Chemical Science

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Z. Zhong, Z. Xiao, X. Liu, W. Cao and X. Feng, *Chem. Sci.*, 2020, DOI: 10.1039/D0SC03776A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemical-science

View Article Online
DOI: 10.1039/D0SC03776A

ARTICLE

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

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

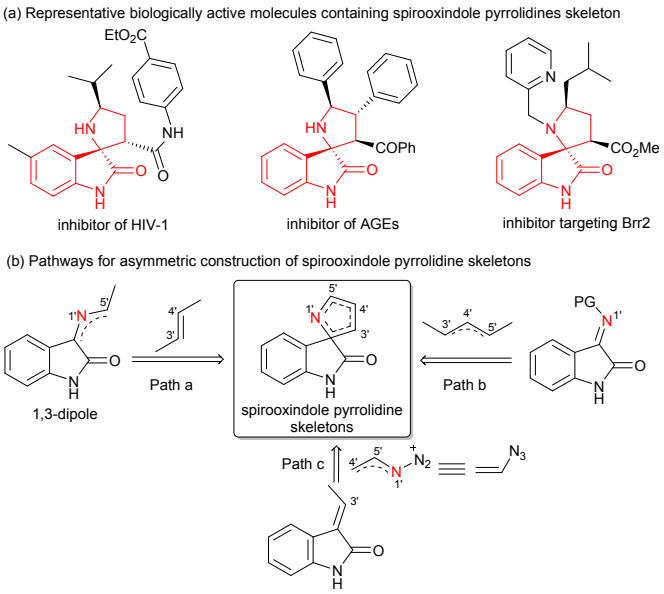
Ziwei Zhong, [a] Zhijie Xiao, [a] Xiaohua Liu, [a] Weidi Cao*[a] and Xiaoming Feng*[a]

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%), excellent diastereo- and enantioselectivities (up to 98% ee, >19:1 dr), even at a 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.[1] As a significant subset of such aza-spirocylic compounds, 3,2'-pyrrolidinyl spirooxindoles and their analogous (pyrrolines), which bear stereocenters at C3' and C5'-positions of the pyrrolidine core, exhibit notable biological activities,[2] such as inhibitor of HIV-1,[2d] inhibitor of AGEs[2e] and inhibitor targeting Brr2 (Scheme 1a).[2f] 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.[3] The related cycloaddition can undergo different construction pathways, for examples, enantioselective 1,3-dipolar cycloaddition between azomethine ylide and electron deficient alkenes are well established (Scheme 1b, path a).[3g-h] In contrast to the rapid development with azomethine ylide as the nitrogen-partner, electron-poor iminooxindole as the nitrogen-partner were less developed. The desired skeleton can be constructed by [3 + 2] annulation with cyclopropane or allylic silane as 1,3-dipoles, and cascade reaction with nitroalkane-mesylate (Scheme 1b, path b).[3i-k] Regardless of these advances, it would be expected more discoveries of novel asymmetric methodologies leading to 3,2'-pyrrolidinyl spirooxindole skeletons.

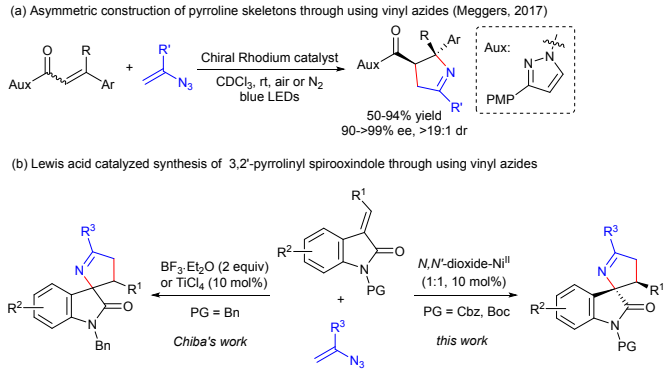
Vinyl azide,[4] featuring both alkene and azide motif conjugated together, has emerged as a versatile building block due to its unique property, in the synthesis of nitrogen heterocyclic compounds, for instance 1-pyrroline via formal 1,3-dipolar cycloaddition with alkene.[4d-4e] Despite the prominent advances, catalytic asymmetric reactions of vinyl azides are extremely rare.[5] To the best of our knowledge, the only related work is a visible-light-induced catalytic asymmetric [3 + 2] photocycloaddition of vinyl azides with α,β-unsaturated *N*-acylpyrazoles reported by Meggers and coworkers.[5b] And enantiometrically pure 1-pyrrolines were obtained with a chiral rhodium complex as the catalyst (Scheme 2a). Recently, Chiba's group took advantage of this strategy to realize the synthesis of racemic 3,2'-pyrrolinyl spirooxindoles, high yields and dr values could be achieved in the presence of stoichiometric $BF_3{\cdot}Et_2O$, by contrast, lower diastereoselectivities were obtained for some substrates with the use of 10 mol% of $TiCl_4$ as the catalyst (Scheme 2b, left).[6a] It was worth mentioning that Wan's group used vinyl azides and diazooxindoles constructing the similar racemic skeleton via Rh(II)-catalyzed [1+1+3] annulation at a higher temperature.[6b]



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

[a] *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: [^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H} NMR, HPLC spectra, CD spectra (PDF). X-ray crystallographic data for **3ja** (CIF)]. See DOI: 10.1039/x0xx00000x



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

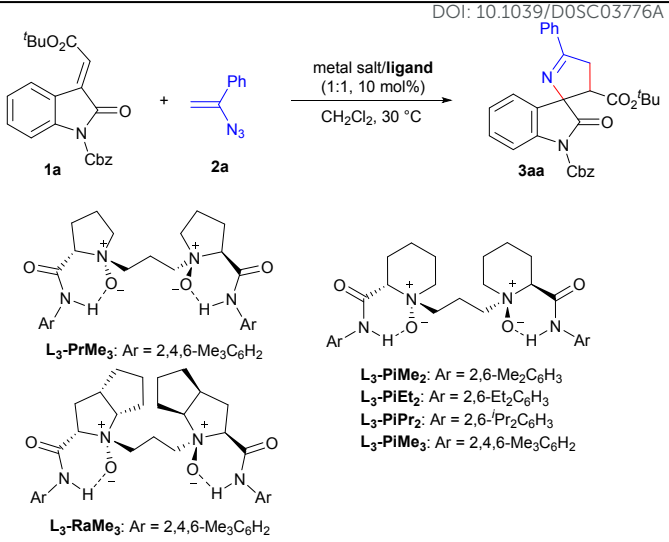
Given the performance of chiral *N*,*N*'-dioxide-metal complexes[7] in activation and stereocontrol of (*E*)-alkenyloxindoles, we envisage that with careful choice of this kind of chiral ligands and metal salts, the catalytic asymmetric cycloaddition of (*E*)-alkenyloxindoles with vinyl azide as the nitrogen source would be suitable for enantioselective construction of chiral 3,2'-pyrrolinyl spirooxindole skeletons (Scheme 1b, path c). Herein, we wish to present a chiral *N*,*N*'-dioxide-Ni^{II} complex mediated catalytic asymmetric conjugate addition/Schmidt-type rearrangement of vinyl azides with (*E*)-alkenyloxindoles (Scheme 2b, right). Both α-aliphatic and α-aromatic substituted vinyl azides could be transformed into 3'-carbonyl-5'-substituted 3,2'-pyrrolinyl 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 $Sc(OTf)_3$, $Mg(OTf)_2$ and $Ni(OTf)_2$, were evaluated by coordinating with (*S*)-pipecolic acid derived *N*,*N*'-dioxide ligand **L$_3$-PiMe$_3$** (entries 1–3). It was found that the complex of $Ni(OTf)_2$ could give the desired product **3aa** with better results (entry 3, 85% yield, 80% ee) in CH_2Cl_2 at 30 °C. The exploration of the counterions of the nickel salts (entries 3–5) suggested that the non-coordinated counterion (BF_4^-) led to a little boost of enantioselectivity (entry 5, 86% yield, 83% ee). Then, we chose $Ni(BF_4)_2{\cdot}6H_2O$ as the metal salt to investigate the effect of the chiral backbone of the *N*,*N*'-dioxide ligands. It revealed **L$_3$-PiMe$_3$** was superior to both *L*-proline derived **L$_3$-PrMe$_3$** and *L*-ramipril derived **L$_3$-RaMe$_3$** (entries 5–7). The use of **L$_3$-PiMe$_2$** without a methyl group at the *para*-position of the phenyl group of the amide moiety improved the enantioselectivity to 86% ee (entry 8). Further exploration of the amide moiety of the *N*,*N*'-dioxide ligand showed that the complex of **L$_3$-PiEt$_2$**/$Ni(BF_4)_2{\cdot}6H_2O$ could give the best result (entry 9 vs entry 10, 88% yield, 91% ee). Comparatively, when chiral bisoxazoline ligand, **BINAP** or chiral phosphoric acid were used as the ligands, moderate yields and low ee values were achieved (see ESI for details). Other

Table 1. Optimization of the reaction conditions[a]

View Article Online
DOI: 10.1039/D0SC03776A



Entry	Metal salt	Ligand	Yield (%)[b]	dr[c]	ee (%)[d]
1	$Sc(OTf)_3$	**L$_3$-PiMe$_3$**	48	>19:1	25
2	$Mg(OTf)_2$	**L$_3$-PiMe$_3$**	80	>19:1	77
3	$Ni(OTf)_2$	**L$_3$-PiMe$_3$**	85	>19:1	80
4	$Ni(NTf_2)_2$	**L$_3$-PiMe$_3$**	87	>19:1	80
5	$Ni(BF_4)_2{\cdot}6H_2O$	**L$_3$-PiMe$_3$**	86	>19:1	83
6	$Ni(BF_4)_2{\cdot}6H_2O$	**L$_3$-PrMe$_3$**	80	>19:1	82
7	$Ni(BF_4)_2{\cdot}6H_2O$	**L$_3$-RaMe$_3$**	76	>19:1	70
8	$Ni(BF_4)_2{\cdot}6H_2O$	**L$_3$-PiMe$_2$**	84	>19:1	86
9	$Ni(BF_4)_2{\cdot}6H_2O$	**L$_3$-PiEt$_2$**	88	>19:1	91
10	$Ni(BF_4)_2{\cdot}6H_2O$	**L$_3$-PiPr$_2$**	95	>19:1	71
11[e]	$Ni(BF_4)_2{\cdot}6H_2O$	**L$_3$-PiEt$_2$**	95	>19:1	92
12[e,f]	$Ni(BF_4)_2{\cdot}6H_2O$	**L$_3$-PiEt$_2$**	86	>19:1	92

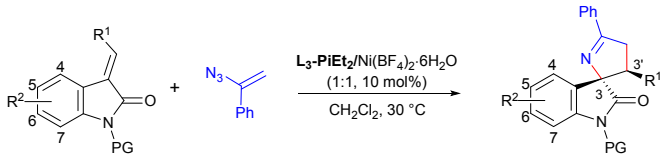
[a] Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), **2a** (0.10 mmol) and metal salt/**ligand** (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) at 30 °C for 24 h. [b] Isolated yield of **3aa**. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase. [e] **2a** (2.0 equiv.) was used. [f] 5 mol% catalyst loading.

parameters such as solvents and additives were investigated as well, however, no better results were obtained (see 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 maintained (entry 12). Therefore, the optimal reaction conditions were established as **1a** (0.1 mmol), **2a** (0.2 mmol), **L$_3$-PiEt$_2$**/$Ni(BF_4)_2{\cdot}6H_2O$ (1:1, 10 mol%), in CH_2Cl_2 at 30 °C for 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^1) 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 ester groups were 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

View Article Online
DOI: 10.1039/D0SC03776A

Table 2. Substrate scope for (*E*)-alkenyloxindoles[a]



1a-1n: PG = Cbz
1o-1p: PG = Boc

2a

3aa-3na: PG = Cbz
3oa-3pa: PG = Boc

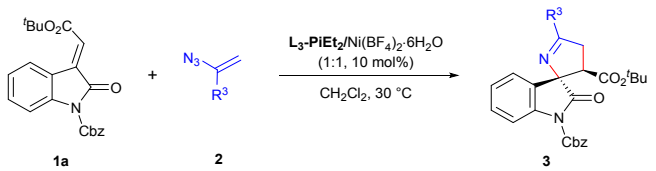
Entry	R^1	R^2	Yield (%)[b]	dr[c]	ee (%)[d]
1	$CO_2{}^tBu$	H	95 (**3aa**)	>19:1	92
2	CO_2Me	H	91 (**3ba**)	>19:1	85
3	CO_2Et	H	90 (**3ca**)	>19:1	89
4	$CO_2{}^iPr$	H	92 (**3da**)	>19:1	89
5	CO_2Ph	H	92 (**3ea**)	>19:1	86
6	CO_2Bn	H	91 (**3fa**)	>19:1	91
7	$CO_2{}^tBu$	5-F	93 (**3ga**)	>19:1	91
8	$CO_2{}^tBu$	5-Cl	87 (**3ha**)	>19:1	91
9	$CO_2{}^tBu$	5-Br	85 (**3ia**)	>19:1	91
10	$CO_2{}^tBu$	5-Me	95 (**3ja**)	>19:1	88
11	$CO_2{}^tBu$	5-OMe	91 (**3ka**)	>19:1	87
12	$CO_2{}^tBu$	6-CF_3	88 (**3la**)	>19:1	95
13	$CO_2{}^tBu$	7-F	81 (**3ma**)	>19:1	94
14	$CO_2{}^tBu$	5,6-F_2	98 (**3na**)	>19:1	90
15[e]	$CO_2{}^tBu$	H	80 (**3oa**)	>19:1	98
16[e]	COPh	H	82 (**3pa**)	>19:1	88

[a] Unless otherwise noted, all reactions were carried out with **1** (0.10 mmol, PG = Cbz), **2a** (0.20 mmol) and **L$_3$-PiEt$_2$**/Ni(BF$_4$)$_2$·6H$_2$O (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) at 30 °C for 24 h. [b] Isolated yield of **3**. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase. [e] PG = Boc. Boc = tert-butoxycarbonyl, Cbz = benzyloxycarbonyl.

bearing electron withdrawing halogen groups (F, Cl, Br) at C5-position delivered **3ga**–**3ia** with higher ee values (entries 7–9) than those with electron donating groups (entries 10–11, **3ja**–**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 15–16), and the slightly lower yields were attributed to the decomposition of **1o** and **1p** through deprotection of Boc group in the presence of Lewis acid. Furthermore, the absolute configuration of **3ja** was determined to be (3*S*, 3'*R*) by the X-ray diffraction analysis.[8]

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 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**–**3ac**). In contrast, the same substituents at the *meta*-position of phenyl rings delivered the products **3ad**–**3ae** with lower ee value (81–82% ee). Compared with those vinyl azides involving electron-donating groups (Me, ^{n}Bu) at the *para*-position of aryl group (entries 5–6), vinyl azides bearing electron-withdrawing halogen groups (F, Cl) and ester group exhibited higher reactivities (87–93%) with excellent enantioselectivities (entries 7–9, 94–96% ee, **3ah**–**3aj**). The condensed-ring and heteroaromatic substrates were also

Table 3. Substrate scope for vinyl azides[a]



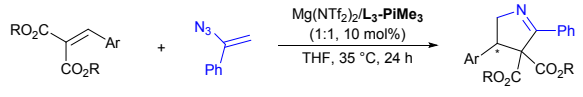
1a **2** **3**

Entry[a]	R^3	Yield (%)[b]	dr[c]	ee (%)[d]
1	2-$MeOC_6H_4$	95 (**3ab**)	>19:1	92
2	2-ClC_6H_4	91 (**3ac**)	>19:1	94
3	3-$MeOC_6H_4$	90 (**3ad**)	>19:1	81
4	3-ClC_6H_4	92 (**3ae**)	>19:1	82
5	4-MeC_6H_4	92 (**3af**)	>19:1	84
6	4-^{n}BuC_6H_4	91 (**3ag**)	>19:1	80
7	4-FC_6H_4	93 (**3ah**)	>19:1	95
8	4-ClC_6H_4	87 (**3ai**)	>19:1	96
9	4-$CO_2EtC_6H_4$	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

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), **2** (0.20 mmol) and **L$_3$-PiEt$_2$**/Ni(BF$_4$)$_2$·6H$_2$O (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) at 30 °C for 24 h. [b] Isolated yield of **3**. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis on a chiral stationary phase. Cbz = benzyloxycarbonyl.

tolerated in this reaction, readily affording spiropyrrolines **3ak**–**3al** in 85–95% yields and 90–94% ee, albeit with a lower dr value for **3al** (83:17 dr). Furthermore, α-alkyl substituted vinyl azides, such as cyclohexyl and benzyl, were applicable as well, and offered the corresponding products **3am** and **3an** in good yields (86–88%) with excellent stereocontrol (entries 12–13, 93–95% ee, >19:1 dr).

Subsequently, we also tested various types of electron-deficient alkene to broaden the synthetic scope Alkylidene malonates **4** reacted with **2a** smoothly by switching the catalyst to Mg(NTf$_2$)$_2$/**L$_3$-PiMe$_3$** in THF, the corresponding chiral 1-pyrroline derivatives **5** could be achieved with good yields with high enantioselectivities (Scheme 3). Other electron-deficient alkenes were also examined, such as chromenes, chalcone and so on, but the low reactivity was found or hetero-Diels–Alder reaction tended to occur (see ESI for details).



4a: Ar = 4-BrC_6H_5, R = Et
4b: Ar = 3-MeC_6H_5, R = Et
4c: Ar = Ph, R = Me

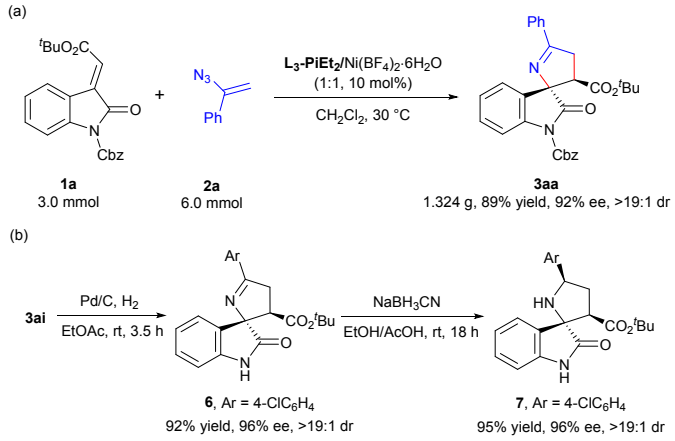
2a

5a: 76% yield, 92% ee
5b: 72% yield, 90% ee
5c: 70% yield, 88% ee

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

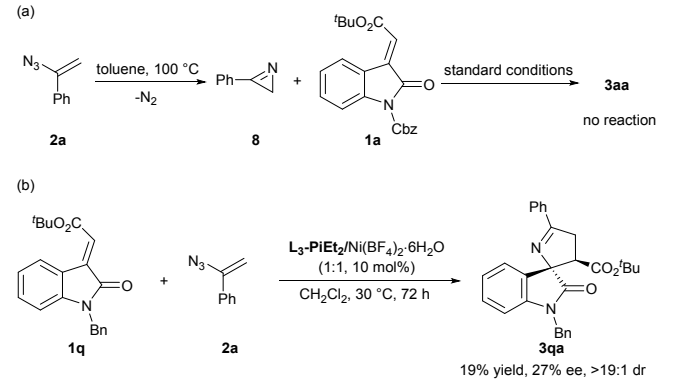
To evaluate the synthetic value of the catalytic system, a scale-up experiment was carried out (Scheme 4a). The (*E*)-alkenyloxindole **1a** (3.0 mmol) reacted with vinyl azide **2a** (6.0 mmol) smoothly and gave the desired product **3aa** in 89% yield, 92% ee and >19:1 dr in the presence of **L-PiEt$_2$**/Ni(BF$_4$)$_2$·6H$_2$O complex (10 mol%). Upon treatment of the product **3ai** with Pd/C under 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).[9]



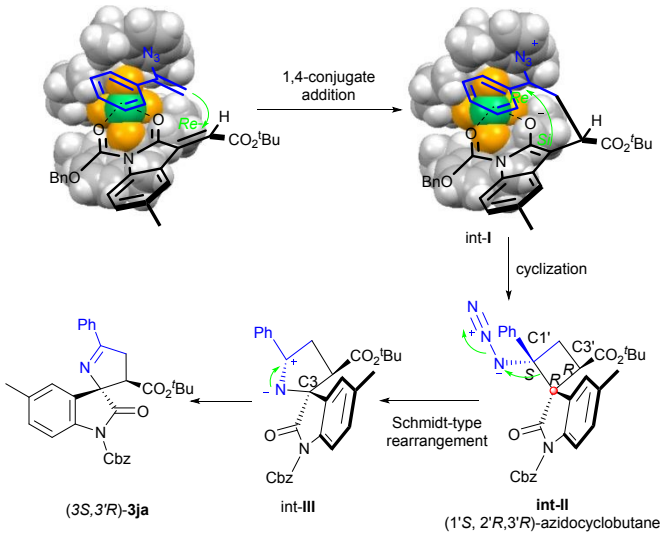
Scheme 4 (a) Scale-up synthesis of **3aa**; (b) transformation of the product **3ai**.

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.[4] When azirine **8** was used to react with **1a** under the standard conditions, no reaction occurred, ruling out the reaction pathway of undergoing 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 was 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 current catalytic system. The activation mode might be different from previous report using *N*-Bn or *N*-H based (*E*)-alkenyloxindole in the racemic version.[6a]



Scheme 5 Control experiments.

Based on the results of control experiment, X-ray structure of the product **3ja**[8] and $Ni(BF_4)_2{\cdot}6H_2O$/**L_3-PiEt$_2$** complex,[10] a possible reaction mechanism was proposed (Scheme 6). Firstly, (*E*)-alkenyloxindole **1j** was activated by bidentate coordination with the $Ni(BF_4)_2{\cdot}6H_2O$/**L_3-PiEt$_2$** complex.[11] 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_3-PiEt$_2$**. 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 spectroscopy (see 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_2 to form **int-III** through antiperiplanar migration, and the stereochemistry of C3 retains.[12] Finally, the imidization of **int-III** affords the desired product (3*S*, 3'*R*)-**3ja.**



Scheme 6 The proposed catalytic cycle and working mode.

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 chiral *N,N'*-dioxide/$Ni(BF_4)_2{\cdot}6H_2O$ complex benefited this reaction efficiently to afford diverse chiral spiropyrroline 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-spirocylic compounds by using vinyl azides are ongoing in our laboratory.

Safety notice: vinyl azides are classified as organic azides, which 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.

View Article Online
DOI: 10.1039/D0SC05768K

Acknowledgements

We appreciate the National Natural Science Foundation of China (No. 21801174) for financial support.

Notes and references

1 (a) B. D. Morris and M. R. Prinsep, *J. Nat. Prod.*, 1999, **62**, 688; (b) M. S. M. Pearson, N. Floquet, C. Bello, P. Voge, R. Plantier-Royon, J. Szymoniak, P. Bertus and J. B. Behr, *Bioorg. Med. Chem.*, 2009, **17**, 8020; (c) A. Khan, P. Wood, J. Moskal, *U.S. Patent* 20110306586, December 15, 2011; (d) Y. Hayashi, K. Sankar, H. Ishikawa, Y. Nozawa, K. Mizoue and H. Kakeya, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3863; (e) Y. Hayashi, M. Shoji, J. Yamaguchi, K. Sato, S. Yamaguchi, T. Mukaiyama, K. Sakai, Y. Asami, H. Kakeya and H. Osada, *J. Am. Chem. Soc.*, 2002, **124**, 12078; (f) Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673; (g) C. V. Galliford, K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748.

2 (a) Y. A. Ivanenkov, S. V. Vasilevski, E. K. Beloglazkina, M. E. Kukushkin, A. E. Machulkin, M. S. Veselov, N. V. Chufarova, E. S. Chernyaginab, A. S. Vanzcool, N. V. Zyk, D. A. Skvortsov, A. A. Khutornenko, A. L. Rusanov, A. G. Tonevitsky, O. A. Dontsova and A. G. Majouga, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 404; (b) W. Tan, X. T. Zhu, S. Zhang, G. J. Xing, R. Y. Zhu and F. Shi, *RSC Adv.*, 2013, **3**, 10875; (c) G. Bhaskar, Y. Arun, C. Balachandran, C. Saikumar and P. T. Perumal, *Eur. J. Med. Chem.*, 2012, **51**, 79; (d) K. Hagiwara, T. Murakami, G. Xue, Y. Shimizu, E. Takeda, Y. Hashimoto, K. Honda, Y. Kondoh, H. Osada, Y. Tsunetsugu-Yokota, Y. Aida, *Biochem. Biophys. Res. Commun.*, 2010, **394**, 721; (e) A. Kaur, S. Baldev, B. Vyas and O. Silakari, *Eur. J. Med. Chem.*, 2014, **79**, 282; (f) M. Ito, M. Iwatani, T. Yamamoto, T. Tanaka, T. Kawamoto, D. Morishita, A. Nakanishi and H. Maezaki, *Bioorg. Med. Chem. Lett.*, 2017, **25**, 4753.

3 (a) Y. M. Cao, F. F. Shen, F. T. Zhang and R. Wang, *Chem. Eur. J.*, 2013, **19**, 1184; (b) F. Tan and H. G. Cheng, *Targets in Heterocyclic Systems,* 2017, **21**, 158; (c) D. I. Jiang, S. D. Dong, W. F. Tang, T. Lu and D. Du, *J. Org. Chem.,* 2015, **80**, 11593; (d) L. Chen, Z. J. Wu, M. L. Zhang, D. F. Yue, X. M. Zhang, X. Y. Xu, W. C. Yuan, *J. Org. Chem.,* 2015, **80**, 12668; (e) P. Yang, X. Wang, F. Chen, Z. B. Zhang, C. Chen, L. Peng and L. X. Wang, *J. Org. Chem.,* 2017, **82**, 3908; (f) K. Q. Chen, Y. Li, C. L. Zhang, D. Q. Sun and S. Ye, *Org. Biomol. Chem.,* 2016, **14**, 2007; (g) X. Fang and C. J. Wang, *Org. Biomol. Chem.*, 2018, **16**, 2591; (h) H. Z. Gui, Y. Wei and M. Shi, *Chem. Asian J.*, 2020, **15**, 1225; (i) J. P. MacDonald, B. H. Shupe, J. D. Schreiber and A. K. Franz, *Chem. Commun.,* 2014, **50**, 5242; (j) S. Hajra and B. Jana, *Org. Lett.,* 2017, **19**, 4778; (k) A. A. Akaev and E. M. Budynina, *J. Org. Chem.*, 2019, **84**, 3340.

4 (a) M. O. Forster and S. H. Newman, *J. Chem. Soc., Trans.*, 1910, **97**, 2570; (b) M. O. Forster and S. H. Newman, *J. Chem. Soc., Trans.*, 1911, **99**, 1277; (c) N. Jung and S. Bräse, *Angew. Chem., Int. Ed.*, 2012, **51**, 12169; (d) E. A. Anderson and X. Bi, *Chem. Soc. Rev.*, 2017, **46**, 7208; (e) H. Hayashi, A. Kaga and S. Chiba, *J. Org. Chem.*, 2017, **82**, 11981.

5 (a) N. Thirupathi, F. Wei, C. H. Tung and Z. H. Xu, *Nat. Commun.*, 2019, **10**, 3158; (b) X. Q. Huang, X. Y. Li, X. L. Xie, K. Harms, R. Riedel and E. Meggers, *Nat. Commun.*, 2017, **8**, 2245; (c) T. Nakanishi, J. Kikuchi, A. Kaga, S. Chiba and M. Terada, *Chem. Eur. J.,* 2020, **26**, 8230.

6 (a)X. Zhu and S. Chiba, *Chem. Commun.*, 2016, **52**, 2473; (b) R. X. Yi, L. L. Qian and B. S. Wan, *Chin. J. Catal.*, 2019, **40**, 177.

7 For reviews of *N,N'*-dioxide ligands, see: (a) X. H. Liu, L. L. Lin and X. M. Feng, *Acc. Chem. Res.*, 2011, **44**, 574; (b) X. H. Liu, L. L. Lin and X. M. Feng, *Org. Chem. Front.*, 2014, **1**, 298; (c) X. H. Liu, H. F. Zheng, Y. Xia, L. L. Lin and X. M. Feng, *Acc. Chem. Res.*, 2017, **50**, 2621; (d) X. H. Liu, S. X. Dong, L. L. Lin and X. M. Feng, *Chin. J. Chem.,* 2018, **36**, 791; (e) Z. Wang, X. H. Liu, X. M. Feng, *Aldrichimica ACTA*, 2020, **53**, 3; (f) D. Zhang, Z. S. Su, Q. W. He, Z. K. Wu, Y. Q. Zhou, C. J. Pan, X. H. Liu and X. M. Feng, *J. Am. Chem. Soc.*, 2020, 142, **37**, 15975; (g) X. B. Lin, Z. Tan, W. K. Yang, W. Yang, X. H. Liu and X. M. Feng, *CCS Chem.*, 2020, **2**, 1423; (h) J. Xu, Z. W. Zhong, M. Y. Jiang, Y. Q. Zhou, X. H. Liu, X. M. Feng, DOI: 10.31635/ccschem.020.202000443.

8 For X-ray structure of product: CCDC: 1977126 (**3ja**).

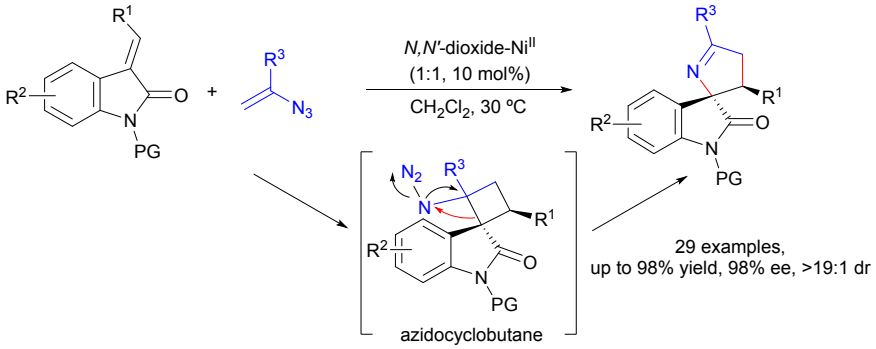
9 The absolute configuration of **5** was determined to be (3*S*, 3'*R*, 5'*R*) by NOESY spectra.

10 For X-ray structure of catalyst ($Ni(BF_4)_2{\cdot}6H_2O$/**L_3-PiEt$_2$**): J. Guo, X. H. Liu and X. M. Feng, *Chem. Commun.*, 2018, **54**, 12254. CCDC: 1831759.

11 (a) J. Guo, Y. B. Liu, X. Q. Li, X. H. Liu, L. L. Lin and X. M. Feng, *Chem. Sci.*, 2016, **7**, 2717; (b) X. J. Lian, S. S. Guo, G. Wang, L. L. Lin, X. H. Liu and X. M. Feng, *J. Org. Chem.*, 2014, **79**, 7703; (c) H. F. Zheng, P. He, Y. B. Liu, Y. L. Zhang, L. L. Lin, X. H. Liu and X. M. Feng, *Chem. Commun.*, 2014, **50**, 8794; (d) M. S. Xie, X. X. Wu, G. Wang, L. L. Lin and X. M. Feng, *Acta Chim. Sinica,* 2014, **72**, 856; (e) Y. H. Zhou, Y. Lu, X. Y. Hu, H. J. Mei, L. L. Lin, X. H. Liu and X. M. Feng, *Chem. Commun.*, 2017, **53**, 2060; (f) Y. H. Zhou, L. L. Lin, X. H. Liu, X. Y. Hu, Y. Lu, X. Y. Zhang, and X. M. Feng, *Angew. Chem., Int. Ed.*, 2018, **57**, 9113.

12 (a) X. M. Zhang, Y. Q. Tu, F. M. Zhang, Z. H. Chen and S. H. Wang, *Chem. Soc. Rev.*, 2017, **46**, 2272; (b) X. J. Wen, X. Y. Li, X. Luo, W. J. Wang, S. Song and N. Jiao, *Chem. Sci.*, 2020, **11**, 4482.

View Article Online
DOI: 10.1039/D0SC03776A



Lewis acid catalyzed asymmetric synthesis of 3,2'-pyrrolinyl spirooxindoles skeletons via conjugate addition/Schmidt-type rearrangement of vinyl azides and (*E*)-alkenyloxindoles.