmussen, K. D. Stewart, and S. J. Wittenberger, *Org. Lett.*, 2002, **4**, 1427. (m) G. Rasso, L. Auzzas, L. Pinna, V. Zambrano, F. Zanardi, L. Battistini, L. Marzocchi, D. Acquotti, and G. Casiraghi, *J. Org. Chem.*, 2002, **67**, 5338. (n) G. Rasso, L. Auzzas, L. Pinna, V. Zambrano, F. Zanardi, L. Battistini, E. Gaetani, C. Curti, and G. Casiraghi, *J. Org. Chem.*, 2003, **68**, 5881. (o) D. M. Barnes, L. Bhagavatula, J. DeMattei, A. Gupta, D. R. Hill, S. Manna, M. A. McLaughlin, P. Nichols, R. Premchandran, M. W. Rasmussen, Z. Tian, and S. J. Wittenberger, *Tetrahedron Asymmetry*, 2003, **14**, 3541. (p) L. Battistini, C. Curti, F. Zanardi, G. Rasso, L. Auzzas, and G. Casiraghi, *J. Org. Chem.*, 2004, **69**, 2611. (q) C. Curti, F. Zanardi, L. Battistini, A. Sartori, G. Rasso, L. Auzzas, A. Roggio, L. Pinna, and G. Casiraghi, *J. Org. Chem.*, 2006, **71**, 225.
6. M. Pichon, J.-C. Jullian, B. Figadère, and A. Cavé, *Tetrahedron Lett.*, 1998, **39**, 1755.
7. (a) T. Hartmann and L. Witte, *Alkaloids: Chemical and Biological Perspectives*; ed. by S. W. Pelletier, Pergamon Press: New York, 1995; Chapter 4, pp. 155-233. (b) A. R. Mattocks, *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: London, 1986. (c) R. Pereda-Miranda, *Phytochemistry of Medicinal Plants*; ed. by J. T. Arnason, R. Mata, J. T. Romeo, Plenum Press: New York, 1995; Chapter 5, pp. 103-108. (d) J. R. Liddell, *Nat. Prod. Rep.*, 1999, **16**, 499 and references therein. (e) G. Casiraghi, F. Zanardi, G. Rasso, and L. Pinna, *Org. Prep. Proced. Int.*, 1996, **28**, 641 and references therein.
8. D. A. Evans, S. J. Miller, T. Lectka, and P. von Matt, *J. Am. Chem. Soc.*, 1999, **121**, 7559.
9. The effect of a small amount of alcohol as an additive in Mukaiyama aldol reactions was also reported. (a) Y. Yamashita, H. Ishitani, H. Shimizu, and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 3292. (b) Y. Shimada, Y. Matsuoka, R. Irie, and T. Katsuki, *Synlett*, 2004, 57.