


 Cite this: *RSC Adv.*, 2025, 15, 7644

 Received 1st December 2024  
Accepted 8th February 2025

DOI: 10.1039/d4ra08471c

[rsc.li/rsc-advances](https://rsc.li/rsc-advances)

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

 Yanshun Li,<sup>ab</sup> Shiqin Sun,<sup>ab</sup> Luzhen Jiao,<sup>ab</sup> Nanxing Gao<sup>ab</sup> and Guorui Cao<sup>\*ab</sup>

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-indenopybox-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

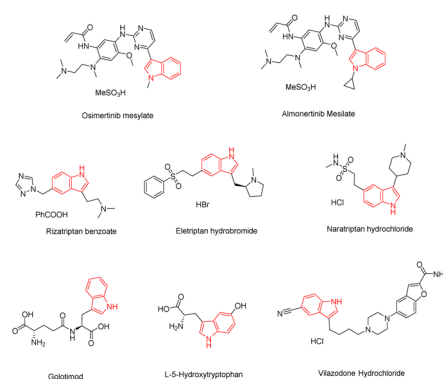
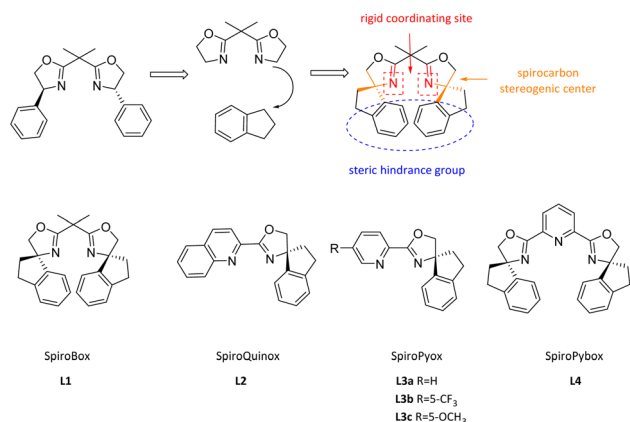


Fig. 1 Some commercial drugs with C-3 functionalized indoles.

<sup>a</sup>Department of Biological and Chemical Engineering, Shandong Vocational College of Science and Technology, Weifang 261053, China

<sup>b</sup>College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042, China

 † Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4ra08471c>


Scheme 1 Design and synthesis of spiro indanyl *N,N*-ligands.

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 metalocycle 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

Table 1 Scope of metals and ligands<sup>a</sup>

Entry	Ligand	Metal	x	y	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

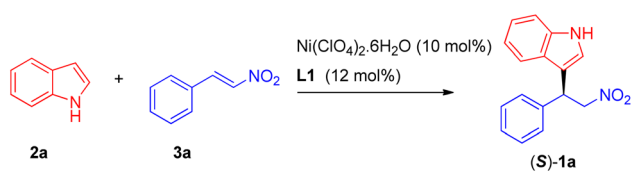
<sup>a</sup> Reaction conditions: **2a** (0.1 mmol), **3a** (0.1 mmol), toluene (1 mL), monitored by TLC. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> The absolute configurations were assigned as *S* by comparison with literature data.<sup>16</sup> <sup>e</sup> 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 Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>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).

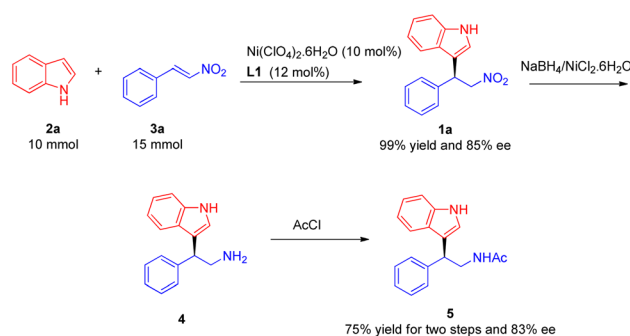
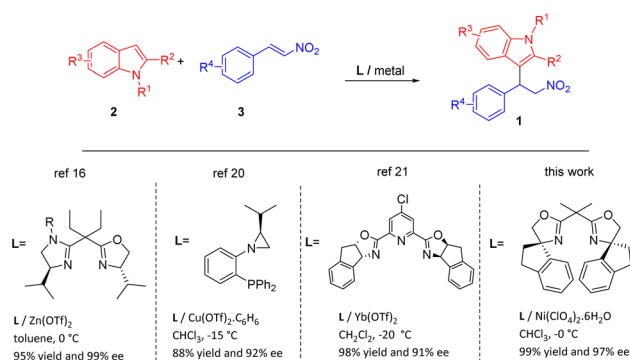
To the best of our knowledge, the use of a Ni complex in the asymmetric Friedel–Crafts alkylation reaction of indole with nitroalkenes has not been reported. We compared the catalytic activities of Ni(II)/spiroBox with those from other studies. As shown in Scheme 3, Ni(ClO<sub>4</sub>)<sub>2</sub>·6H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


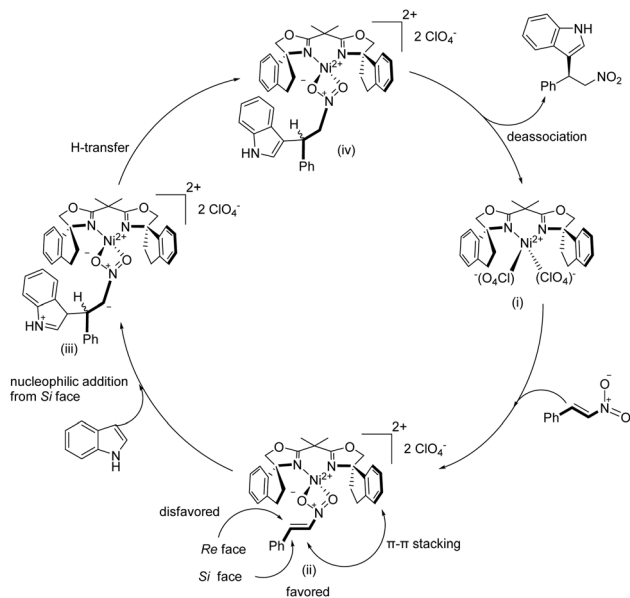
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Product	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	H	H	H	H	<b>1a</b>	98	93
2	H	H	H	4-CH <sub>3</sub>	<b>1b</b>	98	89
3	H	H	H	4-OCH <sub>3</sub>	<b>1c</b>	96	89
4	H	H	H	4 F	<b>1d</b>	98	88
5	H	H	H	4-Br	<b>1e</b>	97	94
6	H	H	H	3-OCH <sub>3</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 Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O (3.6 mg, 0.01 mmol) were dissolved in CHCl<sub>3</sub> (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.

## Notes and references

- 1 Y. Han, W. Dong, Q. Q. Guo, X. F. Li and L. J. Huang, *Eur. J. Med. Chem.*, 2020, **203**, 112506.
- 2 E. Keles, M. Yahya, E. Aktan, B. Aydinler, N. Seferoglu, A. Barsella and Z. Seferoglu, *J. Photochem. Photobiol., A*, 2020, **402**, 112818.
- 3 H. J. Song, J. L. Xie, W. T. Xu, Y. X. Liu, J. J. Zhang and Q. M. Wang, *J. Agric. Food Chem.*, 2020, **68**, 5555.
- 4 F. Omar, A. M. Tareq, A. M. Alqahtani, K. Dhama, M. A. Sayeed, T. B. Emran and J. S. Gandara, *Molecules*, 2021, **26**, 2297.
- 5 N. Tumey, M. Robarge, E. Gleason and J. P. Song, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3287.
- 6 A. Kumari and R. K. Singh, *Bioorg. Chem.*, 2019, **89**, 103021.
- 7 K. Nepali, H. Y. Lee and J. P. Liou, *J. Med. Chem.*, 2019, **62**, 2851.
- 8 O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, **12**, 1877.
- 9 G. Calderari and D. Seebach, *Helv. Chim. Acta*, 1985, **68**, 1592.
- 10 N. H. Greig, X. F. Pei, T. T. Soncrant, D. K. Ingram and A. Brossi, *Med. Res. Rev.*, 1995, **15**, 3.
- 11 R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576.
- 12 W. Zhuang, R. G. Hazell and K. A. Jørgensen, *Org. Biomol. Chem.*, 2005, **3**, 2566.
- 13 J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem., Int. Ed.*, 2008, **47**, 4016.
- 14 E. Dündar and C. Tanyeli, *Tetrahedron Lett.*, 2021, **73**, 153153.
- 15 H. Liu, S. F. Lu, J. X. Xu and D. M. Du, *Chem.–Asian J.*, 2008, **3**, 1111.
- 16 M. S. Islam, A. M. A. A. Majid, Z. A. A. Othman and A. Barakat, *Tetrahedron: Asymmetry*, 2014, **25**, 245.
- 17 W. G. Huang, H. S. Wang, G. B. Huang, Y. M. Wu and Y. M. Pan, *Eur. J. Org. Chem.*, 2012, **2012**, 5839.
- 18 Z. L. Yuan, Z. Y. Lei and M. Shi, *Tetrahedron: Asymmetry*, 2008, **19**, 1339.
- 19 K. Venkatanna, S. Y. Kumar, M. Karthick, R. Padmanaban and C. R. Ramanathan, *Org. Biomol. Chem.*, 2019, **17**, 4077.



- 20 A. Buchcic, A. Zawisza, S. Leśniak and M. Rachwalski, *Catalysts*, 2020, **10**, 971.
- 21 B. Karimi, E. Jafari, F. Mansouri and M. Tavakolian, *Sci. Rep.*, 2023, **13**, 14736.
- 22 L. Xie, H. L. Ma, J. Q. Li, Y. Yu, Z. H. Qin and B. Fu, *Org. Chem. Front.*, 2017, **4**, 1858.
- 23 R. Sun, Z. X. Qiu, G. R. Cao and D. W. Teng, *Tetrahedron*, 2020, **76**, 131201.
- 24 C. Fischer and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 4594.
- 25 H. Ren, X. Y. Song, S. R. Wang, L. J. Wang and Y. Tang, *Org. Lett.*, 2018, **20**, 3858.
- 26 H. Y. Xu, P. Yang, P. Chuanprasit, H. Hirao and J. R. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 5112.
- 27 R. R. Liu, D. J. Wang, L. Wu, B. Xiang, G. Q. Zhang, J. R. Gao and Y. X. Jia, *ACS Catal.*, 2015, **5**, 6524.
- 28 M. P. Carroll and J. Guiry, *Chem. Soc. Rev.*, 2014, **43**, 819.
- 29 Y. Liu, W. Li and J. Zhang, *Natl. Sci. Rev.*, 2017, **4**, 326.
- 30 J. H. Xie and Q. L. Zhou, *Acc. Chem. Res.*, 2008, **41**, 581.
- 31 G. B. Bajracharya, *J. Nepal. Chem. Soc.*, 2011, **28**, 1.
- 32 Y. S. Li, N. X. Gao, G. R. Cao and D. W. Teng, *New J. Chem.*, 2022, **46**, 6121.
- 33 Y. S. Li, M. Q. Dong, N. X. Gao, G. R. Cao and D. W. Teng, *Appl. Organomet. Chem.*, 2022, **36**, e6635.
- 34 Y. X. Jia, S. F. Zhu, Y. Yang and Q. L. Zhou, *J. Org. Chem.*, 2006, **71**, 75.

