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# Ni(II)/spiroBox-catalyzed asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes†

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Nickel complexes of chiral spiroBox ligand catalyzed Friedel–Crafts alkylation reaction of indoles with nitroalkenes. Excellent yields (up to 99%) and enantiomeric excess (ee) values (up to 97%) were obtained with a broad scope of substrates. This catalytic system provides a facile synthesis of optically active 2-indolyl-1-nitro derivatives with high yield and enantioselectivity.

## Introduction

The indole skeleton is one of the most extensively distributed heterocycles in nature and is widely used in the synthesis of pharmaceuticals, dyes, agrochemicals, and bioactivators.<sup>1–4</sup> The functionalization of C-3 indoles with other active substances is an effective and frequently used strategy to search for and design new drugs<sup>5,6</sup> (Fig. 1). The nitro group is the strongest electron-withdrawing group and is considered a versatile and unique functional group in medicinal chemistry. Due to the electron-deficient sites within molecules and their interaction with biological nucleophiles present in living systems, nitro-containing drugs have a long history of use in many therapeutic areas,<sup>7</sup> such as metronidazole, nifedipine, entacapone, and nitrazepam. Nitroalkenes are attractive Michael acceptors in the synthesis of nitro-containing compounds and can be easily transformed into a wide range of different functionalities.<sup>8,9</sup> The C-3 alkylated products of indoles with nitroalkenes can be used as precursors for the synthesis of clinical anticholinergic drugs.<sup>10</sup> Numerous groups have conducted research in this field, and asymmetric Friedel–Crafts (F–C) alkylation reactions have appeared to be a reliable strategy for synthesizing C-3 alkylated products of indoles with nitroalkenes. Different types of organic and organometallic catalysts indicate positive catalytic effectiveness.

Herrera<sup>11</sup> developed the first enantioselective F–C alkylation of indoles with nitroalkenes using thiourea-based organocatalyst, which provided optically active 2-indolyl-1-nitro derivatives in fairly good yields and enantioselectivities. Zhuang<sup>12</sup> showed that chiral hydrogen-bonding bis-sulfonamides were effective catalysts for the enantioselective F–C alkylation of indoles with nitroalkenes. Itoh<sup>13</sup> reported a chiral phosphoric

acid-catalyzed F–C alkylation of indoles with nitroalkenes to generate F–C adducts with excellent enantioselectivities, and the use of 3 Å molecular sieves led to efficient F–C alkylation in the presence of the chiral phosphoric acid. Dündar<sup>14</sup> described the use of chiral bifunctional quinine and 2-aminoDMAP-based squaramide organocatalysts for F–C alkylation of indoles and nitroalkenes, reporting high enantioselectivity (up to >99% ee) and moderate chemical yields (up to 80%). Zn(II) – catalyzed asymmetric F–C alkylation of indoles with nitroalkenes has been reported using different chiral ligands, such as diphenylamine-tethered bis(oxazoline) and bis(thiazoline) ligands,<sup>15</sup> oxazoline–imidazoline ligands,<sup>16</sup> bifunctional abietic-acid-derived thiourea ligands,<sup>17</sup> BINAM and H8-BINAM-based chiral imines ligands,<sup>18</sup> and bipyridine ligands.<sup>19</sup> Copper(I) trifluoromethanesulfonate benzene complex<sup>20</sup> and chloro-indeno pybox-Yb(OTf)<sub>3</sub> complex,<sup>21</sup> reported by Ramanathan and Tavakolian, respectively, also demonstrated excellent catalytic performance for this reaction under optimal conditions, respectively. Nickel is earth-abundant and many nickel complexes have been shown to be efficient catalysts for asymmetric synthesis.<sup>22–27</sup> However, there has been little work on constructing optically active 2-indolyl-1-nitro derivatives by utilizing nickel salts. Ligand design has been identified as a key

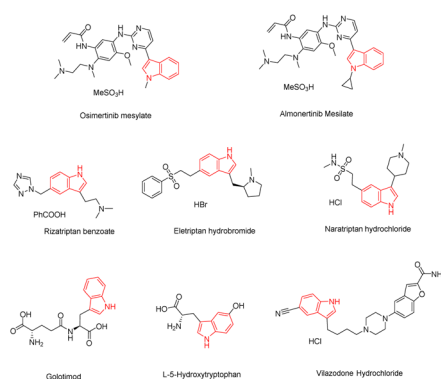


Fig. 1 Some commercial drugs with C-3 functionalized indoles.

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aspect in the development of nickel complexes for these valuable motifs.<sup>28,29</sup>

Since the past decades, chiral ligands based on spiro skeletons have received increasing attention and have gradually developed into a new type of chiral ligand with distinctive characteristics.<sup>30,31</sup> In view of the previous work of our research group, we designed and synthesized spiro indanyl *N,N*-ligands (Scheme 1). Compared with other ligands, we hypothesized that the *N,N*-ligands modified with a more rigid and bulky linker between the two coordinating sites could form a more rigid metallocycle with fewer available conformations, thereby enhancing the enantiofacial differentiation. The design strategies and synthetic routes of the ligands are outlined in Scheme 1. The Co(II)/spiroBox and Zn(II)/spiroQuinox complexes were successfully used as catalysts in the asymmetric Mukaiyama–Mannich reaction<sup>32</sup> and F–C alkylation reaction,<sup>33</sup> respectively. In continuation of our ongoing program aimed at exploring chiral spiro ligands, we report a complex of Ni(II) and chiral spiroBox ligand that catalyzed the asymmetric F–C alkylation reaction of indoles with nitroalkenes to construct optically active 2-indolyl-1-nitro derivatives. High yields (up to 99%) and excellent ee values (up to 97%) were obtained at 0 °C when catalyzed by the complex of spiroBox and Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O in CHCl<sub>3</sub>.

## Results and discussion

We commenced our investigation with the reaction of indole **2a** and nitroalkene **3a**. An initial test revealed that the reaction catalyzed with the complexes of **L1** and five Lewis acids gave very little product at 0 °C. Unsatisfactory yields and enantioselectivities were obtained when the reaction temperature was raised from 0 °C to 20 °C (Table 1, entries 1–4).

We were pleased to find that the complex of **L1** and Ni(OTf)<sub>2</sub> proved beneficial for the reaction, yielding product **1a** in 98% yield and 64% ee value (Table 1, entry 5). The absolute configuration of **1a** was assigned as *S* by comparison with literature data.<sup>16</sup> Subsequently, we screened different Ni(II) salts and found them crucial for the reaction (Table 1, entries 6–9). The reaction catalyzed with the complex of **L1** and Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O gave improved yield and ee value (98% yield and 73% ee, Table


Entry	Ligand	Metal	<i>x</i>	<i>y</i>	Yield <sup>b</sup> (%)	ee <sup>c,d</sup> (%)
1 <sup>e</sup>	<b>L1</b>	Zn(OTf) <sub>2</sub>	5	6	52	24
2 <sup>e</sup>	<b>L1</b>	Cu(OTf) <sub>2</sub>	5	6	44	41
3 <sup>e</sup>	<b>L1</b>	Fe(OTf) <sub>2</sub>	5	6	19	21
4 <sup>e</sup>	<b>L1</b>	Sc(OTf) <sub>3</sub>	5	6	37	0
5 <sup>e</sup>	<b>L1</b>	Ni(OTf) <sub>2</sub>	5	6	96	64
6	<b>L1</b>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	5	6	98	73
7	<b>L1</b>	Ni(acac) <sub>2</sub>	5	6	81	53
8	<b>L1</b>	NiCl <sub>2</sub> ·6H <sub>2</sub> O	5	6	56	29
9	<b>L1</b>	NiBr <sub>2</sub> ·6H <sub>2</sub> O	5	6	69	34
10	<b>L2</b>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	5	6	74	36
11	<b>L3a</b>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	5	6	83	30
12	<b>L3b</b>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	5	6	88	23
13	<b>L3c</b>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	5	6	79	19
14	<b>L4</b>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	5	6	89	55
15	<b>L1</b>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	7.5	9	98	77
16	<b>L1</b>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	10	12	98	81

<sup>a</sup> Reaction conditions: **2a** (0.1 mmol), **3a** (0.1 mmol), toluene (1 mL), monitored by TLC. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> The absolute configurations were assigned as **S** by comparison with literature data.<sup>16</sup> <sup>e</sup> 0 °C, 20 h, and then 20 °C.

1, entry 6). Other Ni(II) salts, such as Ni(acac)<sub>2</sub>, NiCl<sub>2</sub>·6H<sub>2</sub>O, and NiBr<sub>2</sub>·6H<sub>2</sub>O, resulted in moderate yields and lower ee values (Table 1, entries 7–9). The following test showed that the reaction catalyzed with the complexes of Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and chiral oxazoline ligands **L2**–**L4** yielded products in high yields but lower ee values (Table 1, entries 10–14). The ee values could be elevated when the catalyst loading increased to 7.5% and 10% (Table 1, entries 15 and 16).

The reaction was investigated under various conditions using a 10% loading of the complex of  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  and **L1**. As summarized in Table 2, we examined the effect of four different solvents—dichloromethane, chloroform, acetonitrile, and tetrahydrofuran—on the reaction yields and enantioselectivities at 0 °C (Table 2, entries 1–4). The results disclosed that chloroform was a more beneficial solvent for the reaction than toluene (Table 2, entry 2 vs. Table 1, entry 16). Subsequent optimization of the substrate ratio indicated that the best results were obtained with a molar ratio of **2a** to **3a** of 1 : 1.5 (Table 2, entries 5–7), suggesting that optimal results were achieved when the reactions were carried out at 0 °C. Relatively lower product yields and ee values were obtained when the reaction was performed at –10 °C or –20 °C (Table 2, entries 8 and 9).

The generality of the reactions was investigated under optimized conditions. A variety of substituted indoles and substituted nitroalkenes were examined. The results are summarized in Table 3; nitroalkenes with either electron-rich or electron-deficient substituents, such as –Me, –MeO, –Br, and –F on the aryl group (Table 3, entries 2–6), reacted smoothly with

Table 2 Optimization of the reaction conditions<sup>a</sup>


Entry	2a/3a (mmol)	T (°C)	Solvent	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	0.1/0.1	0	CH <sub>2</sub> Cl <sub>2</sub>	99	81
2	0.1/0.1	0	CHCl <sub>3</sub>	99	88
3	0.1/0.1	0	CH <sub>3</sub> CN	88	77
4	0.1/0.1	0	THF	79	59
5	0.1/0.12	0	CHCl <sub>3</sub>	99	89
6	0.1/0.15	0	CHCl <sub>3</sub>	98	93
7	0.1/0.2	0	CHCl <sub>3</sub>	95	78
8	0.1/0.15	−10	CHCl <sub>3</sub>	65	92
9	0.1/0.15	−20	CHCl <sub>3</sub>	17	89

<sup>a</sup> Reaction condition: solvent (1 mL), monitored by TLC. <sup>b</sup> Isolated yield.<sup>c</sup> Determined by HPLC analysis.

indole **2a** to obtain corresponding products in good to high yields (96–98%) and enantiomeric excess (82–94%).

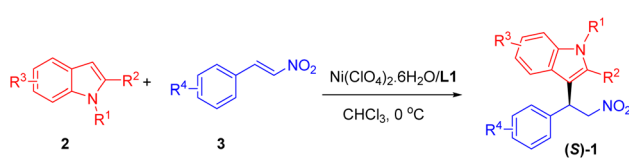
Furthermore, nitroalkene **3a** was reacted with various substituted indoles, resulting in high yields and excellent enantioselectivities in the case of *N*-alkylated indoles (Table 3, entries 8 and 9) and indoles substituted with both electron-donating and

electron-withdrawing groups on the C-5, C-6, and C-7 positions (Table 3, entries 13–18). C-2 and C-4 substituted indoles produced products with lower ee values or racemic products, likely due to steric hindrance (Table 3, entries 10–12).

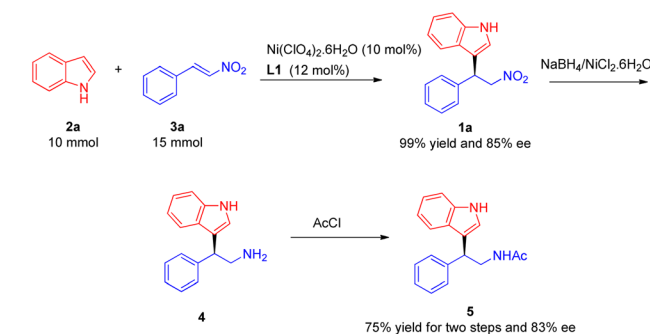
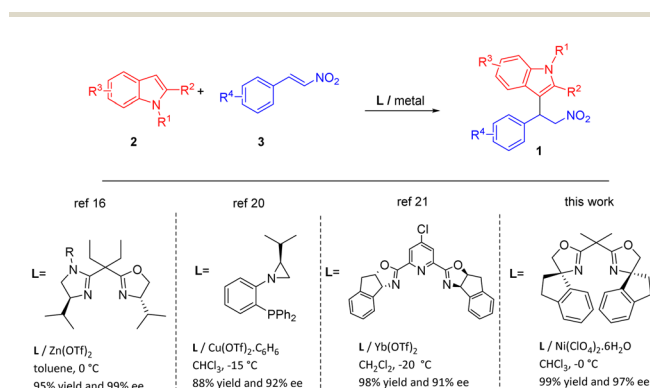
To test the scalability of this protocol, a gram-scale synthesis was conducted under the optimized conditions. The desired product **1a** was obtained in 99% yield and 85% ee value. Product **1a** was subsequently treated with NaBH<sub>4</sub> at 0 °C, resulting in chiral tryptamine derivative **4**, which could be isolated in 78% yield and 83% ee value as the corresponding acetylation derivative **5** (Scheme 2).

To the best of our knowledge, the use of a Ni complex in the asymmetric Friedel–Crafts alkylation reaction of indole with nitroalkenes has not been reported. We compared the catalytic activities of Ni(II)/spiroBox with those from other studies. As shown in Scheme 3, Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and spiro ligand in CHCl<sub>3</sub> at 0 °C proved suitable for the reaction.

Zhou<sup>34</sup> proposed a mechanism through a transition-state model for the Lewis acid-catalyzed F–C reaction of nitroalkenes and indoles, which introduced the 1,3-binding species with the metal of the chiral ligand. The mechanism can be explained using a catalytic cycle in Scheme 4. Firstly, to minimize unfavorable steric interactions between the benzene ring of the nitroalkene and the indane group on the oxazoline ring, the four-membered intermediate (ii) is generated by the coordination of the nitro and the spiroBox to Ni(II). Additionally, π–π stacking between the nitroalkene aromatic ring and the indane moiety of

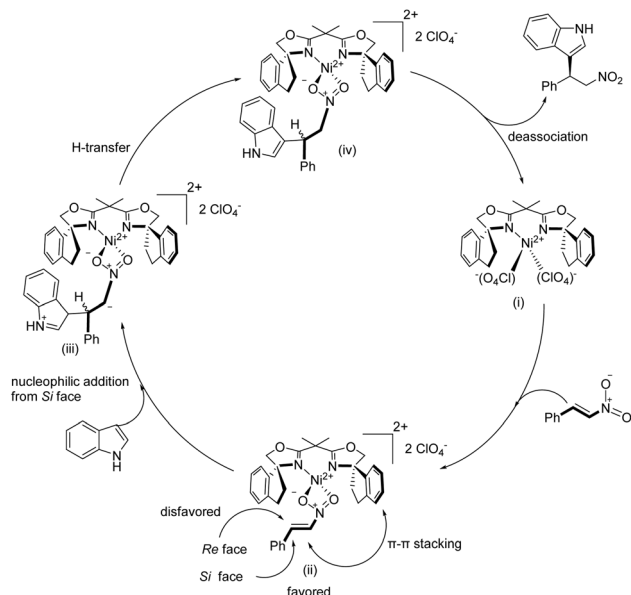
Table 3 Substrate scope of indoles and nitroalkenes<sup>a</sup>


Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Product	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	H	H	H	H	<b>1a</b>	98	93
2	H	H	H	4-CH <sub>3</sub>	<b>1b</b>	98	89
3	H	H	H	4-OCH <sub>3</sub>	<b>1c</b>	96	89
4	H	H	H	4-F	<b>1d</b>	98	88
5	H	H	H	4-Br	<b>1e</b>	97	94
6	H	H	H	3-OCH <sub>3</sub>	<b>1f</b>	97	94
7	H	H	H	2-Br	<b>1g</b>	96	82
8	−CH <sub>3</sub>	H	H	H	<b>1h</b>	99	94
9	−Bn	H	H	H	<b>1i</b>	96	97
10	H	−CH <sub>3</sub>	H	H	<b>1j</b>	95	10
11	H	−Ph	H	H	<b>1k</b>	89	11
12	H	H	4-CH <sub>3</sub>	H	<b>1l</b>	83	0
13	H	H	5-OCH <sub>3</sub>	H	<b>1m</b>	92	85
14	H	H	5-OBn	H	<b>1n</b>	94	89
15	H	H	5-Cl	H	<b>1o</b>	92	83
16	H	H	5-Br	H	<b>1p</b>	93	90
17	H	H	6-CH <sub>3</sub>	H	<b>1q</b>	90	86
18	H	H	7-CH <sub>3</sub>	H	<b>1r</b>	86	87

<sup>a</sup> Reaction conditions: **2** (0.1 mmol), **3** (0.15 mmol), Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (0.01 mmol), **L1** (0.012 mmol), CHCl<sub>3</sub> (1 mL), 0 °C, monitored by TLC.<sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC.Scheme 2 Gram-scale reaction and synthetic transformation of **1a**.

Scheme 3 Control experiments involving Ni(II)/spiroBox and other metal complexes.





**Scheme 4** Proposed catalytic cycle for the Friedel–Crafts alkylation of indole with nitroalkene.

the ligand causes the intermediate to adopt a fixed conformation. The nucleophilic addition of indole to the Si-face from the intermediate (ii) produces the intermediate (iii). Subsequently, H-transfer (iv), followed by dissociation, yields the *S* product and regenerates the Ni(II)/spiroBox catalyst (i).

## Experimental section

### General procedure for asymmetric Friedel–Crafts alkylation reaction

**L1** (4.6 mg, 0.012 mmol) and  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  (3.6 mg, 0.01 mmol) were dissolved in  $\text{CHCl}_3$  (1.0 mL) in a Schlenk tube under an Ar atmosphere at room temperature for 1 h. Nitroalkene (0.15 mmol) was then added, and the mixture was stirred at 0 °C for 30 min before indole (0.1 mmol) was added. The mixture was stirred at 0 °C until the reaction was complete (monitored by TLC). The solvent was removed under vacuum, and the residue was purified by chromatography on silica gel with petroleum ether/ethyl acetate 3 : 1 (v/v) to yield the product.

General procedures for the synthesis of ligands are shown in ESI files, S3–S7.†

## Conclusions

We reported a Ni(II)/spiroBox ligand complex catalytic asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes. This method provides facile access to the synthesis of 2-indolyl-1-nitro derivatives in high yields (up to 99%) and excellent ee values (up to 97%). Highlights of this method include mild reaction conditions, a wide substrate scope, and the use of a cheap and environmentally benign metal catalyst. Further applications of spiro ligands in other asymmetric transformations are currently being developed in our laboratory.

## Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Author contributions

Yanshun Li: formal analysis; investigation; methodology; validation. Shiqin Sun and Luzhen Jiao: formal analysis; validation. Nanxing Gao: project administration; validation. Guorui Cao: conceptualization; resources.

## Conflicts of interest

There are no conflicts to declare.

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