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Catalytic Asymmetric Synthesis of Chiral Spiro-cyclopropyl Oxindoles from 3-Alkenyl-oxindoles and Sulfoxonium Ylides

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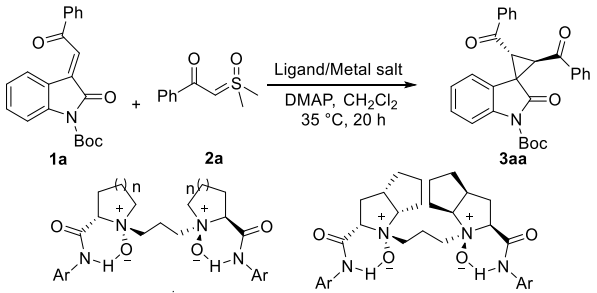
Abstract: A new enantioselective cyclopropanation of 3-alkenyl-oxindoles with sulfoxonium ylides was realized by using a chiral *N*,*N*′-dioxide/Mg(OTf)$_2$ complex as the catalyst. Various chiral spiro-cyclopropyl oxindoles containing two or three continuous chiral carbon centres were obtained in high yields (up to 99%) with good dr (up to 97:3 dr) and high *ee* values (up to 94% *ee*).

Keywords: asymmetric cyclopropanation; 3-alkenyl-oxindoles; *N*,*N*′-dioxides; sulfoxonium ylides; spiro-cyclopropyl oxindoles

Spiro-cyclopropyl oxindoles motifs are widely present in clinical pharmaceuticals and bioactive compounds,[1] such as HIV inhibitors,[2] kinase inhibitors[3] as well as antitumor agents.[4] Over the past decades, several methodologies have been developed for the construction of chiral spiro-cyclopropyl oxindoles skeletons, mainly including transition metal-catalyzed cyclopropanation of diazo oxindoles with alkenes,[5] organocatalytic Michael-initiated ring-closure reactions between α,β-unsaturated carbonyl compounds and 3-chloro-oxindoles,[6] 3-alkylidene oxindoles and alkyl halides,[7] oxindoles and bromo-nitroolefins.[8] Alternatively, our group reported chiral Lewis acid-catalyzed asymmetric cyclopropanation for construction of spiro-cyclopropyl oxindoles.[9] Phenyliodonium ylide was selected to generate *in situ* free triplet carbene reacting with 3-alkenyl-oxindoles in the presence of a chiral *N*,*N*′-dioxide/Ni(II) complex.[9a]

Sulfur (sulfonium and sulfoxonium) ylides[10] are important synthetic intermediates for cyclization reactions,[11] Stevens rearrangements,[10a,12] and they can also be used as carbene precursors in various carbene-participant reactions.[13] Among these efficient transformations, the reports of catalytic asymmetric reactions involving sulfoxonium ylide are rare.[14] Shibasaki and Matsunaga described an enantioselective cyclopropanation of enones and an *N*-acylpyrrole with dimethyloxosulfonium methylide using La-Li$_3$-(biphenyldiolate)$_3$ catalysts.[14a] The same group also reported the synthesis of chiral epoxides and oxetanes from ketones and dimethyloxosulfonium methylide catalyzed by the heterobimetallic catalysts.[14b-14d] Herein, we report our efforts in developing an *N*,*N*′-dioxide-Mg(II)

Table 1. Optimization of the reaction conditions.[a]



Entry	Ligand	Metal salt	Yield [%][b]	dr[c]	*ee* [%][c]
1	**L-PiPr$_2$**	Ni(OTf)$_2$	66	93:7	0
2	**L-PiPr$_2$**	Zn(OTf)$_2$	69	95:5	0
3	**L-PiPr$_2$**	Mg(OTf)$_2$	91	94:6	75
4	**L-PrPr$_2$**	Mg(OTf)$_2$	83	97:3	72
5	**L-RaPr$_2$**	Mg(OTf)$_2$	90	95:5	73
6	**L-PiEt$_2$**	Mg(OTf)$_2$	89	96:4	70
7	**L-PiPr$_3$**	Mg(OTf)$_2$	81	94:6	40
8[d]	**L-PiPr$_2$**	Mg(OTf)$_2$	99	92:8	91
9[e]	**L-PiPr$_2$**	Mg(OTf)$_2$	99	78:22	92

[a] Unless otherwise noted, the reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), ligand/metal salt (1:1, 10 mol%) and DMAP (1 equiv.) in CH_2Cl_2 (1.0 mL) under nitrogen atmosphere at 35 °C for 20 h.
[b] Isolated yield.
[c] Determined by chiral HPLC for the major diastereoisomer.
[d] DMAP (0.1 equiv.) was used. Reaction time was 16 h.
[e] Without DMAP.

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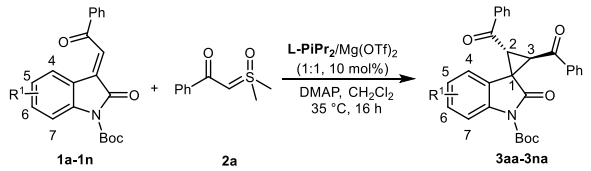
Table 2. Substrate scope of 3-phenacylideneoxindoles.[a]



Entry	R^1	Yield [%][b]	dr[c]	*ee* [%][d]
1	H	99 (**3aa**)	92:8	91
2	5-F	99 (**3ba**)	93:7	93
3	5-Cl	97 (**3ca**)	95:5	92
4	5-Br	99 (**3da**)	95:5	91
5	5-I	95 (**3ea**)	95:5	81
6	5-O_2N	81 (**3fa**)	95:5	66
7	5-F_3CO	98 (**3ga**)	90:10	91
8	5-Me	99 (**3ha**)	92:8	93
9	5-MeO	99 (**3ia**)	92:8	94
10	6-F	93 (**3ja**)	92: 8	93
11	6-Cl	97 (**3ka**)	92:8	92
12	6-Br	99 (**3la**)	92:8	92
13	7-F	91 (**3ma**)	97:3	93
14	5,7-2Me	99 (**3na**)	93:7	93

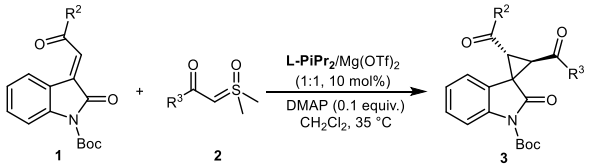
[a] Unless otherwise noted, the reactions were performed with **L-PiPr2**/Mg(OTf)$_2$ (1:1, 10 mol%), **1** (0.1 mmol), **2a** (0.11 mmol) and DMAP (0.1 equiv.) in CH_2Cl_2 (1.0 mL) under nitrogen atmosphere at 35 °C for 16 h.
[b] Isolated yield.
[c] Determined by chiral HPLC for the major diastereoisomer.
[d] Determined by chiral HPLC analysis.

complex catalytic system[15] for the catalytic asymmetric cyclopropanation of 3-alkenyl-oxindoles with sulfoxonium ylides to synthesize spiro-cyclopropyl oxindole derivatives.

Initially, *N*-Boc-3-phenacylideneoxindole **1a** and sulfoxonium ylide **2a** were chosen as the model substrates to optimize the reaction conditions. Various metal salts were screened by coordinating with **L-PiPr2** in the presence of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 at 35 °C (Table 1, entries 1-3). Both **L-PiPr2**/Ni(II) and **L-PiPr2**/Zn(II) complexes could promote the reaction but gave racemic products (Table 1, entries 1 and 2). The desired product **3aa** could be obtained in 91% yield, 94:6 dr and 75% *ee* by using **L-PiPr2**/Mg(II) complex as the catalyst (Table 1, entry 3). The investigation of the chiral backbone of the *N*,*N*′-dioxide ligands showed that L-pipecolic acid derived **L-PiPr2** was superior to L-proline-derived **L-PrPr2** and L-ramipril-derived **L-RaPr2** in term of enantioselectivity (Table 1, entry 3 *vs.* entries 4 and 5). Decreasing or increasing the steric hindrance of the amide moiety of the *N*,*N*′-dioxide ligands led to lower enantioselectivities (Table 1, entry 3 *vs.* entries 6 and 7). Then the amount of DMAP was screened. **3aa** could be obtained in 99% yield within 16 h in the presence of 0.1 equiv. DMAP, the enantioselectivity of the cyclopropanation was improved sharply (91% *ee*), along with slight decreasing of diastereoselectivity (Table 1, entry 8). A lower diastereoselectivity (78:22 dr) of the reaction was observed without the use of DMAP (Table 1, entry 9). On the basis of the ESI-MS analysis, a characteristic signal of [DMAP+**2a**+Na^+] at m/z 341.1286 (m/z calcd 341.1294) was observed when mixing DMAP with **2a**, suggesting DMAP had an interaction with sulfoxonium ylide, which may be the reason that improving the diastereoselectivity of the reaction. Therefore, the optimal reaction conditions were established as **L-PiPr2**/Mg(OTf)$_2$ (1:1, 10 mol%), DMAP (0.1 equiv.) in CH_2Cl_2 at 35 °C for 16 h.

The substrate scope was then evaluated. Diverse C5 position-substituted oxindoles could react with **2a** smoothly to give the corresponding products **3aa**-**3ea, 3ga**-**3ia** in 95-99% yield with 90:10-95:5 dr and 81-93% *ee* (Table 2, entries 1-5 and 7-9). The absolute configuration of **3ca** was determined to be (2*R*,3*R*) by X-ray crystallography analysis.[16] The reaction of **1f** bearing a strong electron-withdrawing group at the C5 position was performed as well with 95:5 dr and a moderate level of enantioselectivity (Table 2, entry 6). Both C6 and C7 position-substituted **1j**-**1m** were tolerated, affording the products in 91-99% yields,

Table 3. Substrate scope of **1** and sulfoxonium ylides.[a]



Entry	R^2, R^3	Yield [%][b]	dr[c]	*ee* [%][d]
1[e]	2-ClC_6H_4, 2-ClC_6H_4	61 (**3ab**)	87:13	93
2	3-ClC_6H_4, 3-ClC_6H_4	99 (**3ac**)	95:5	91
3	4-ClC_6H_4, 4-ClC_6H_4	98 (**3ad**)	95:5	88
4	4-FC_6H_4, 4-FC_6H_4	99 (**3ae**)	94:6	89
5	4-BrC_6H_4, 4-BrC_6H_4	99 (**3af**)	94:6	90
6	4-MeC_6H_4, 4-MeC_6H_4	75 (**3ag**)	87:13	94
7	4-$MeOC_6H_4$, 4-$MeOC_6H_4$	99 (**3ah**)	86:14	92
8[f]	4-FC_6H_4, Ph	98 (**3ai**)	85:15	83
9[f]	4-ClC_6H_4, Ph	96 (**3aj**)	86:14	83
10[g]	MeO, Ph	94 (**3ak**)	86:14	82
11	Me, Me	82 (**3al**)	95:5	77

[a] Unless otherwise noted, the reactions were performed with **L-PiPr2**/Mg(OTf)$_2$ (1:1, 10 mol%), **1** (0.1 mmol), **2** (0.11 mmol) and DMAP (0.1 equiv.) in CH_2Cl_2 (1.0 mL) under nitrogen atmosphere at 35 °C for 16 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] Determined by chiral HPLC for the major diastereoisomer.
[e] The reaction was performed at 50 °C for 10 h.
[f] **L-PrPr2** was used instead of **L-PiPr2**.
[g] **L-PiEt2Me** was used instead of **L-PiPr2**, DMAP (0.8 equiv.) was used.

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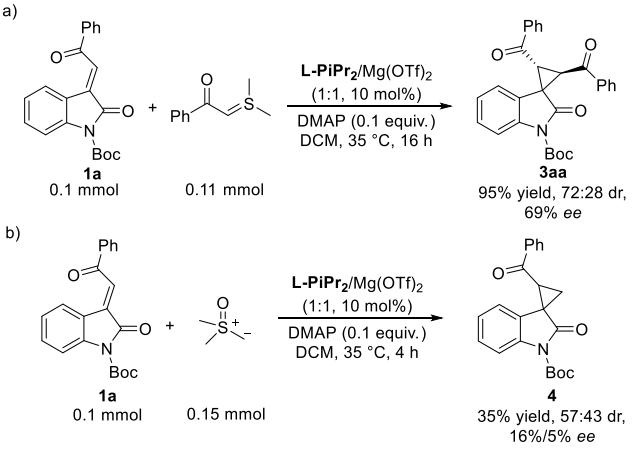
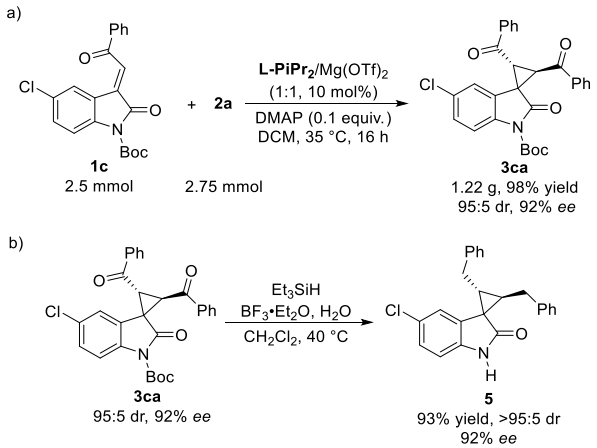
92:8-97:3 dr and 92-93% *ee* (Table 2, entries 10-13). The cyclopropanation of 5,7-dimethyl substituted **1n** with **2a** successfully proceeded to give good results (Table 2, entry 14).



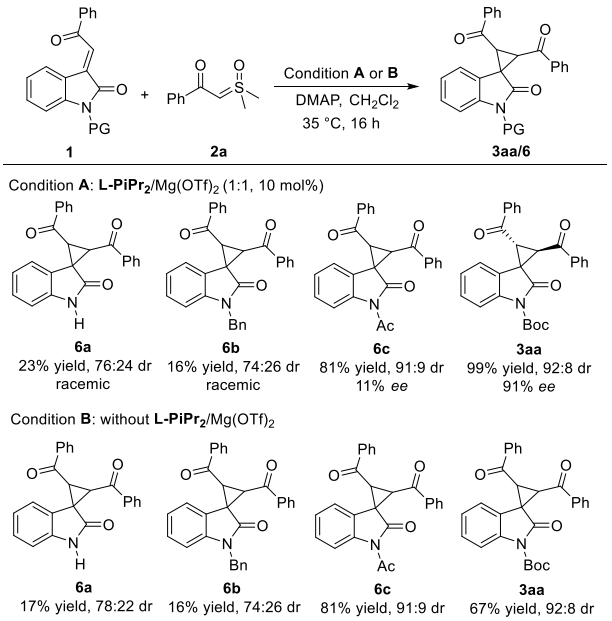
Scheme 1. Experimental results about other sulfur ylides.

Subsequently, we turned our attention to exploring the effects of the substituents R^2 and R^3 of acyl motifs in substrates **1** and **2**. The *ortho*-chloro-substituted product **3ab** was obtained in a lower yield than those with *meta*- or *para*-chloro-substituents (Table 3, entry 1 *vs.* entries 2 and 3). The enantioselective cyclopropanation could proceed smoothly no matter what R^2 and R^3 were electron-donating or electron-withdrawing substituents at *para*-position of the phenyl group, providing **3ad**-**3ah** in 75-99% yields, 86:14-95:5 dr and 88-94% *ee* (Table 3, entries 4-7). It was worth to note that the product **3ai**–**3ak** which contained three continuous chiral carbon centers were obtained with good results (Table 3, entries 8-10). **3al** ($R^2 = R^3 =$ Me) could also be achieved in 82% yield, 95:5 dr with 77% *ee* (Table 3, entry 11). In addition, some other sulfonium ylides were also explored under the standard conditions. Stabilized sulfonium ylide reacted with **1a** smoothly and gave the desired product **3aa** in 95% yield with 72:28 dr and 69% *ee* (Scheme 1a). The non-stabilized ylide like



Scheme 2. Scale-up reaction and derivatization.

Table 4. Control experiments.[a]



[a] The reactions were performed with **L-PiPr**$_2$/Mg(OTf)$_2$ (1:1, 10 mol%), **1** (0.1 mmol), **2a** (0.11 mmol) and DMAP (0.1 equiv.) in CH_2Cl_2 (1.0 mL) under nitrogen atmosphere at 35 °C for 16 h. Isolated yield. Dr was determined by ^{1}H NMR analysis. *Ee* was determined by chiral HPLC for the major diastereoisomer.

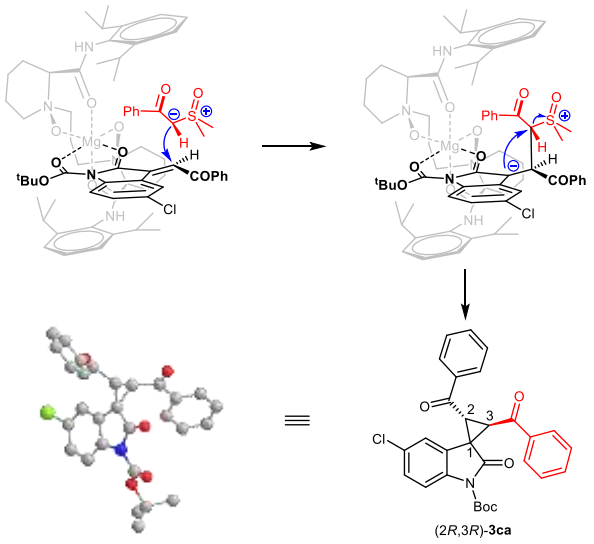
dimethyloxosulfonium methylide reacted with **1a** affording the product **4** in 35% yield, 57:43 dr and 16%/5% *ee* (Scheme 1b).

To evaluate the synthetic potential of this methodology, a gram scale reaction of **3ca** was carried out. **1c** (2.5 mmol) reacted with sulfoxonium ylide **2a** (2.75 mmol) smoothly, affording the desired product **3ca** in 98% yield (1.22 g), 95:5 dr and 92% *ee* (Scheme 2a). Furthermore, treating the product **3ca** with triethyl silane and boron trifluoride accessed **5** in 93% yield without loss of stereoselectivity (Scheme 2b).

Next, several control experiments were performed to investigate the mechanism of the cyclopropanation between 3-alkenyl-oxindoles and sulfoxonium ylides (Table 4). When 3-phenacylideneoxindole or *N*-Bn-3-phenacylideneoxindole was used instead of bidentate **1a** to react with **2a**, products **6a** or **6b** were obtained without any enantioselectivity. The yields of products **6a** and **6b** are low no matter with or without **L PiPr**$_2$/Mg(OTf)$_2$ complex in the reaction, suggesting that *N*-H and *N*-Bn substrates has low activities owing to lower electrophilicity. In addition, ^{1}H NMR spectra suggested that the acidic proton *N*-H of substrate interferes with the sulfoxonium ylide.[17] When an acetyl group was induced as a protecting group, the reaction could proceed well and afforded the desired product **6c** in 81% yield with 11% *ee* under condition **B**. When the reaction without **L-PiPr**$_2$/Mg(OTf)$_2$, the yield of **3aa** product reduced to 67%. These results suggested that the Boc group

combining to the nitrogen atom played a crucial role in achieving high reactivity and stereoselectivity.

Based on the X-ray crystal structure of the **L-PiPr$_2$**/Mg(OTf)$_2$ complex,[18] as well as the control experiments and our previous works,[15c] *N*-Boc-3-phenacylideneoxindole as the electron-deficient 2π component, the **L-PiPr$_2$**/Mg(OTf)$_2$ complex can lower the LUMO energy to increase its electrophilicity. On the other hand, the nucleophilicity of the sulfoxonium ylide will decrease if its carbonyl groups combine with the **L-PiPr$_2$**/Mg(OTf)$_2$ complex, which is against the first nucleophilic attack step. Thus, we tend to think that the catalyst coordinates with *N*-Boc-3-alkenyloxindole was superior to sulfoxonium ylide in this cyclopropanation. Meanwhile, a possible transition state model was described in Scheme 3. The tetradentate **L-PiPr$_2$** and the bidentate 3-phenacylideneoxindole **1c** coordinate with Mg(II) in an octahedral fashion. The *Si*-face of the 3-phenacylideneoxindole was shielded by the neighboring 2,6-diisopropylphenyl group of the ligand and sulfoxonium ylide attacked from the *Re*-face and the formed carbanion subsequently underwent S_N2 substitution along with the leaving of dimethylsulfoxide to achieve the product (2*R*,3*R*)-**3ca**.



Scheme 3. Proposed transition state model.

In summary, we have developed an efficient chiral *N*,*N*′-dioxide/Mg(OTf)$_2$ complex catalytic system for the asymmetric cyclopropanation of a series of 3-alkenyl-oxindoles with sulfoxonium ylides. The corresponding spiro-cyclopropyl oxindoles were obtained in high yields with good dr and high *ee* values. Further exploration of the reaction mechanism is currently underway.

Experimental Section

A dry reaction tube was charged with *N*-Boc-3-phenacylideneoxindole **1a** (0.10 mmol), Mg(OTf)$_2$ (3.2 mg, 10 mol%) and the ligand **L-PiPr$_2$** (6.5 mg, 10 mol%) in anhydrous CH_2Cl_2 (1.0 mL) under nitrogen atmosphere. The mixture was stirred at 35 °C for 0.5 h followed by addition of sulfoxonium ylide **2a** (0.11 mmol) and DMAP (1.2 mg, 0.1 equiv.) and then continued to stir at 35 °C for another 16 h. The residue was purified by flash chromatography on silica gel (ethylacetate/petroleum ether = 1:9 – 1:4) to afford the desired products.

Acknowledgments

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[16] CCDC 1838113 (**3ca**)

[17] If *N*-H substrate was mixed with sulfoxonium ylide, the chemical shift of *N*-H moved from 8.03 ppm to 8.60 ppm, suggesting that the acidic proton of *N*-H substrate interferes with the sulfoxonium ylide (See the spectra in the SI).

[18] CCDC 1838115 [**L-PiPr**$_2$/Mg(OTf)$_2$ complex]

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Catalytic Asymmetric Synthesis of Chiral Spiro-cyclopropyl Oxindoles from 3-Alkenyl-oxindoles and Sulfoxonium Ylides

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