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Lewis 酸催化下 3-烷基-2-吲哚烯与 α,β-不饱和 *N*-磺酰基亚胺的[2＋4]环化反应

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摘要 通过 Lewis 酸催化下 3-烷基-2-吲哚烯与 α,β-不饱和 *N*-磺酰基亚胺的[2＋4]环化反应, 以中等至良好的收率、极好的非对映选择性, 合成了具有潜在抗肿瘤活性的吲哚衍生哌啶类化合物. 该工作解决了 3-烷基-2-吲哚烯参与的[2＋4]环化反应中的挑战性问题, 丰富了 3-烷基-2-吲哚烯化学的研究内容. 此外, 该反应为高原子经济性合成含吲哚母核的哌啶衍生物提供了新方法.

关键词 3-烷基-2-吲哚烯; α,β-不饱和 *N*-磺酰基亚胺; [2＋4]环化反应; 吲哚衍生物

Lewis Acid-Catalyzed [2＋4] Cyclization of 3-Alkyl-2-vinylindoles with α,β-Unsaturated *N*-Sulfonyl Ketimines

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Abstract A Lewis acid-catalyzed [2＋4] cyclization of 3-alkyl-2-vinylindoles with α,β-unsaturated *N*-sulfonyl ketimines was established, and indole-containing piperidines with potential antitumor activity were synthesized in moderate to good yields (up to 95% yield) and generally excellent diastereoselectivities (up to＞95∶5 *dr*). This work has confronted the challenges in exploring the [2＋4] cyclization of 3-alkyl-2-vinylindoles, which will enrich the chemistry of 3-alkyl-2-vinylindoles. In addition, this approach provides an atom-economic method for the synthesis of indole-containing piperidines.

Keywords 3-alkyl-2-vinylindole; α,β-unsaturated *N*-sulfonyl ketimine; [2＋4] cyclization; indole derivative

1 Introduction

Indole skeleton exists in a number of natural products, bioactive molecules and materials,[1] leading to much attention with focuses on the synthesis of indole derivatives.[2] Design and development of reactions involving indole-based platform molecules is the most convenient approach to construct indole skeletons.[3] In recent years, vinylindoles,[4] including 3-vinylindoles,[5] 2-vinylindoles[6-9] and other vinylindoles,[10-11] have proven to be versatile platform molecules for the synthesis of indole derivatives. 3-Alkyl-2-vinylindoles belong to a class of highly reactive vinylindoles with multiple reactive sites, and have become important building blocks for constructing indole-based heterocycles.[6-8]

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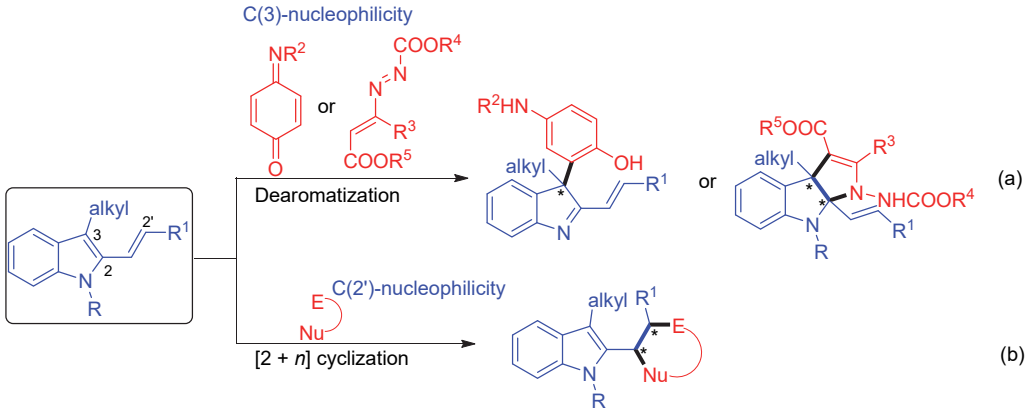
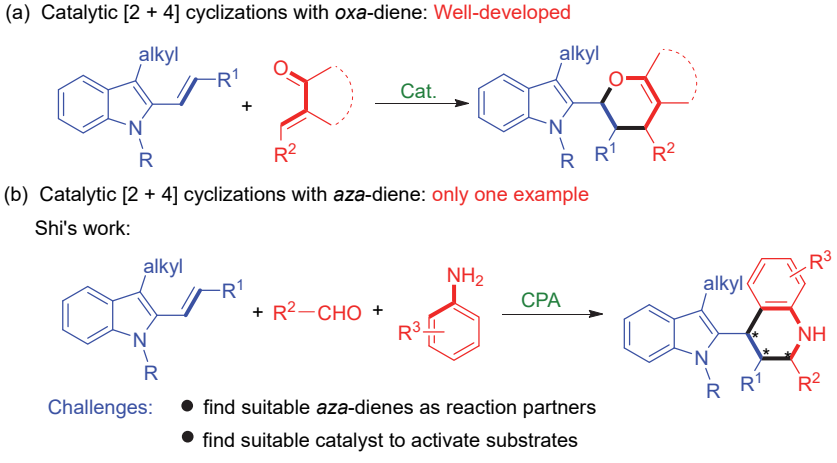
As shown in Scheme 1, 3-alkyl-2-vinylindoles could participate in two main types of reactions with different reaction partners. Namely, they can act as nucleophiles in catalytic C(3)-nucleophilicity dearomative substitution with quinone monoimides[6a] and cyclization with azoalkenes[6b] (Scheme 1, a). In addition, in most cases, they can act as mono-olefins in catalytic [2+*n*] cyclizations (Scheme1, b). Among these transformations, catalytic [2+*n*] cyclization of 3-alkyl-2-vinylindoles has proven to be a powerful reaction, which provides valuable access to diverse indole-containing heterocycles.[7-8]

Among catalytic [2+*n*] cyclizations of 3-alkyl-2-vinylindoles, catalytic [2+4] cyclizations of 3-alkyl-2-vinylindoles have attracted great interest from chemist due to their unique applications in the construction of indole-containing six-membered heterocyclic frameworks.[8] However, the reaction partners of most established catalytic [2+4] cyclizations of 3-alkyl-2-vinylindoles are *oxa*-dienes (Scheme 2, a).[8b-8e] By sharp contrast, catalytic [2+4] cyclizations of 3-alkyl-2-vinylindoles with *aza*-dienes has scarcely been reported. To date, there are only one example of catalytic [2+4] cyclizations of 3-alkyl-2-vinylindoles with *aza*-dienes. In 2015, Shi's group[8a] realized the organocatalytic asymmetric [2+4] cyclization of 3-alkyl-2-vinylindoles with aryl imines *in situ* generated from arylamines and aldehydes (Scheme 2, b). Despite this valuable example, the catalytic [2+4] cyclizations of 3-alkyl-2-vinylindoles with *aza*-dienes are rather limited and challenging. The challenges of this type reaction mainly include finding suitable azadienes as reaction partners and a suitable catalyst to activate the substrate. So, it is a great challenge to develop catalytic [2+4] cyclizations of 3-alkyl-2-vinylindoles with *aza*-dienes.

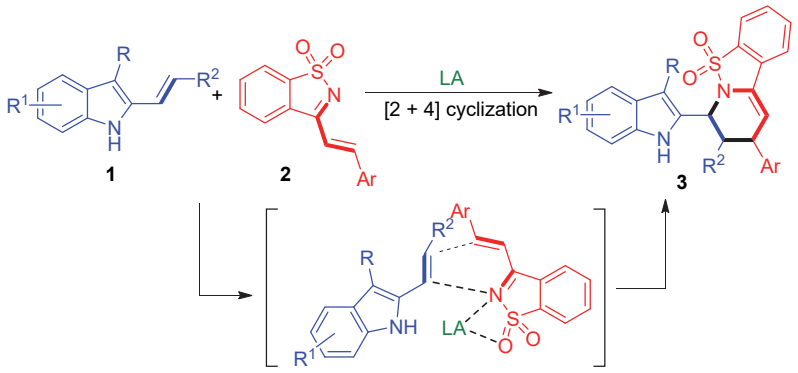
To solve the above challenges and based on our long-lasting efforts on indole chemistry,[12] we designed a Lewis acid (LA)-catalyzed [2+4] cyclizations of 3-alkyl-2-vinylindoles with *α*,*β*-unsaturated *N*-sulfonyl ketimines (Scheme 3). The *α*,*β*-unsaturated *N*-sulfonyl ketimines were selected as suitable reaction partners because of their high reactivity as *aza*-dienes in catalytic cyclizations.[13-15] The selection of LA as a suitable catalyst is based on that LA can easily coordinate with the sulfonyl moiety and imine moiety of *α*,*β*-unsaturated *N*-sulfonyl ketimines, thus facilitating a regioselective [2+4] cyclization of 3-alkyl-2-vinylindoles **1** with *α*,*β*-unsaturated *N*-sulfonyl ketimines **2** to generate indole-containing piperidines **3**.



Scheme 1 Profile of catalytic reactions of 3-alkyl-2-vinylindoles



Scheme 2 Profile of [2+4] cyclizations of 3-alkyl-2-vinylindoles



Scheme 3 Design of LA-catalyzed [2+4] cyclization of 3-alkyl-2-vinylindoles with *α*,*β*-unsaturated *N*-sulfonyl ketimines

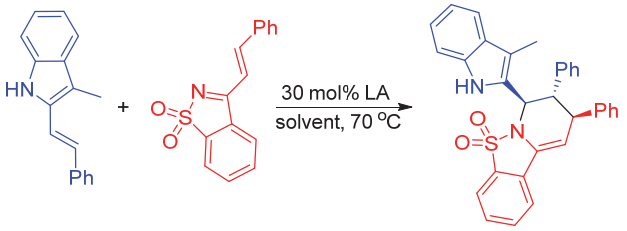
Herein, we report a Lewis acid-catalyzed [2+4] cyclization of 3-alkyl-2-vinylindoles with *α*,*β*-unsaturated *N*-sulfonyl ketimines, which afforded indole-containing piperidines in moderate to good yields (up to 95% yield) and generally excellent diastereoselectivities (up to>95∶5 *dr*).

2 Results and discussion

To test the feasibility of the designed LA-catalyzed [2+4] cyclization, the reaction of 3-alkyl-2-vinylindole **1a** with *α*,*β*-unsaturated *N*-sulfonyl ketimine **2a** in the presence of $Cu(OTf)_2$ was carried out at 70 ℃ in CH_3CN (Table 1, Entry 1). As expected, the desired [2+4] cyclization occurred to afford the indole-containing piperidine **3aa** with an excellent diastereoselectivity albeit in low yield (39% yield, >95∶5 *dr*). To improve the yield, a series of Lewis acids were screened (Entries 2～8). It was discovered that $Sc(OTf)_3$ was the best Lewis acid in terms of the yield (Entry 6). So, $Sc(OTf)_3$ was selected as the most suitable Lewis acid for this [2+4] cyclization. Then, the evaluation of representative solvents (Entries 9～13) showed that CH_3CN was still the best solvent.

Subsequently, other reaction conditions were further optimized (Table 2). As listed in Entries 1～3, the reaction temperature either increased or decreased, and it was discovered that 70 ℃ was still the best reaction temperature. Then, the molar ratio of the reactants (Entries 4～8) and the volume of solvent (Entries 9, 10) were modulated, however, the yield of the reaction did not increase further. Finally, when the catalyst loading was reduced from 30 mol% to 20

Table 1 Evaluation of catalysts and solvents[a]

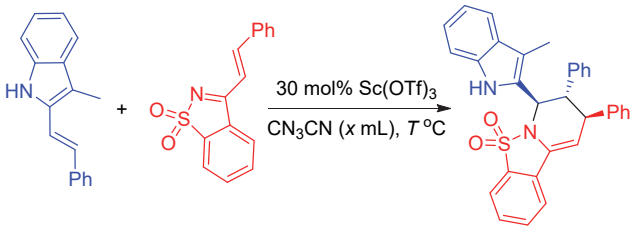


1a 2a (±)-3aa

Entry	LA	Solvent	*dr*[b]	Yield[c]/%
1	$Cu(OTf)_2$	CH_3CN	>95∶5	39
2	$Mg(OTf)_2$	CH_3CN	—	N.R.
3	$Fe(OTf)_3$	CH_3CN	>95∶5	57
4	$ZnCl_2$	CH_3CN	—	Trace
5	$Y(OTf)_3$	CH_3CN	—	Trace
6	$Sc(OTf)_3$	CH_3CN	>95∶5	76
7	$Yb(OTf)_3$	CH_3CN	—	Trace
8	$Zn(OTf)_2$	CH_3CN	—	N.R.
9	$Sc(OTf)_3$	DCE	83∶17	53
10	$Sc(OTf)_3$	THF	—	Trace
11	$Sc(OTf)_3$	Acetone	—	Trace
12	$Sc(OTf)_3$	AcOEt	>95∶5	56
13	$Sc(OTf)_3$	toluene	75∶25	21

[a] Unless indicated otherwise, the reaction was performed on a 0.1 mmol scale in a solvent (1 mL) in the presence of 30 mol% Lewis acid at 70 ℃ for 8 h, and the molar ratio of **1a**/**2a** was 1∶2. [b] *dr* values were determined by ^1H NMR. [c] Isolated yield of **3aa**. N.R.=no reaction.

Table 2 Further optimization of reaction conditions[a]



1a 2a (±)-3aa

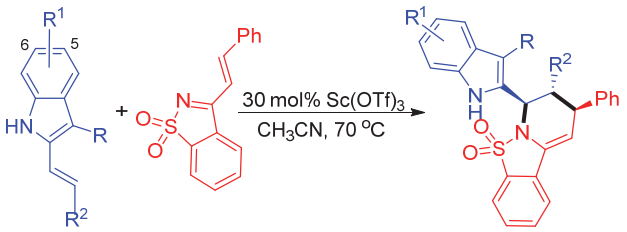
Entry	*T*/℃	*n*(**1a**)∶*n*(**2a**)	*x*	*dr*[b]	Yield[c]/%
1	70	1∶2	1	>95∶5	76
2	50	1∶2	1	>95∶5	22
3	90	1∶2	1	>95∶5	53
4	70	1∶1.5	1	>95∶5	22
5	70	1∶3	1	>95∶5	72
6	70	1.5∶1	1	>95∶5	55
7	70	2∶1	1	>95∶5	68
8	70	3∶1	1	>95∶5	62
9	70	1∶2	0.5	>95∶5	71
10	70	1∶2	2	>95∶5	70
11[d]	70	1∶2	1	>95∶5	68

[a] Unless indicated otherwise, the reaction was performed on a 0.1 mmol scale in CH_3CN in the presence of 30 mol% $Sc(OTf)_3$ for 8 h. [b] *dr* values were determined by ^1H NMR. [c] Isolated yield of **3aa**. [d] 20 mol% $Sc(OTf)_3$.

mol%, the indole-containing piperidine **3aa** could be generated with a decreased yield of 68% (Entry 11). Thus, the reaction conditions in Entry 1 was set as the optimal one.

After establishing the optimal reaction conditions, the investigation on the substrate scope of 3-alkyl-2-vinylindoles **1** by the reaction with *α*,*β*-unsaturated *N*-sulfonyl ketimine **2a** was carried out. As shown in Table 3, 3-alkyl-2-vinylindoles **1** bearing different R/R^1/R^2 groups could participate in this [2+4] cyclizations with *α*,*β*-unsaturated *N*-sulfonyl ketimine **2a** smoothly to afford indole-containing piperidine derivatives **3** in generally good yields (61% to 91%) with moderate to excellent diastereoselectivities (78∶22 *dr* to >95∶5 *dr*). In detail, 3-alkyl-2-vinylindoles **1b**～**1d** with different substituents at C(3)-position of the indole ring were employed for this reaction, delivering the target products **3ba**～**3da** (Entries 2～4). Moreover, this protocol was also applicable to substrates **1e**～**1g** bearing various R^1 substituents at C(5)- and C(6)-positions of the indole ring (Entries 5～7), affording indole-containing piperidines **3ea**～**3ga** in high yields (up to 91% yield) and good diastereoselectivities (up to >95∶5 *dr*). In addition, a series of *ortho*-, *meta*- and *para*-substituted phenyl groups were utilized as suitable R^2 groups for the 3-alkyl-2-vinylindoles **1** (Entries 8～14), delivering the corresponding products **3ha**～**3na** in moderate to good yields (61% to 89%) and diastereoselectivities (78∶22 *dr* to 93∶7 *dr*).

Table 3 Substrate scope of 3-alkyl-2-vinylindoles **1**[a]



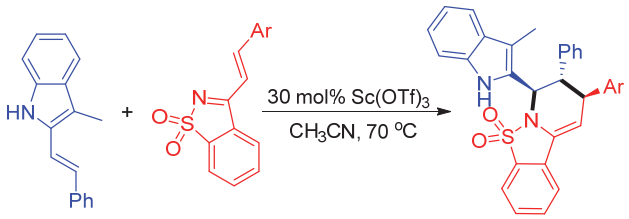
1 **2a** (±)-**3**

Entry	R/R^1/R^2 (**1**)	**3**	*dr*[b]	Yield[c]/%
1	Me/H/Ph (**1a**)	**3aa**	>95∶5	76
2	Et/H/Ph (**1b**)	**3ba**	>95∶5	64
3	Bn/H/Ph (**1c**)	**3ca**	78∶22	62
4	Ph/H/Ph (**1d**)	**3da**	85∶15	68
5	Me/5-Cl/Ph (**1e**)	**3ea**	>95∶5	86
6	Me/5-Me/Ph (**1f**)	**3fa**	88∶12	91
7	Me/6-Cl/Ph (**1g**)	**3ga**	>95∶5	87
8	Me/H/*o*-BrC$_6$H$_4$ (**1h**)	**3ha**	83∶17	62
9	Me/H/*o*-FC$_6$H$_4$ (**1i**)	**3ia**	91∶9	61
10	Me/H/*m*-MeOC$_6$H$_4$ (**1j**)	**3ja**	89∶11	89
11	Me/H/*m*-MeC$_6$H$_4$ (**1k**)	**3ka**	90∶10	78
12	Me/H/*m*-FC$_6$H$_4$ (**1l**)	**3la**	93∶7	65
13	Me/H/*m*-BrC$_6$H$_4$ (**1m**)	**3ma**	92∶8	70
14	Me/H/*p*-MeC$_6$H$_4$ (**1n**)	**3na**	78∶22	75

[a] Unless indicated otherwise, the reaction was performed on a 0.2 mmol scale in CH$_3$CN in the presence of 30 mol% Sc(OTf)$_3$ at 70 ℃ for 8 h, and the molar ratio of **1**/**2a** was 1∶2. [b] *dr* values were determined by ^{1}H NMR. [c] Isolated yield of **3**.

Next, the substrate scope with respect to *α*,*β*-unsaturated *N*-sulfonyl ketimines **2** was explored. As illustrated in Table 4, a series of *α*,*β*-unsaturated *N*-sulfonyl ketimines **2b**～**2h** bearing electronically different substituents at either *ortho*-, *meta*- or *para*-position of the phenyl ring could successfully participate in this reaction (Entries 2～8), producing the corresponding products **3ab**～**3ah** in moderate to good yields (62% to 95%) with overall excellent diastereoselectivities (88∶12 *dr* to >95∶5 *dr*). Notably, *α*,*β*-unsaturated *N*-sulfonyl ketimines **2i**～**2k** bearing 2-naphthyl group and heteroaryl groups could also successfully be utilized as reaction partners to give products **3ai**～**3ak** (Entries 9～11).

Table 4 Substrate scope of *α*,*β*-unsaturated *N*-sulfonyl ketimines **2**[a]

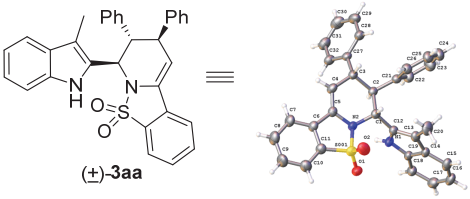


1a **2** (±)-**3**

Entry	Ar (**2**)	**3**	*dr*[b]	Yield[c]/%
1	C$_6$H$_5$ (**2a**)	**3aa**	>95∶5	76
2	*o*-MeOC$_6$H$_4$(**2b**)	**3ab**	93∶7	75
3	*o*-ClC$_6$H$_4$(**2c**)	**3ac**	>95∶5	62
4	*m*-MeOC$_6$H$_4$ (**2d**)	**3ad**	91∶9	76
5	*m*-MeC$_6$H$_4$ (**2e**)	**3ae**	>95∶5	62
6	*p*-MeOC$_6$H$_4$ (**2f**)	**3af**	88∶12	71
7	*p*-FC$_6$H$_4$ (**2g**)	**3ag**	>95∶5	89
8	*p*-ClC$_6$H$_4$ (**2h**)	**3ah**	>95∶5	95
9	2-Naphthyl (**2i**)	**3ai**	>95∶5	71
10	3-Thienyl (**2j**)	**3aj**	87∶13	80
11	5-Methyl-2-furyl (**2k**)	**3ak**	>95∶5	56

[a] Unless indicated otherwise, the reaction was performed on a 0.2 mmol scale in CH$_3$CN in the presence of 30 mol% Sc(OTf)$_3$ at 70 ℃ for 8 h, and the molar ratio of **1a**/**2** was 1∶2. [b] *dr* values were determined by ^{1}H NMR. [c] Isolated yield of **3**.

The structures of all products **3** were determined by ^{1}H NMR, ^{13}C NMR, IR and HRMS spectra. In addition, the structure of product **3aa** was confirmed by X-ray analysis of its single crystal (Scheme 4),[16] and the relative configuration of product **3aa** was also identified as (*trans*,*trans*) by X-ray analysis and nuclear overhauser effect (NOE) experiment.



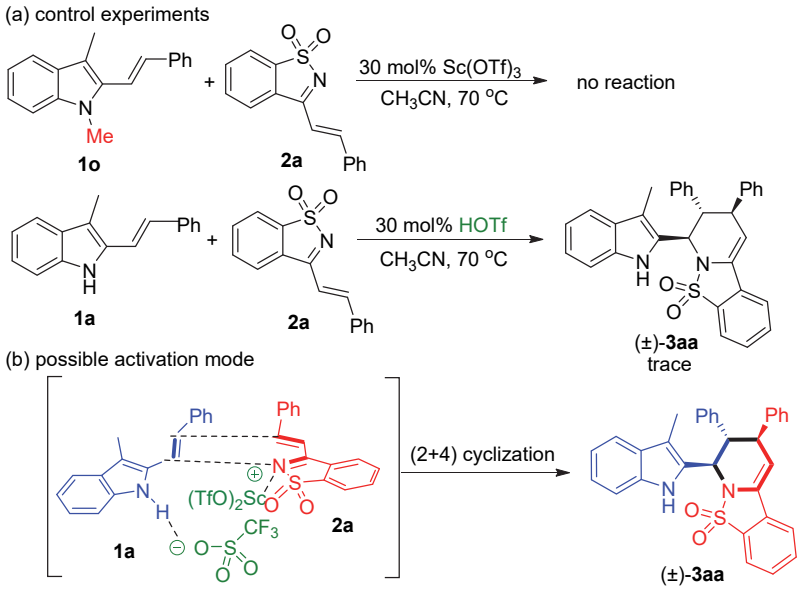
(±)-**3aa**

Scheme 4 X-ray single-crystal structure of **3aa**

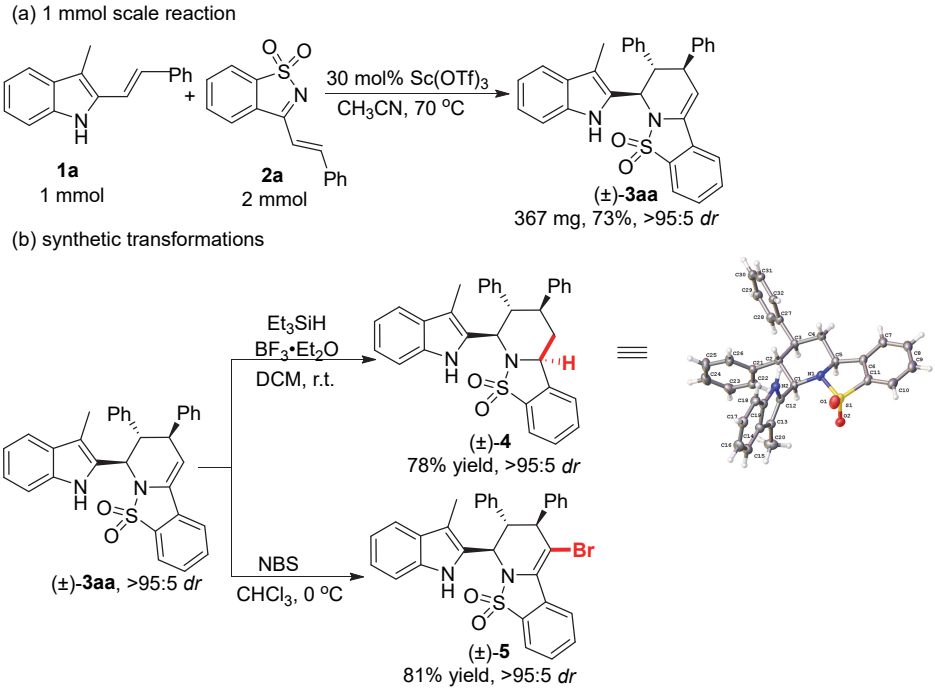
In order to get some clue on the reaction pathway and the activation mode of this LA-catalyzed [2+4] cyclization, several control experiments were performed under optimized reaction conditions (Scheme 5, a). First, *N*-methyl protected 3-alkyl-2-vinylindole **1o** was employed in the reaction instead of *N*-unprotected counterpart **1a**. No reaction occurred, which indicated that the NH group played a crucial role in this reaction. Considering that $Sc(OTf)_3$ can hydrolyze into HOTf in the presence of a trace of water in the reaction system, HOTf was employed as a catalyst under the standard conditions, and only trace amount of product **3aa** was detected. This phenomenon suggested that $Sc(OTf)_3$ was the real catalyst for this [2+4] cyclization.

Based on the results of the control experiments, a possible reaction pathway for this [2+4] cyclization is suggested (Scheme 5, b). The *α*,*β*-unsaturated *N*-sulfonyl ketimine **2a** is activated by the coordination interaction of scandium cation. On the other hand, the NH group of 3-alkyl-2-vinylindole **1a** forms a hydrogen bond with triflate anion. Then, a [2+4] cyclization occurs to give indole-containing piperidine **3aa** in an excellent diastereoselectivity.

To demonstrate the utility of the reaction, the catalytic [2+4] cyclizations of **1a** with **2a** was performed on a 1 mmol scale (Scheme 6, a). Compared with the small-scale reaction, this 1 mmol scale reaction smoothly afforded product **3aa** in a similar yield with a maintained excellent



Scheme 5 Control experiments and possible activation mode



Scheme 6 1 mmol scale reaction and synthetic transformations

diastereoselectivity (73% yield, >95 ∶ 5 *dr*). Moreover, indole-containing piperidines **3** have the potential to participate in synthetic transformations (Scheme 6, b). For example, enamine moiety of product **3aa** can be reduced in the presence of Et_3SiH/BF_3•Et_2O to give compound **4** in good yield and the relative configuration of newly generated stereocenter in product **4** was identified by X-ray analysis of its single crystal.[17] In addition, the bromination of product **3aa** can afford compound **5** in 81% yield.

More importantly, to find the possible bioactivities of indole-containing piperidines, the investigation on the cytotoxicity of some selected products **3** against human breast cancer cell line MCF-7 was performed. As shown in Figure 1, several products **3** exhibited some extent of cytotoxicity against MCF-7 cells and the IC_{50} value was ranging from 49.3 to 125.0 μg/mL. The evaluation results indicate that the indole-containing piperidines have potential antitumor activity, which might find their future applications in medicinal chemistry.

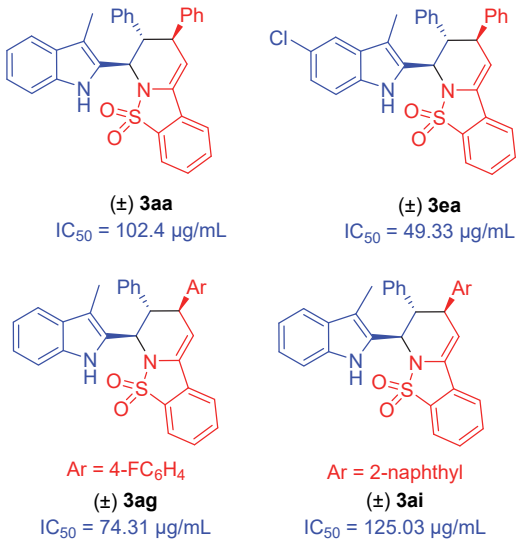


Figure 1 Investigation on the antitumor activity of indole-containing piperidines

3 Conclusions

In summary, a LA-catalyzed [2+4] cyclization of 3-alkyl-2-vinylindoles with *α*,*β*-unsaturated *N*-sulfonyl ketimines has been established, which afforded indole-containing piperidines with potential antitumor activity in moderate to good yields (up to 95% yield) and excellent diastereoselectivities (up to>95 ∶ 5 *dr*). This work can be performed in gram scale and the products can undergo synthetic transformations. What's more, this reaction has confronted the challenges in exploring the [2+4] cyclizations of 3-alkyl-2-vinylindoles, which will enrich the chemistry of 3-alkyl-2-vinylindoles. In addition, this approach provides an atom-economic method for the synthesis of indole-containing piperidines.

4 Experimental section

4.1 General information

^{1}H NMR and ^{13}C NMR spectra were measured at 400 and 100 MHz on NMR equipment (Bruker DPX 400 MHz), respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS (ESI) was determined by a HRMS/MS (Bruker microTOF-Q II) instrument. The the single crystal X-ray diffraction analysis of compounds **3aa** was carried on an X-ray detector (Bruker D8 Venture) with Mo Kα (λ=0.071073 nm) as X-ray source, and the thermal ellipsoid was drawn at the 30% probability level. Analytical grade solvents for the column chromatography were distilled before use. All starting materials commercially available were used directly. Substrates **1**[6] and **2**[3-4] were synthesized according to the literature methods.

4.2 General procedure for the synthesis of products 3

1 (0.2 mmol), **2** (0.4 mmol) and $Sc(OTf)_3$ (0.06 mmol) were added to a reaction tube. Then, CH_3CN (2 mL) was added to the reaction mixture, which was stirred at 70 ℃ for 8 h. After the completion of the reaction which was indicated by thin layer chromatography (TLC), the reaction mixture was directly purified through preparative thin layer chromatography on silica gel (petroleumether/ethyl acetate, *V* ∶ *V*=3 ∶ 1) to afford pure products **3**.

7-(3-Methyl-1*H*-indol-2-yl)-8,9-diphenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3aa**): White solid, 76.3 mg (76% yield), >95 ∶ 5 *dr*. m.p. 186～188 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.05 (s, 1H), 7.77～7.70 (m, 2H), 7.69～7.63 (m, 1H), 7.59～7.52 (m, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.25～7.21 (m, 1H), 7.21～7.14 (m, 3H), 7.13～7.06 (m, 1H), 7.04～6.94 (m, 6H), 6.90～6.81 (m, 2H), 5.93 (s, 1H), 5.28 (d, *J*=10.8 Hz, 1H), 4.09 (d, *J*=10.4 Hz, 1H), 3.52～3.38 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.1, 138.1, 136.8, 133.3, 133.2, 133.1, 130.1, 129.6, 128.7, 128.4, 128.1, 128.0, 127.6, 127.1, 127.0, 122.3, 121.2, 121.0, 119.1, 118.9, 113.4, 110.8, 106.5, 54.6, 53.9, 47.6, 8.5; IR (KBr) *v*: 3406, 3027, 1698, 1508, 1476, 1375, 741, 698, 616 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{25}N_2O_2S$ $[M-H]^-$ 501.1642, found 501.1621.

7-(3-Ethyl-1*H*-indol-2-yl)-8,9-diphenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ba**): White solid, 66.0 mg (64% yield), >95 ∶ 5 *dr*. m.p. 189～191 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06 (s, 1H), 7.75～7.69 (m, 2H), 7.67～7.61 (m, 1H), 7.56～7.50 (m, 1H), 7.42 (d, *J*=8.0 Hz, 1H), 7.26～7.24 (m, 1H), 7.21～7.16 (m, 3H), 7.13～7.07 (m, 1H), 7.05～6.95 (m, 6H), 6.91～6.84 (m, 2H), 5.93 (s, 1H), 5.30 (d, *J*=10.8 Hz, 1H), 4.12 (d, *J*=10.8 Hz, 1H), 3.53～3.43 (m, 1H), 2.69～2.41 (m, 2H), 0.99 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.1, 138.1, 137.2, 133.4, 133.1, 133.0, 130.1, 129.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.1, 127.0, 126.8, 122.3, 121.2, 121.0, 119.9, 119.6, 118.8, 111.0, 106.3, 54.7,

53.8, 47.3, 17.5, 14.3; IR (KBr) *v*: 3584, 3028, 2964, 1868, 1305, 1174, 763, 565 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_2S$ $[M-H]^-$ 515.1798, found 515.1822.

7-(3-Benzyl-1*H*-indol-2-yl)-8,9-diphenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ca**): White solid, 71.7 mg (62% yield), 78∶22 *dr.* m.p. 219～221 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.27 (s, 1H), 7.80～7.74 (m, 1H), 7.74～7.69 (m, 1H), 7.67～7.60 (m, 1H), 7.56～7.49 (m, 1H), 7.30～7.26 (m, 1H), 7.23～7.19 (m, 3H), 7.16～7.03 (m, 5H), 7.02～6.93 (m, 5H), 6.93～6.79 (m, 5H), 5.94 (s, 1H), 5.41 (d, *J*=10.8 Hz, 1H), 4.19～4.03 (m, 2H), 3.91 (d, *J*=16.8 Hz, 1H), 3.59～3.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.1, 140.7, 138.1, 137.2, 133.4, 133.3, 133.1, 130.3, 129.6, 128.9, 128.7, 128.6, 128.3, 128.2, 128.1, 127.2, 127.1, 125.6, 122.6, 121.3, 121.2, 120.1, 119.2, 116.3, 111.0, 106.5, 54.6, 53.8, 47.7, 30.6; IR (KBr) *v*: 3580, 3031, 1868, 1792, 1733, 1507, 740, 471 cm^{-1}; HRMS (ESI) calcd for $C_{38}H_{29}N_2O_2S$ $[M-H]^-$ 577.1955, found 577.1984.

8,9-Diphenyl-7-(3-phenyl-1*H*-indol-2-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3da**): White solid, 76.7 mg (68% yield), 85∶15 *dr.* m.p. 176～178 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.46 (s, 1H), 7.81 (d, *J*=8.0 Hz, 1H), 7.76～7.71 (m, 1H), 7.71～7.64 (m, 1H), 7.62～7.56 (m, 1H), 7.40～7.31 (m, 4H), 7.31～7.26 (m, 2H), 7.26～7.20 (m, 1H), 7.19～7.08 (m, 4H), 7.02～6.95 (m, 1H), 6.95～6.84 (m, 3H), 6.81～6.73 (m, 2H), 6.46～6.39 (m, 2H), 5.90 (s, 1H), 5.40 (d, *J*=10.8 Hz, 1H), 3.91 (d, *J*=10.4 Hz, 1H), 3.44～3.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.0, 137.6, 136.7, 134.1, 133.3, 133.2, 133.0, 130.3, 129.6, 128.4, 128.1, 128.0, 127.7, 127.0, 126.8, 126.3, 122.8, 121.2, 121.1, 119.9, 119.8, 111.0, 106.6, 55.2, 53.6, 47.4; IR (KBr) *v*: 3028, 2918, 1732, 1600, 1305, 1174, 763, 699 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{27}N_2O_2S$ $[M-H]^-$ 563.1798, found 563.1819.

7-(5-Chloro-3-methyl-1*H*-indol-2-yl)-8,9-diphenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ea**): White solid, 92.2 mg (86% yield), >95∶5 *dr.* m.p. 180～182 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.13 (s, 1H), 7.77～7.69 (m, 2H), 7.69～7.63 (m, 1H), 7.58～7.52 (m, 1H), 7.31～7.28 (m, 1H), 7.22～7.10 (m, 4H), 7.05～6.95 (m, 6H), 6.88～6.79 (m, 2H), 5.93 (s, 1H), 5.23 (d, *J*=10.8 Hz, 1H), 4.10 (d, *J*=10.8 Hz, 1H), 3.50～3.38 (m, 1H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.0, 138.0, 133.4, 133.2, 133.1, 130.3, 129.8, 129.7, 129.3, 128.6, 128.2, 128.1, 127.3, 127.1, 124.7, 122.7, 121.3, 121.1, 118.7, 111.9, 106.7, 54.6, 53.9, 47.4, 8.5; IR (KBr) *v*: 3027, 2918, 2348, 1470, 1306, 1174, 1062, 763, 699 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{25}ClN_2O_2SNa$ $[M+Na]^+$ 559.1217, found 559.1230.

7-(3,5-Dimethyl-1*H*-indol-2-yl)-8,9-diphenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3fa**): White solid, 93.9 mg (91% yield), 88∶12 *dr.* m.p. 175～177 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.96 (s, 1H), 7.77～7.68 (m, 2H), 7.68～7.60 (m, 1H), 7.58～7.50 (m, 1H), 7.23～7.16 (m, 3H), 7.16～7.10 (m, 2H), 7.05～6.95 (m, 5H), 6.94～6.89 (m, 1H), 6.89～6.81 (m, 2H), 5.92 (s, 1H), 5.27 (d, *J*=10.8 Hz, 1H), 4.08 (d, *J*=10.4 Hz, 1H), 3.51～3.39 (m, 1H), 2.37 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.1, 138.2, 135.3, 133.4, 133.2, 130.2, 129.6, 129.0, 128.5, 128.2, 128.1, 127.8, 127.2, 127.1, 123.9, 121.3, 121.1, 118.9, 113.1, 110.5, 106.4, 54.6, 54.0, 47.6, 21.5, 8.6; IR (KBr) *v*: 3587, 3027, 2915, 1844, 1717, 1507, 1174, 763, 550 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_2S$ $[M+H]^+$ 517.1944, found 517.1948.

7-(6-Chloro-3-methyl-1*H*-indol-2-yl)-8,9-diphenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ga**): White solid, 93.3 mg (87% yield), >95∶5 *dr.* m.p. 248～250 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.09 (s, 1H), 7.78～7.70 (m, 2H), 7.70～7.63 (m, 1H), 7.59～7.53 (m, 1H), 7.25～7.15 (m, 5H), 7.04～6.92 (m, 6H), 6.87～6.79 (m, 2H), 5.94 (s, 1H), 5.23 (d, *J*=11.2 Hz, 1H), 4.10 (d, *J*=10.4 Hz, 1H), 3.48～3.39 (m, 1H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.0, 138.0, 137.1, 133.3, 133.1, 130.3, 128.5, 128.4, 128.2, 128.1, 128.0, 127.3, 127.1, 121.3, 121.1, 120.0, 119.7, 110.8, 106.7, 54.6, 53.9, 47.5, 8.5; IR (KBr) *v*: 3027, 2918, 1470, 1309, 1174, 1062, 763, 699 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{25}ClN_2O_2SNa$ $[M+Na]^+$ 559.1217, found 559.1202.

8-(2-Bromophenyl)-7-(3-methyl-1*H*-indol-2-yl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ha**): White solid, 71.9 mg (62% yield), 83∶17 *dr.* m.p. 213～215 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.22 (s, 1H), 7.76～7.71 (m, 2H), 7.69～7.63 (m, 1H), 7.58～7.53 (m, 1H), 7.44～7.35 (m, 2H), 7.31～7.26 (m, 1H), 7.25～7.17 (m, 4H), 7.12～7.07 (m, 1H), 7.05～6.95 (m, 4H), 6.89～6.82 (m, 1H), 5.95 (s, 1H), 5.34 (d, *J*=11.2 Hz, 1H), 4.37～4.27 (m, 1H), 3.99 (d, *J*=10.4 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 140.6, 138.1, 136.5, 133.5, 133.2, 132.7, 130.2, 129.4, 128.5, 128.4, 128.3, 127.9, 127.5, 127.2, 126.6, 126.3, 122.5, 121.2, 121.1, 119.0, 118.8, 113.2, 110.9, 106.1, 53.5, 51.0, 48.7, 8.7; IR (KBr) *v*: 3421, 3057, 1844, 1576, 1317, 1175, 761, 551 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{24}BrN_2O_2S$ $[M-H]^-$ 579.0747, found 579.0750.

8-(2-Fluorophenyl)-7-(3-methyl-1*H*-indol-2-yl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ia**): White solid; 63.4 mg (61% yield), 91∶9 *dr.* m.p. 174～176 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.11 (s, 1H), 7.76～7.70 (m, 2H), 7.68～7.62 (m, 1H), 7.58～7.52 (m, 1H), 7.36 (d, *J*=8.0 Hz, 1H), 7.25～7.16 (m, 4H), 7.12～7.06 (m, 1H), 7.04～6.94 (m, 4H), 6.93～6.57 (m, 3H), 5.91 (s, 1H), 5.50 (d, *J*=11.2 Hz, 1H), 4.18 (d, *J*=10.8 Hz, 1H), 3.88～3.75 (m, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.0 (*J*=243.9 Hz), 141.8, 136.8, 133.4, 133.3, 130.2, 129.6, 128.9 (*J*=8.8 Hz), 128.5, 127.9, 127.4, 127.2, 125.0, 124.0, 122.4, 121.3, 121.1, 119.1, 118.9, 115.4 (*J*=22.8 Hz), 110.9, 106.1, 52.7, 50.2, 46.4, 8.5; ^{19}F NMR (376 MHz, $CDCl_3$) *δ*: −114.6; IR (KBr) *v*: 3446, 1716, 1558, 1304, 1175, 1062, 751, 552 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{24}FN_2O_2S$ $[M-H]^-$ 519.1548, found 519.1547.

8-(3-Methoxyphenyl)-7-(3-methyl-1*H*-indol-2-yl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyri-

dine 5,5-dioxide (**3ja**): White solid, 94.7 mg (89% yield), 89∶11 *dr*. m.p. 181～183 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.77～7.68 (m, 2H), 7.67～7.61 (m, 1H), 7.57～7.49 (m, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.25～7.16 (m, 4H), 7.13～7.06 (m, 1H), 7.05～6.97 (m, 3H), 6.96～6.90 (m, 1H), 6.55 (d, J=8.0 Hz, 1H), 6.51 (d, J=7.6 Hz, 1H), 6.32 (s, 1H), 5.91 (s, 1H), 5.26 (d, J=10.8 Hz, 1H), 4.09 (d, J=10.4 Hz, 1H), 3.50～3.39 (m, 1H), 3.45 (s, 3H), 2.06 (s, 3H); ^{3}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 142.1, 139.7, 136.8, 133.3, 133.2, 133.1, 130.1, 129.6, 129.0, 128.7, 128.5, 128.1, 127.6, 127.0, 122.3, 121.2, 121.1, 120.4, 119.1, 118.9, 113.9, 113.6, 112.9, 110.8, 106.4, 55.0, 54.5, 53.9, 47.2, 8.6; IR (KBr) v: 3385, 2917, 1772, 1470, 1308, 1174, 748, 588 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_3S$ $[M-H]^-$ 531.1748, found 531.1739.

7-(3-Methyl-1*H*-indol-2-yl)-9-phenyl-8-(*m*-tolyl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ka**): Yield: 80.5 mg (78 %); 90:10 *dr*. White solid; m.p. 225～227 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 7.77～7.68 (m, 2H), 7.68～7.61 (m, 1H), 7.56～7.51 (m, 1H), 7.36 (d, J=7.6 Hz, 1H), 7.25～7.17 (m, 4H), 7.13～7.05 (m, 1H), 7.04～6.95 (m, 3H), 6.90～6.78 (m, 2H), 6.69 (s, 1H), 6.60 (d, J=7.6 Hz, 1H), 5.93 (s, 1H), 5.29 (d, J=10.8 Hz, 1H), 4.07 (d, J=10.4 Hz, 1H), 3.49～3.36 (m, 1H), 2.10 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.1, 138.0, 137.5, 136.8, 133.3, 133.2, 133.1, 130.1, 129.6, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 127.7, 127.0, 125.3, 122.2, 121.2, 121.0, 119.0, 118.8, 113.4, 110.8, 106.5, 54.4, 53.9, 47.5, 21.2, 8.5; IR (KBr) v: 3392, 3027, 1868, 1457, 1312, 1174, 783, 585 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_2S$ $[M-H]^-$ 515.1798, found 515.1769.

8-(3-Fluorophenyl)-7-(3-methyl-1*H*-indol-2-yl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3la**): White solid, 67.6 mg (65% yield), 93∶7 *dr*. m.p. 176～178 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.77～7.68 (m, 2H), 7.68～7.61 (m, 1H), 7.58～7.51 (m, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.25～7.16 (m, 4H), 7.14～7.07 (m, 1H), 7.03～6.90 (m, 4H), 6.75～6.67 (m, 1H), 6.66～6.55 (m, 2H), 5.90 (s, 1H), 5.27 (d, J=10.8 Hz, 1H), 4.03 (d, J=10.4 Hz, 1H), 3.56～3.43 (m, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (J=244.2 Hz), 141.6, 140.9, 140.8, 136.9, 133.3, 133.2, 133.2, 130.2, 129.7, 129.6 (J=8.2 Hz), 128.7, 128.6, 128.0, 127.2, 124.0, 122.5, 121.3, 121.1, 119.1, 119.0, 114.8 (J=21.5 Hz), 114.2 (J=20.9 Hz), 113.5, 110.9, 106.1, 54.4, 53.7, 47.6, 8.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −113.2; IR (KBr) v: 3587, 3058, 2917, 1307, 1175, 752, 700, 573 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{24}FN_2O_2S$ $[M-H]^-$ 519.1548, found 519.1547.

8-(3-Bromophenyl)-7-(3-methyl-1*H*-indol-2-yl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ma**): White solid, 81.2 mg (70% yield), 92∶8 *dr*. m.p. 162～164 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 7.78～7.68 (m, 2H), 7.68～7.61 (m, 1H), 7.58～7.51 (m, 1H), 7.38 (d, J=7.6 Hz, 1H), 7.25～7.07 (m, 7H), 7.04～6.95 (m, 3H), 6.82～6.73 (m, 1H), 6.60 (d, J=7.6 Hz, 1H), 5.90 (s, 1H), 5.27 (d, J=10.8 Hz, 1H), 4.02 (d, J=10.8 Hz, 1H), 3.51～3.40 (m, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.6, 140.6, 136.9, 133.3, 133.2, 130.4, 130.3, 129.6, 129.4, 128.7, 128.6, 128.1, 128.0, 127.5, 127.3, 127.1, 122.6, 122.1, 121.3, 121.1, 119.2, 119.0, 113.7, 110.9, 106.1, 54.5, 53.6, 47.6, 8.6; IR (KBr) v: 3567, 2964, 1868, 1521, 1275, 1020, 749, 668 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{24}BrN_2O_2S$ $[M-H]^-$ 579.0747, found 579.0756.

7-(3-Methyl-1*H*-indol-2-yl)-9-phenyl-8-(*p*-tolyl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3na**): White solid, 77.4 mg (75% yield), 78:22 *dr*. m.p. 192～194 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.74～7.68 (m, 2H), 7.65～7.60 (m, 1H), 7.54～7.48 (m, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.25～7.19 (m, 4H), 7.12～7.07 (m, 1H), 7.03～6.97 (m, 3H), 6.84～6.78 (m, 2H), 6.78～6.70 (m, 2H), 5.91 (s, 1H), 5.28 (d, J=11.2 Hz, 1H), 4.06 (d, J=10.4 Hz, 1H), 3.50～3.40 (m, 1H), 2.15 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.2, 136.8, 136.5, 135.0, 133.3, 133.2, 133.1, 130.1, 129.6, 128.8, 128.7, 128.4, 128.1, 127.9, 127.8, 127.0, 122.2, 121.2, 121.0, 119.1, 118.8, 110.9, 106.6, 54.0, 52.0, 47.6, 21.0, 8.6; IR (KBr) v: 3587, 3026, 2917, 1305, 1174, 1062, 755, 549 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_2S$ $[M-H]^-$ 515.1798, found 515.1810.

9-(2-Methoxyphenyl)-7-(3-methyl-1*H*-indol-2-yl)-8-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ab**): White solid, 79.8 mg (75% yield), 93∶7 *dr*. m.p. 203～205 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.70～7.66 (m, 1H), 7.65～7.60 (m, 1H), 7.56～7.50 (m, 1H), 7.34 (d, J=7.6 Hz, 1H), 7.25～7.20 (m, 2H), 7.16～7.07 (m, 2H), 7.00～6.93 (m, 4H), 6.92～6.86 (m, 3H), 6.68 (d, J=8.0 Hz, 1H), 5.85 (s, 1H), 5.31 (d, J=10.8 Hz, 1H), 4.64 (d, J=10.0 Hz, 1H), 3.64～3.57 (m, 1H), 3.44 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.1, 138.2, 136.8, 133.2, 133.1, 132.5, 130.2, 129.8, 129.8, 128.8, 128.6, 128.2, 128.1, 128.0, 127.6, 126.8, 122.2, 121.2, 120.9, 120.8, 119.0, 118.8, 113.3, 111.0, 110.8, 107.4, 55.3, 54.3, 53.0, 40.0, 8.5; IR (KBr) v: 3566, 3030, 1312, 1174, 1025, 754, 698, 457 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_3S$ $[M-H]^-$ 531.1748, found 531.1749.

9-(2-Chlorophenyl)-7-(3-methyl-1*H*-indol-2-yl)-8-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ac**): White solid, 66.5 mg (62% yield), ＞95∶5 *dr*. m.p. 183～185 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.73 (d, J=7.6 Hz, 1H), 7.70～7.60 (m, 2H), 7.57～7.50 (m, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.33～7.27 (m, 1H), 7.26～7.16 (m, 3H), 7.14～7.07 (m, 2H), 7.02～6.94 (m, 4H), 6.94～6.86 (m, 2H), 5.80 (s, 1H), 5.35 (d, J=10.8 Hz, 1H), 4.71 (d, J=9.6 Hz, 1H), 3.80～3.68 (m, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.1, 137.3, 136.9, 134.0, 133.3, 133.2, 132.9, 130.2, 129.9, 129.5, 128.8, 128.3, 128.2, 128.0, 127.5, 127.3, 127.2, 122.4, 121.3, 121.1, 119.1, 119.0, 113.6, 110.9, 105.9, 54.0, 52.6, 43.8, 8.6; IR (KBr) v: 3392, 3058, 2917, 1471, 1175, 1062, 758, 699, 552 cm^{-1}; HRMS (ESI) calcd

for $C_{32}H_{24}ClN_2O_2S$ [M－H]$^-$ 535.1252, found 535.1248.

9-(3-Methoxyphenyl)-7-(3-methyl-1*H*-indol-2-yl)-8-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ad**): White solid, 80.8 mg (76% yield); 91∶9 *dr.* m.p. 184～186 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.07 (s, 1H), 7.77～7.70 (m, 2H), 7.69～7.63 (m, 1H), 7.60～7.52 (m, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.25～7.21 (m, 1H), 7.14～7.06 (m, 2H), 7.04～6.94 (m, 4H), 6.89～6.83 (m, 2H), 6.71 (d, *J*=8.0 Hz, 1H), 6.58 (d, *J*=7.6 Hz, 1H), 6.49 (s, 1H), 5.92 (s, 1H), 5.27 (d, *J*=11.2 Hz, 1H), 4.07 (d, *J*=10.4 Hz, 1H), 3.65 (s, 3H), 3.52～3.40 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 158.5, 138.3, 136.8, 134.0, 133.3, 133.1, 133.0, 130.1, 129.6, 129.0, 128.7, 128.1, 127.7, 127.0, 122.3, 121.2, 121.0, 119.0, 118.9, 113.8, 113.4, 110.8, 106.8, 55.2, 54.7, 53.9, 46.7, 8.5; IR (KBr) *v*: 3567, 3030, 2917, 1457, 1297, 1174, 1046, 751, 700 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_3S$ [M－H]$^-$ 531.1748, found 531.1740.

7-(3-Methyl-1*H*-indol-2-yl)-8-phenyl-9-(*m*-tolyl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ae**): White solid, 64.0 mg (62% yield), ＞95∶5 *dr.* m.p. 210～212 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.07 (s, 1H), 7.77～7.69 (m, 2H), 7.69～7.62 (m, 1H), 7.58～7.51 (m, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.25～7.21 (m, 1H), 7.12～6.93 (m, 7H), 6.89～6.78 (m, 3H), 6.74 (d, *J*=7.6 Hz, 1H), 5.92 (s, 1H), 5.27 (d, *J*=10.8 Hz, 1H), 4.05 (d, *J*=10.4 Hz, 1H), 3.51～3.39 (m, 1H), 2.24 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 141.9, 138.2, 138.1, 136.8, 133.3, 133.2, 133.0, 130.1, 129.7, 128.7, 128.6, 128.2, 128.1, 128.0, 127.8, 127.6, 127.0, 125.2, 122.3, 121.2, 121.1, 119.1, 118.9, 113.4, 110.8, 106.7, 54.4, 53.9, 47.4, 21.4, 8.5; IR (KBr) *v*: 3567, 3031, 1318, 1172, 1131, 752, 700, 517 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_2S$ (M－H)$^-$ 515.1798, found 515.1808.

9-(4-Methoxyphenyl)-7-(3-methyl-1*H*-indol-2-yl)-8-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3af**): White solid, 75.5 mg (71% yield), 88∶12 *dr.* m.p. 170～172 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06 (s, 1H), 7.76～7.68 (m, 2H), 7.68～7.61 (m, 1H), 7.58～7.51 (m, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 7.25～7.21 (m, 1H), 7.12～7.06 (m, 1H), 7.04～6.95 (m, 4H), 6.93～6.83 (m, 4H), 6.74～6.69 (m, 2H), 5.90 (s, 1H), 5.27 (d, *J*=10.8 Hz, 1H), 4.04 (d, *J*=10.4 Hz, 1H), 3.74 (s, 3H), 3.48～3.37 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 163.0, 160.5, 137.9, 137.8, 137.7, 136.9, 133.4, 133.3, 133.2, 130.2, 129.6, 129.5, 129.4, 128.7, 128.2, 128.1, 128.0, 127.5, 127.2, 122.3, 121.3, 121.0, 119.1, 118.9, 115.4, 115.2, 110.8, 106.0, 54.7, 54.0, 53.9, 46.9, 8.5; IR (KBr) *v*: 3566, 3031, 1942, 1247, 1174, 1030, 753 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_2O_3S$ [M－H]$^-$ 531.1748, found 531.1749.

9-(4-Fluorophenyl)-7-(3-methyl-1*H*-indol-2-yl)-8-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ag**): White solid, 92.6 mg (89% yield), ＞95∶5 *dr.* m.p. 182～184 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06 (s, 1H), 7.76～7.71 (m, 2H), 7.70～7.64 (m, 1H), 7.61～7.51 (m, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.25～7.21 (m, 1H), 7.12～7.06 (m, 1H), 7.03～6.99 (m, 3H), 7.00～6.79 (m, 7H), 5.88 (s, 1H), 5.28 (d, *J*=10.4 Hz, 1H), 4.08 (d, *J*=10.4 Hz, 1H), 3.48～3.34 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 161.8 (*J*=244.3 Hz), 137.9, 137.8, 137.8, 133.7, 133.4, 133.3, 130.3, 129.6, 129.5, 128.7, 128.2, 128.1, 127.5, 127.3, 122.4, 121.3, 121.1, 119.1 (*J*=15.7 Hz), 115.4 (*J*=21.1 Hz), 110.9, 106.0, 54.8, 53.9, 46.9, 8.6; ^{19}F NMR (376 MHz, $CDCl_3$) *δ*: －115.4; IR (KBr) *v*: 3566, 3031, 1507, 1318, 1174, 1062, 834, 754 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{24}FN_2O_2S$ [M－H]$^-$ 519.1548, found 519.1565.

9-(4-Chlorophenyl)-7-(3-methyl-1*H*-indol-2-yl)-8-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ah**): White solid, 80.4 mg (95% yield), ＞95∶5 *dr.* m.p. 199～201 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.06 (s, 1H), 7.75～7.70 (m, 2H), 7.68～7.63 (m, 1H), 7.58～7.52 (m, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 7.25～7.20 (m, 1H), 7.18～7.13 (m, 2H), 7.12～7.07 (m, 1H), 7.04～6.94 (m, 4H), 6.94～6.88 (m, 2H), 6.88～6.79 (m, 2H), 5.86 (s, 1H), 5.28 (d, *J*=10.8 Hz, 1H), 4.08 (d, *J*=10.4 Hz, 1H), 3.46～3.36 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 140.6, 137.8, 136.9, 133.5, 133.4, 133.2, 132.7, 130.3, 129.4, 129.4, 128.7, 128.6, 128.2, 128.0, 127.4, 127.3, 122.4, 121.3, 121.1, 119.1, 118.9, 113.5, 110.8, 105.6, 54.5, 53.9, 46.9, 8.5; IR (KBr) *v*: 3587, 3030, 1303, 1173, 1014, 827, 755, 599 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{24}ClN_2O_2S$ [M－H]$^-$ 535.1252, found 535.1272.

7-(3-Methyl-1*H*-indol-2-yl)-9-(naphthalen-2-yl)-8-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ai**): White solid, 78.4 mg (71% yield), ＞95∶5 *dr.* m.p. 226～228 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.10 (s, 1H), 7.80～7.71 (m, 3H), 7.71～7.62 (m, 3H), 7.59～7.52 (m, 1H), 7.47～7.39 (m, 3H), 7.35 (d, *J*=8.0 Hz, 1H), 7.26～7.21 (m, 1H), 7.14～7.05 (m, 2H), 7.02～6.94 (m, 4H), 6.90～6.82 (m, 2H), 5.98 (s, 1H), 5.33 (d, *J*=10.8 Hz, 1H), 4.27 (d, *J*=10.0 Hz, 1H), 3.65～3.54 (m, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 139.6, 138.1, 136.9, 133.5, 133.3, 132.5, 130.2, 129.7, 128.7, 128.2, 128.1, 127.7, 127.6, 127.2, 126.9, 126.2, 125.8, 122.4, 121.3, 121.2, 119.1, 118.9, 113.6, 110.9, 106.5, 54.5, 54.0, 47.6, 8.5; IR (KBr) *v*: 3055, 2917, 1470, 1306, 1174, 1062, 1026, 746, 699 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{28}N_2O_2SNa$ [M＋Na]$^+$ 575.1763, found 575.1783.

7-(3-Methyl-1*H*-indol-2-yl)-8-phenyl-9-(thien-3-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3aj**): White solid, 81.3 mg (80% yield), 87∶13 *dr.* m.p. 181～183 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.08 (s, 1H), 7.77～7.70 (m, 2H), 7.69～7.61 (m, 1H), 7.57～7.49 (m, 1H), 7.35 (d, *J*=8.0 Hz, 1H), 7.26～7.20 (m, 1H), 7.19～7.15 (m, 1H), 7.12～6.96 (m, 5H), 6.94～6.84 (m, 2H), 6.81～6.75 (m, 1H), 6.70 (d, *J*=4.8 Hz, 1H), 5.95 (s, 1H), 5.25 (d, *J*=10.8 Hz, 1H), 4.25 (d, *J*=10.4 Hz, 1H), 3.51～3.38 (m, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.4, 138.6, 136.9, 133.2, 132.9, 130.2, 129.6, 128.8, 128.2, 128.0, 127.7, 127.3, 127.0, 125.7, 122.4, 121.7, 121.3, 121.1, 119.1, 118.9, 113.4, 110.9, 105.9, 53.9,

53.8, 42.7, 8.5; IR (KBr) *v*: 3391, 3029, 2917, 1674, 1470, 1306, 1174, 757, 545 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{24}N_2O_2S_2Na$ $[M+Na]^+$ 531.1171, found 531.1189.

7-(3-Methyl-1*H*-indol-2-yl)-9-(5-methylfuran-2-yl)-8-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridine 5,5-dioxide (**3ak**): White solid, 56.7 mg (56% yield), ＞95∶5 *dr*. m.p. 214～216 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.08 (s, 1H), 7.77～.71 (m, 2H), 7.68～7.64 (m, 1H), 7.58～7.52 (m, 1H), 7.35 (d, *J*=8.0 Hz, 1H), 7.29～7.27 (m, 1H), 7.13～7.04 (m, 4H), 7.02～6.93 (m, 3H), 5.93 (s, 1H), 5.72 (d, *J*=8.4 Hz, 2H), 5.21 (d, *J*=10.8 Hz, 1H), 4.19 (d, *J*=10.4 Hz, 1H), 3.74～3.68 (m, 1H), 2.21 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 151.9, 151.4, 138.6, 133.4, 133.2, 132.7, 130.3, 130.2, 129.6, 128.8, 128.2, 127.8, 127.7, 127.2, 122.4, 121.2, 119.1, 118.9, 113.4, 110.9, 107.4, 106.1, 103.9, 40.9, 40.1, 35.2, 13.6, 8.4; IR (KBr) *v*: 3029, 2922, 2852, 1456, 1306, 1174, 1026, 753 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{26}N_2O_3SNa$ $[M+Na]^+$ 529.1556, found 529.1558.

4.3 Procedure for one-mmol-scale reaction

1a (233.0 mg, 1.0 mmol), **2a** (538.0 mg, 2.0 mmol) and catalyst $Sc(OTf)_3$ (147.5 mg, 0.3 mol) were added to a reaction bottle. Then, CH_3CN (10 mL) was added to the reaction mixture, which was stirred at 70 ℃ for 8 h. The solution was concentrated under the reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleumether/ethyl acetate, *V*∶*V*=3∶1) to afford pure product **3aa** (367 mg, 73% yield).

4.4 Procedure for the synthesis of **4**, **5**

To a solution of **3aa** (0.05 mmol) in dichloromethane (DCM) (1.0 mL) were added Et_3SiH (0.5 mmol) and BF_3•Et_2O (1.0 mmol) at room temperature. After 10 min, the mixture was purification by flash chromatography on silica gel to give 19.7 mg (78% yield) of compound **4** as a White solid. ＞95∶5 *dr*. m.p. 178～180 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.22 (s, 1H), 7.70 (d, *J*=7.6 Hz, 1H), 7.66～7.59 (m, 1H), 7.56～7.49 (m, 1H), 7.40 (d, *J*=8.0 Hz, 1H), 7.37～7.28 (m, 2H), 7.20～7.06 (m, 6H), 7.03～6.73 (m, 6H), 4.90 (d, *J*=9.6 Hz, 1H), 4.67 (d, *J*=11.6 Hz, 1H), 3.46～3.31 (m, 2H), 2.77 (d, *J*=12.8 Hz, 1H), 2.25～2.11 (m, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.2, 138.2, 137.1, 137.0, 136.1, 132.9, 129.4, 128.7, 128.5, 127.9, 127.5, 126.8, 122.4, 121.3, 119.2, 118.9, 113.5, 110.9, 61.2, 56.6, 55.4, 48.9, 36.4, 8.2; IR (KBr) *v*: 2920, 1471, 1306, 1174, 762, 699 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{28}N_2O_2SNa$ $[M+Na]^+$ 527.1763, found 527.1770.

Compound **3aa** (25.1 mg, 0.05 mmol) and *N*-bromosuccinimide (NBS) (10.7 mg, 0.06 mmol) were added to a reaction tube. Then, $CHCl_3$ (1.0 mL) was added and the reaction mixture was stirred at 0 ℃ for 0.5 h. After the completion of the reaction, which was indicated by TLC, the reaction mixture was directly purified through preparative thin layer chromatography on silica gel to afford pure 23.5 mg (81% yield) of products **5** as white solid. ＞95∶5 *dr*. m.p. 189～191 ℃; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.85 (d, *J*=8.0 Hz, 1H), 8.01 (s, 1H), 7.81～7.69 (m, 2H), 7.68～7.60 (m, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 7.25～7.16 (m, 4H), 7.12～7.06 (m, 1H), 7.06～6.89 (m, 6H), 6.87～6.77 (m, 2H), 5.27 (d, *J*=11.6 Hz, 1H), 4.23 (d, *J*=10.4 Hz, 1H), 3.67～3.61 (m, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 141.4, 137.6, 136.9, 134.2, 133.1, 132.0, 130.7, 129.2, 128.7, 128.5, 128.3, 127.9, 127.4, 127.3, 126.9, 126.2, 119.2, 119.0, 114.0, 110.9, 108.2, 57.7, 56.4, 54.0, 8.6; IR (KBr) *v*: 3587, 3030, 1303, 1173, 1014, 827, 755, 599 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{25}BrN_2O_2SNa$ $[M+Na]^+$ 603.0712, found 603.0726.

Supporting Information ^1H NMR and ^{13}C NMR spectra of products **3**～**5**, single-crystal data of product **3aa**, and biological evaluation of selected products **3**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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