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# Catalytic asymmetric synthesis of 3,2'-pyrrolinyl spirooxindoles *via* conjugate addition/Schmidt-type rearrangement of vinyl azides and (*E*)-alkenyloxindoles†

Ziwei Zhong,<sup>ID</sup> Zhijie Xiao,<sup>ID</sup> Xiaohua Liu,<sup>ID</sup> Weidi Cao<sup>ID</sup>\* and Xiaoming Feng<sup>ID</sup>\*

A catalytic asymmetric conjugate addition/Schmidt-type rearrangement of vinyl azides and (*E*)-alkenyloxindoles was realized. It afforded a variety of optically active 3,2'-pyrrolinyl spirooxindoles with high yields (up to 98%), and excellent diastereo- and enantioselectivities (up to 98% ee, >19 : 1 dr), even at the gram-scale in the presence of a chiral *N,N'*-dioxide–nickel(II) complex. In addition, a possible catalytic cycle and transition state model were proposed to rationalize the stereoselectivity.

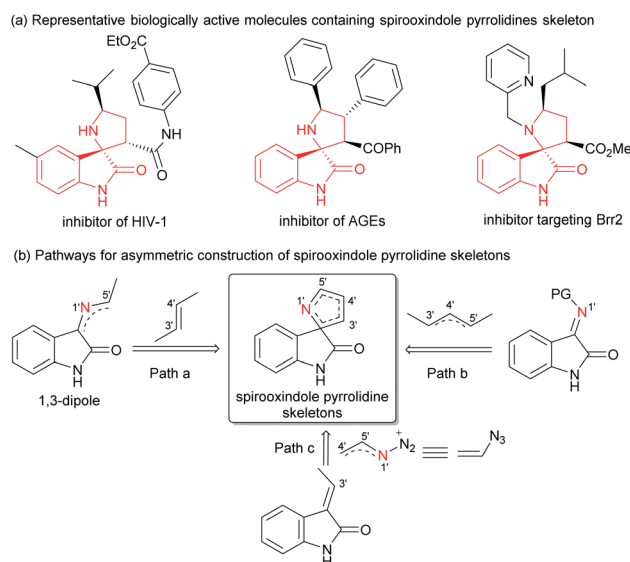
## Introduction

Aza-spirocyclic fragments are ubiquitous in numerous natural products and pharmaceuticals.<sup>1</sup> As a significant subset of such aza-spirocyclic compounds, 3,2'-pyrrolidinyl spirooxindoles and their analogues (pyrrolines), which bear stereocenters at C3' and C5'-positions of the pyrrolidine core, exhibit notable biological activities,<sup>2</sup> such as the inhibitor of HIV-1,<sup>2d</sup> inhibitor of AGES<sup>2e</sup> and inhibitor targeting Brr2 (Scheme 1a).<sup>2f</sup> Thus, the enantioselective construction of these useful skeletons has attracted great interest in the past decades. Catalytic asymmetric [3 + 2] cycloaddition of oxindole derivatives containing the nitrogen sources at the C3 position is demonstrated to be the most common and efficient approach for building the five-membered pyrrolidinyl ring.<sup>3</sup> The related cycloaddition can undergo different construction pathways, for example, enantioselective 1,3-dipolar cycloaddition between azomethine ylides and electron deficient alkenes is well established (Scheme 1b, path a).<sup>3g,h</sup> In contrast to the rapid development with an azomethine ylide as the nitrogen-partner, electron-poor iminoxindole as the nitrogen-partner is less developed. The desired skeleton can be constructed by [3 + 2] annulation with cyclopropane or allylic silane as 1,3-dipoles, and a cascade reaction with nitroalkane-mesylate (Scheme 1b, path b).<sup>3i-k</sup> Regardless of these advances, more discoveries of novel asymmetric methodologies leading to 3,2'-pyrrolidinyl spirooxindole skeletons would be expected.

Vinyl azide,<sup>4</sup> featuring both alkene and azide motifs conjugated together, has emerged as a versatile building block due to its unique properties, in the synthesis of nitrogen heterocyclic compounds, for instance 1-pyrroline *via* formal 1,3-dipolar cycloaddition with an alkene.<sup>4d,e</sup> Despite prominent advances, catalytic asymmetric reactions of vinyl azides are extremely rare.<sup>5</sup> To the best of our knowledge, the only related work is a visible-light-induced catalytic asymmetric [3 + 2] photocycloaddition of vinyl azides with  $\alpha,\beta$ -unsaturated *N*-acylpyrroles reported by Meggers and coworkers.<sup>5b</sup> And enantiomerically pure 1-pyrrolines were obtained with a chiral rhodium complex as the catalyst (Scheme 2a). Recently, Chiba's

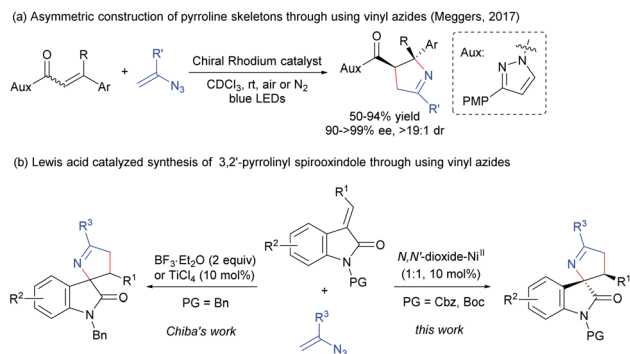
Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: wdcao@scu.edu.cn; xmfeng@scu.edu.cn

† Electronic supplementary information (ESI) available: <sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H} and <sup>19</sup>F{<sup>1</sup>H} NMR, HPLC spectra, and CD spectra (PDF). X-ray crystallographic data for 3ja (CIF). CCDC 1977126. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc03776a



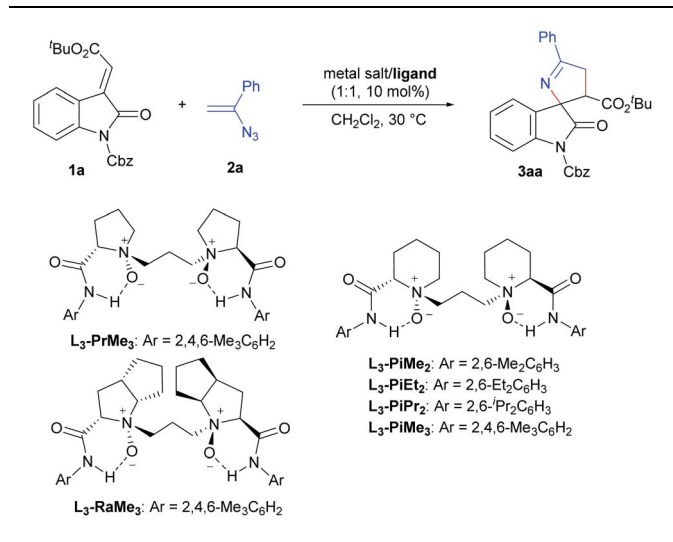
Scheme 1 Asymmetric synthesis of 3,2'-pyrrolidinyl spirooxindoles and their analogues.





Scheme 2 1,3-Dipolar cycloaddition with vinyl azide as the nitrogen source.

Table 1 Optimization of the reaction conditions<sup>a</sup>



Entry	Metal salt	Ligand	Yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>d</sup> (%)
1	Sc(OTf) <sub>3</sub>	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>3</sub>	48	>19 : 1	25
2	Mg(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>3</sub>	80	>19 : 1	77
3	Ni(OTf) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>3</sub>	85	>19 : 1	80
4	Ni(NTf <sub>2</sub> ) <sub>2</sub>	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>3</sub>	87	>19 : 1	80
5	Ni(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>3</sub>	86	>19 : 1	83
6	Ni(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>L</b> <sub>3</sub> - <b>PrMe</b> <sub>3</sub>	80	>19 : 1	82
7	Ni(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>L</b> <sub>3</sub> - <b>RaMe</b> <sub>3</sub>	76	>19 : 1	70
8	Ni(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>L</b> <sub>3</sub> - <b>PiMe</b> <sub>2</sub>	84	>19 : 1	86
9	Ni(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>L</b> <sub>3</sub> - <b>PiEt</b> <sub>2</sub>	88	>19 : 1	91
10	Ni(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>L</b> <sub>3</sub> - <b>PiPr</b> <sub>2</sub>	95	>19 : 1	71
11 <sup>e</sup>	Ni(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>L</b> <sub>3</sub> - <b>PiEt</b> <sub>2</sub>	95	>19 : 1	92
12 <sup>e,f</sup>	Ni(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>L</b> <sub>3</sub> - <b>PiEt</b> <sub>2</sub>	86	>19 : 1	92

<sup>a</sup> Unless otherwise noted, all the reactions were carried out with **1a** (0.10 mmol), **2a** (0.10 mmol) and metal salt/ligand (1 : 1, 10 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) at 30 °C for 24 h. <sup>b</sup> Isolated yield of **3aa**. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by HPLC analysis on a chiral stationary phase. <sup>e</sup> **2a** (2.0 equiv.) was used. <sup>f</sup> 5 mol% catalyst loading.

group took advantage of this strategy to realize the synthesis of racemic 3,2'-pyrrolyl spirooxindoles. High yields and dr values could be achieved in the presence of stoichiometric BF<sub>3</sub>·Et<sub>2</sub>O; by contrast, lower diastereoselectivities were

obtained for some substrates with the use of 10 mol% of TiCl<sub>4</sub> as the catalyst (Scheme 2b, left).<sup>6a</sup> It was worth mentioning that Wan's group used vinyl azides and diazooxindoles constructing a similar racemic skeleton *via* Rh(II)-catalyzed [1 + 1 + 3] annulation at a higher temperature.<sup>6b</sup>

Given the performance of chiral *N,N'*-dioxide-metal complexes<sup>7</sup> in activation and stereocontrol of (*E*)-alkenyloxindoles, we envisage that with careful choice of these kinds of chiral ligands and metal salts, the catalytic asymmetric cycloaddition of (*E*)-alkenyloxindoles with vinyl azide as the nitrogen source would be suitable for enantioselective construction of chiral 3,2'-pyrrolyl spirooxindole skeletons (Scheme 1b, path c). Herein, we wish to present a chiral *N,N'*-dioxide-Ni<sup>II</sup> complex mediated catalytic asymmetric conjugate addition/Schmidt-type rearrangement of vinyl azides with (*E*)-alkenyloxindoles (Scheme 2b, right). Both  $\alpha$ -aliphatic and  $\alpha$ -aromatic substituted vinyl azides could be transformed into 3'-carbonyl-5'-substituted 3,2'-pyrrolyl spirooxindoles in good yield with high to excellent diastereoselectivity and enantioselectivity under mild reaction conditions.

## Results and discussion

In our initial screening, we selected (*E*)-alkenyloxindole **1a** and vinyl azide **2a** as the model substrates to optimize the reaction conditions (Table 1) in view of that 3'-carbonyl substituents are common in the bioactive molecules shown in Scheme 1a. Firstly, various metal salts, such as Sc(OTf)<sub>3</sub>, Mg(OTf)<sub>2</sub> and Ni(OTf)<sub>2</sub>, were evaluated by coordinating with (*S*)-pipercolic acid derived *N,N'*-dioxide ligand **L**<sub>3</sub>-**PiMe**<sub>3</sub> (entries 1–3). It was found that the complex Ni(OTf)<sub>2</sub> could give the desired product **3aa** with better results (entry 3, 85% yield, 80% ee) in CH<sub>2</sub>Cl<sub>2</sub> at 30 °C. The exploration of the counterions of the nickel salts (entries 3–5) suggested that the non-coordinated counterion (BF<sub>4</sub><sup>-</sup>) led to a little increase in the enantioselectivity (entry 5, 86% yield, 83% ee). Then, we chose Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O as the metal salt to investigate the effect of the chiral backbone of the *N,N'*-dioxide ligands. This revealed that **L**<sub>3</sub>-**PiMe**<sub>3</sub> was superior to both *L*-proline derived **L**<sub>3</sub>-**PrMe**<sub>3</sub> and *L*-ramipril derived **L**<sub>3</sub>-**RaMe**<sub>3</sub> (entries 5–7). The use of **L**<sub>3</sub>-**PiMe**<sub>2</sub> without a methyl group at the *para*-position of the phenyl group of the amide moiety improved the enantioselectivity to 86% (entry 8). Further exploration of the amide moiety of the *N,N'*-dioxide ligand showed that the complex **L**<sub>3</sub>-**PiEt**<sub>2</sub>/Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O could give the best result (entry 9 *vs.* entry 10, 88% yield, 91% ee). Comparatively, when a chiral bisoxazoline ligand, **BINAP** or chiral phosphoric acid was used as the ligand, moderate yields and low ee values were achieved (see the ESI† for details). Other parameters such as solvents and additives were investigated as well; however, no better results were obtained (see the ESI† for more details). Enhancing the amount of vinyl azide **2a** (2.0 equiv.) resulted in an improvement of the yield to 95% with 92% ee (entry 11). Upon lowering the catalyst loading to 5 mol%, the yield was reduced to 86% with the enantioselectivity being maintained (entry 12). Therefore, the optimal reaction conditions were established as **1a** (0.1 mmol), **2a** (0.2 mmol), and **L**<sub>3</sub>-**PiEt**<sub>2</sub>/Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (1 : 1, 10 mol%), in CH<sub>2</sub>Cl<sub>2</sub> at 30 °C for



Table 2 Substrate scope for (*E*)-alkenyloxindoles<sup>a</sup>

Entry	R <sup>1</sup>	R <sup>2</sup>	Yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>d</sup> (%)
1	CO <sub>2</sub> <sup>t</sup> Bu	H	95 (3aa)	>19 : 1	92
2	CO <sub>2</sub> Me	H	91 (3ba)	>19 : 1	85
3	CO <sub>2</sub> Et	H	90 (3ca)	>19 : 1	89
4	CO <sub>2</sub> <sup>i</sup> Pr	H	92 (3da)	>19 : 1	89
5	CO <sub>2</sub> Ph	H	92 (3ea)	>19 : 1	86
6	CO <sub>2</sub> Bn	H	91 (3fa)	>19 : 1	91
7	CO <sub>2</sub> <sup>t</sup> Bu	5-F	93 (3ga)	>19 : 1	91
8	CO <sub>2</sub> <sup>t</sup> Bu	5-Cl	87 (3ha)	>19 : 1	91
9	CO <sub>2</sub> <sup>t</sup> Bu	5-Br	85 (3ia)	>19 : 1	91
10	CO <sub>2</sub> <sup>t</sup> Bu	5-Me	95 (3ja)	>19 : 1	88
11	CO <sub>2</sub> <sup>t</sup> Bu	5-OMe	91 (3ka)	>19 : 1	87
12	CO <sub>2</sub> <sup>t</sup> Bu	6-CF <sub>3</sub>	88 (3la)	>19 : 1	95
13	CO <sub>2</sub> <sup>t</sup> Bu	7-F	81 (3ma)	>19 : 1	94
14	CO <sub>2</sub> <sup>t</sup> Bu	5,6-F <sub>2</sub>	98 (3na)	>19 : 1	90
15 <sup>e</sup>	CO <sub>2</sub> <sup>t</sup> Bu	H	80 (3oa)	>19 : 1	98
16 <sup>e</sup>	COPh	H	82 (3pa)	>19 : 1	88

<sup>a</sup> Unless otherwise noted, all the reactions were carried out with **1** (0.10 mmol, PG = Cbz), **2a** (0.20 mmol) and **L**<sub>3</sub>-**PiEt**<sub>2</sub>/Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (1 : 1, 10 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) at 30 °C for 24 h. <sup>b</sup> Isolated yield of **3**. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by HPLC analysis on a chiral stationary phase. <sup>e</sup> PG = Boc. Boc = *tert*-butoxycarbonyl and Cbz = benzyloxycarbonyl.

24 h. It was worth mentioning that the diastereoselectivity could be well controlled during the conditional screening process (>19 : 1 dr).

With the optimized conditions in hand, the substrate scope was then evaluated (Table 2). Various (*E*)-alkenyloxindoles **1** bearing different ester groups (R<sup>1</sup>) could be transformed into the corresponding products **3aa–3fa** in 90–95% yields, >19 : 1 dr and 85–92% ee (entries 1–6), and the enantioselectivities would slightly decrease if less steric hindrance of the ester groups was used (entries 2–4). Regardless of the electronic effect or steric hindrance positions of the substituents on the phenyl ring, this asymmetric reaction proceeded smoothly to afford **3ga–3na** with good results (entries 7–14, 81–98% yields, >19 : 1 dr and 85–95% ee). It was worth mentioning that (*E*)-alkenyloxindoles bearing electron withdrawing halogen groups (F, Cl, and Br) at the C5-position delivered **3ga–3ia** with higher ee values (entries 7–9) than those with electron donating groups (entries 10 and 11, **3ja** and **3ka**). *N*-Boc protected (*E*)-alkenyloxindoles were also tolerated well, giving **3oa** and **3pa** in 80% yield with 98% ee and 82% yield with 88% ee, respectively (entries 15 and 16), and the slightly lower yields were attributed to the decomposition of **1o** and **1p** through deprotection of the Boc group in the presence of the Lewis acid. Furthermore, the absolute configuration of **3ja** was determined to be (3*S*,3'*R*) by the X-ray diffraction analysis.<sup>8</sup>

Table 3 Substrate scope for vinyl azides<sup>a</sup>

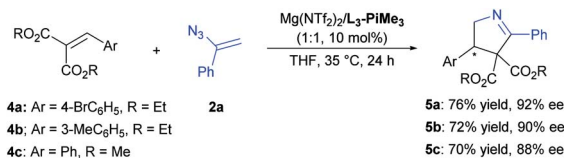
Entry <sup>a</sup>	R <sup>3</sup>	Yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>d</sup> (%)
1	2-MeOC <sub>6</sub> H <sub>4</sub>	95 (3ab)	>19 : 1	92
2	2-ClC <sub>6</sub> H <sub>4</sub>	91 (3ac)	>19 : 1	94
3	3-MeOC <sub>6</sub> H <sub>4</sub>	90 (3ad)	>19 : 1	81
4	3-ClC <sub>6</sub> H <sub>4</sub>	92 (3ae)	>19 : 1	82
5	4-MeC <sub>6</sub> H <sub>4</sub>	92 (3af)	>19 : 1	84
6	4- <sup>n</sup> BuC <sub>6</sub> H <sub>4</sub>	91 (3ag)	>19 : 1	80
7	4-FC <sub>6</sub> H <sub>4</sub>	93 (3ah)	>19 : 1	95
8	4-ClC <sub>6</sub> H <sub>4</sub>	87 (3ai)	>19 : 1	96
9	4-CO <sub>2</sub> EtC <sub>6</sub> H <sub>4</sub>	88 (3aj)	>19 : 1	94
10	2-Naphthyl	95 (3ak)	>19 : 1	94
11	3-Thienyl	85 (3al)	83 : 17	90
12	Cyclohexyl	88 (3am)	>19 : 1	95
13	Benzyl	86 (3an)	>19 : 1	93

<sup>a</sup> Unless otherwise noted, all the reactions were carried out with **1a** (0.10 mmol), **2** (0.20 mmol) and **L**<sub>3</sub>-**PiEt**<sub>2</sub>/Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (1 : 1, 10 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) at 30 °C for 24 h. <sup>b</sup> Isolated yield of **3**. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by HPLC analysis on a chiral stationary phase. Cbz = benzyloxycarbonyl.

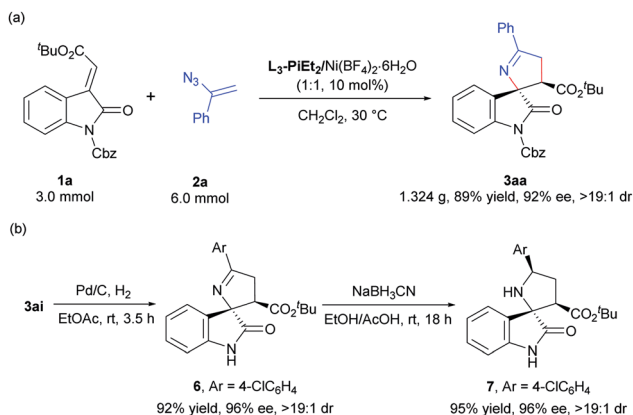
The scope of vinyl azides was next examined under the standard conditions (Table 3). A battery of 3,2'-pyrrolinyl spirooxindoles (**3ab–3aj**) were obtained in high to excellent yields and ee values regardless of the electron-rich or -deficient groups attached to the aryl group of vinyl azides. The reaction of electron-donating 2-methoxy-substituted or electron-withdrawing 2-chloro-substituted vinyl azides gave excellent yields and enantioselectivities (91–95% yields, 92–94% ee, **3ab** and **3ac**). In contrast, the same substituents at the *meta*-position of the phenyl rings delivered the products **3ad** and **3ae** with a lower ee value (81–82% ee). Compared with those vinyl azides involving electron-donating groups (Me and <sup>n</sup>Bu) at the *para*-position of the aryl group (entries 5 and 6), vinyl azides bearing electron-withdrawing halogen groups (F and Cl) and ester groups exhibited higher reactivities (87–93%) with excellent enantioselectivities (entries 7–9, 94–96% ee, **3ah–3aj**). The condensed-ring and heteroaromatic substrates were also tolerated in this reaction, readily affording spiropyrrolines **3ak** and **3al** in 85–95% yields and 90–94% ee, albeit with a lower dr value for **3al** (83 : 17 dr). Furthermore,  $\alpha$ -alkyl substituted vinyl azides, such as with cyclohexyl and benzyl, were applicable as well, and offered the corresponding products **3am** and **3an** in good yields (86–88%) with excellent stereocontrol (entries 12 and 13, 93–95% ee, >19 : 1 dr).

Subsequently, we also tested various types of electron-deficient alkenes to broaden the synthetic scope. Alkylidene malonates **4** reacted with **2a** smoothly upon switching the catalyst to Mg(NTf<sub>2</sub>)<sub>2</sub>/L<sub>3</sub>-**PiMe**<sub>3</sub> in THF, and the corresponding chiral 1-pyrroline derivatives **5** could be achieved with good





Scheme 3 The conjugate addition/Schmidt-type rearrangement of alkyldiene malonates with vinyl azide.

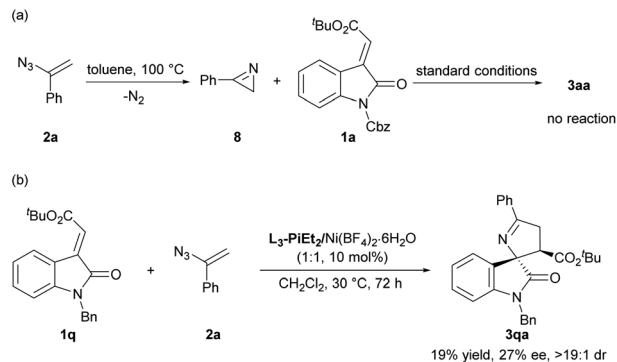


Scheme 4 (a) Scale-up synthesis of **3aa**; (b) transformation of the product **3ai**.

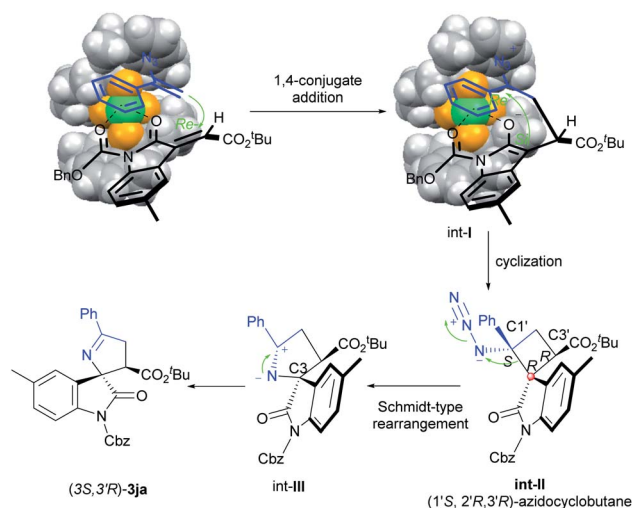
yields and high enantioselectivities (Scheme 3). Other electron-deficient alkenes were also examined, such as chromenes, chalcone and so on, but a low reactivity was found or a hetero-Diels–Alder reaction tended to occur (see the ESI† for details).

To evaluate the synthetic value of the catalytic system, a scale-up experiment was carried out (Scheme 4a). The (*E*)-alkenyloxindole **1a** (3.0 mmol) reacted with vinyl azide **2a** (6.0 mmol) smoothly and gave the desired product **3aa** in 89% yield, 92% ee and >19 : 1 dr in the presence of the **L**-**PiEt**<sub>2</sub>/Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O complex (10 mol%). Treatment of the product **3ai** with Pd/C under a hydrogen atmosphere got rid of the protecting group (Cbz) to afford **6**, which could be further transformed into the functionalized pyrrolidine product **7** in 95% yield with excellent stereoselectivity through hydrogenation (Scheme 4b).<sup>9</sup>

To gain mechanistic insight into the reaction, control experiments were performed as shown in Scheme 5. Phenyl-2*H*-azirine **8** generated from vinyl azide **2a** has been reported as a possible 1,3-dipole precursor in [3 + 2] cycloaddition.<sup>4</sup> When azirine **8** was used to react with **1a** under the standard conditions, no reaction occurred, ruling out the reaction pathway with the aryl-2*H*-azirine (**8**) intermediate (Scheme 5a). Moreover, when *N*-benzyl (*E*)-alkenyloxindole **1q** was explored in this catalytic system, only 19% yield and 27% ee of the desired product were obtained (Scheme 5b), which indicated that the coordinating group unit of the nitrogen protecting group played an important role in achieving high reactivity and enantioselectivity in the current catalytic system. The activation mode might be different from that in a previous report using *N*-Bn or *N*-H based (*E*)-alkenyloxindole in the racemic version.<sup>6a</sup>



Scheme 5 Control experiments.



Scheme 6 The proposed catalytic cycle and working mode.

Based on the results of the control experiment, X-ray structure of the product **3ja**<sup>8</sup> and Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O/**L**<sub>3</sub>-**PiEt**<sub>2</sub> complex,<sup>10</sup> a possible reaction mechanism was proposed (Scheme 6). Firstly, (*E*)-alkenyloxindole **1j** was activated by bidentate coordination with the Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O/**L**<sub>3</sub>-**PiEt**<sub>2</sub> complex.<sup>11</sup> Vinyl azide prefers to undergo asymmetric 1,4-conjugate addition to **1j** from its β-*Re* face because the β-*Si* face was shielded by the nearby 2,6-diethyl phenyl group of **L**<sub>3</sub>-**PiEt**<sub>2</sub>. The subsequent cyclization of *Re*-*Si* attack results in an (1'*S*, 2'*R*, 3'*R*)-azidocyclobutane (**int-II**), which was detected by high resolution mass spectrometry (see the ESI† for more details). In the following Schmidt-type rearrangement, the more electron-rich α-carbon group (C3) shifts to the nitrogen atom with the release of N<sub>2</sub> to form **int-III** through antiperiplanar migration, and the stereochemistry of C3 is retained.<sup>12</sup> Finally, the imidization of **int-III** affords the desired product (3*S*, 3'*R*)-**3ja**.

## Conclusions

We have successfully developed the Lewis acid catalyzed asymmetric synthesis of 3,2'-pyrrolinyl spirooxindoles *via* conjugate addition/Schmidt-type rearrangement of vinyl azides



and (*E*)-alkenyloxindoles. The catalytic system of the chiral *N,N'*-dioxide/Ni(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O complex benefited this reaction efficiently to afford diverse chiral spiro pyrrolone derivatives in good yields with high stereoselectivities (up to 98% yield, >19 : 1 dr and 98% ee), which provided a new method for the synthesis of chiral nitrogen heterocyclic compounds with vinyl azides as the nitrogen source. Besides, a possible catalytic cycle along with the working mode was proposed to elucidate the reaction process and chiral induction. Further investigations on the catalytic asymmetric synthesis of aza-spirocyclic compounds by using vinyl azides are ongoing in our laboratory.

**Safety notice:** vinyl azides are classified as organic azides, and act as versatile building blocks in organic synthesis. However, one should keep in mind the inherent toxicity, instability, shock sensitivity, and explosive power of azides. Great care must be taken when handling these compounds, particularly during concentration and the physical handling of isolated products, due to the explosive potential of the azide functionality.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

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