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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.[1–4] The functionalization of C-3 indoles with other active substances is an effective and frequently used strategy to search for and design new drugs[5,6] (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,[7] 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.[8,9] The C-3 alkylated products of indoles with nitroalkenes can be used as precursors for the synthesis of clinical anticholinergic drugs.[10] 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[11] 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[12] showed that chiral hydrogen-bonding bis-sulfonamides were effective catalysts for the enantioselective F–C alkylation of indoles with nitroalkenes. Itoh[13] 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[14] 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,[15] oxazoline–imidazoline ligands,[16] bifunctional abietic-acid-derived thiourea ligands,[17] BINAM and H8-BINAM-based chiral imines ligands,[18] and bipyridine ligands.[19] Copper(I) trifluoromethanesulfonate benzene complex[20] and chloro-indeno pybox-Yb(OTf)$_3$ complex,[21] 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.[22–27] 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

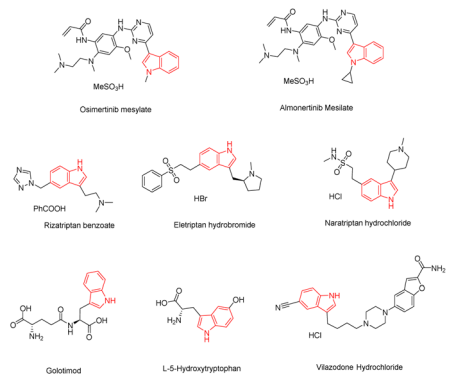

Fig. 1 Some commercial drugs with C-3 functionalized indoles.

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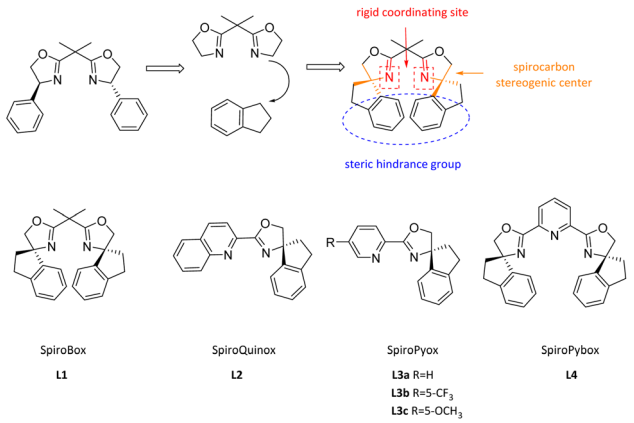


Scheme 1 Design and synthesis of spiro indanyl *N*,*N*-ligands.

aspect in the development of nickel complexes for these valuable motifs.[28,29]

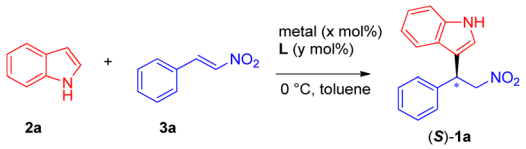
Since the past decades, chiral ligands based on spiro skeletons have received increasing attention and have gradually developed into a new type of chiral ligand with distinctive characteristics.[30,31] In view of the previous work of our research group, we designed and synthesized spiro indanyl *N*,*N*-ligands (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[32] and F–C alkylation reaction,[33] 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 $Ni(ClO_4)_2\cdot 6H_2O$ in $CHCl_3$.

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 $Ni(OTf)_2$ 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.[16] 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 $Ni(ClO_4)_2\cdot 6H_2O$ gave improved yield and ee value (98% yield and 73% ee, Table 1, entry 6). Other Ni(II) salts, such as $Ni(acac)_2$, $NiCl_2\cdot 6H_2O$, and $NiBr_2\cdot 6H_2O$, 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 $Ni(ClO_4)_2\cdot 6H_2O$ 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).

Table 1 Scope of metals and ligands[a]



Entry	Ligand	Metal	*x*	*y*	Yield[b] (%)	ee[c,d] (%)
1[e]	**L1**	$Zn(OTf)_2$	5	6	52	24
2[e]	**L1**	$Cu(OTf)_2$	5	6	44	41
3[e]	**L1**	$Fe(OTf)_2$	5	6	19	21
4[e]	**L1**	$Sc(OTf)_3$	5	6	37	0
5[e]	**L1**	$Ni(OTf)_2$	5	6	96	64
6	**L1**	$Ni(ClO_4)_2\cdot 6H_2O$	5	6	98	73
7	**L1**	$Ni(acac)_2$	5	6	81	53
8	**L1**	$NiCl_2\cdot 6H_2O$	5	6	56	29
9	**L1**	$NiBr_2\cdot 6H_2O$	5	6	69	34
10	**L2**	$Ni(ClO_4)_2\cdot 6H_2O$	5	6	74	36
11	**L3a**	$Ni(ClO_4)_2\cdot 6H_2O$	5	6	83	30
12	**L3b**	$Ni(ClO_4)_2\cdot 6H_2O$	5	6	88	23
13	**L3c**	$Ni(ClO_4)_2\cdot 6H_2O$	5	6	79	19
14	**L4**	$Ni(ClO_4)_2\cdot 6H_2O$	5	6	89	55
15	**L1**	$Ni(ClO_4)_2\cdot 6H_2O$	7.5	9	98	77
16	**L1**	$Ni(ClO_4)_2\cdot 6H_2O$	10	12	98	81

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

The reaction was investigated under various conditions using a 10% loading of the complex of $Ni(ClO_4)_2\cdot 6H_2O$ 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[a]

Entry	2a/3a (mmol)	T (°C)	Solvent	Yield[b] (%)	ee[c] (%)
1	0.1/0.1	0	CH_2Cl_2	99	81
2	0.1/0.1	0	$CHCl_3$	99	88
3	0.1/0.1	0	CH_3CN	88	77
4	0.1/0.1	0	THF	79	59
5	0.1/0.12	0	$CHCl_3$	99	89
6	0.1/0.15	0	$CHCl_3$	98	93
7	0.1/0.2	0	$CHCl_3$	95	78
8	0.1/0.15	−10	$CHCl_3$	65	92
9	0.1/0.15	−20	$CHCl_3$	17	89

[a] Reaction condition: solvent (1 mL), monitored by TLC. [b] Isolated yield. [c] Determined by HPLC analysis.

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

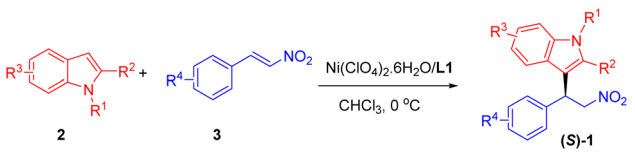
Furthermore, nitroalkene **3a** was reacted with various substituted indoles, resulting in high yields and excellent enantioselectivities in the case of *N*-alkylated indoles (Table 3, entries 8 and 9) and indoles substituted with both electron-donating and electron-withdrawing groups on the C-5, C-6, 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 $NaBH_4$ 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, $Ni(ClO_4)_2 \cdot 6H_2O$ and spiro ligand in $CHCl_3$ at 0 °C proved suitable for the reaction.

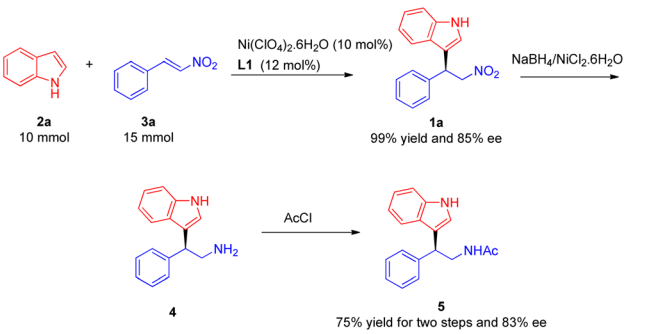
Zhou[34] proposed a mechanism through a transition-state model for the Lewis acid-catalyzed F–C reaction of nitroalkenes and indoles, which introduced the 1,3-binding species with the metal of the chiral ligand. The mechanism can be explained using a catalytic cycle in Scheme 4. Firstly, to minimize 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[a]

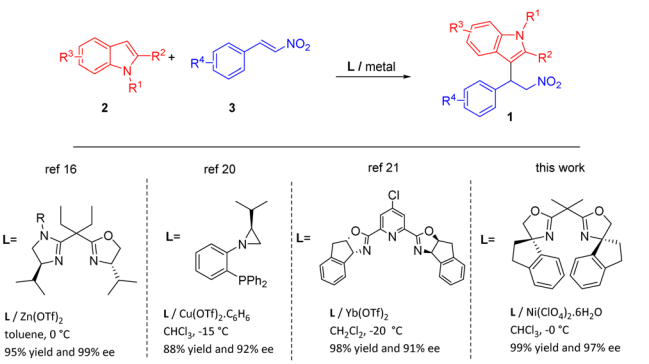


Entry	R^1	R^2	R^3	R^4	Product	Yield[b] (%)	ee[c] (%)
1	H	H	H	H	**1a**	98	93
2	H	H	H	4-CH_3	**1b**	98	89
3	H	H	H	4-OCH_3	**1c**	96	89
4	H	H	H	4 F	**1d**	98	88
5	H	H	H	4-Br	**1e**	97	94
6	H	H	H	3-OCH_3	**1f**	97	94
7	H	H	H	2-Br	**1g**	96	82
8	–CH_3	H	H	H	**1h**	99	94
9	–Bn	H	H	H	**1i**	96	97
10	H	–CH_3	H	H	**1j**	95	10
11	H	–Ph	H	H	**1k**	89	11
12	H	H	4-CH_3	H	**1l**	83	0
13	H	H	5-OCH_3	H	**1m**	92	85
14	H	H	5-OBn	H	**1n**	94	89
15	H	H	5-Cl	H	**1o**	92	83
16	H	H	5-Br	H	**1p**	93	90
17	H	H	6-CH_3	H	**1q**	90	86
18	H	H	7-CH_3	H	**1r**	86	87

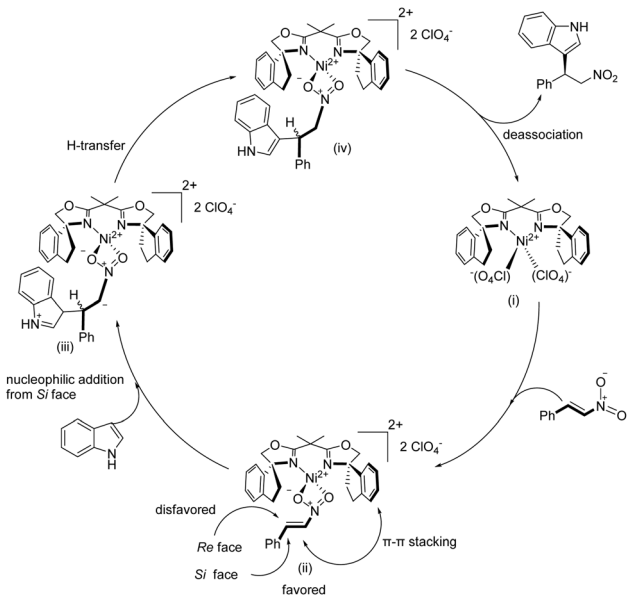
[a] Reaction conditions: **2** (0.1 mmol), **3** (0.15 mmol), $Ni(ClO_4)_2 \cdot 6H_2O$ (0.01 mmol), **L1** (0.012 mmol), $CHCl_3$ (1 mL), 0 °C, monitored by TLC. [b] Isolated yield. [c] Determined by HPLC.



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 $Ni(ClO_4)_2 \cdot 6H_2O$ (3.6 mg, 0.01 mmol) were dissolved in $CHCl_3$ (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.

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. Aydiner, 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.