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Access to distal biaxial atropisomers by iridium catalyzed asymmetric C–H alkylation†

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Distal biaxial atropisomers are typical structures in chiral catalysts and ligands and offer a wide variety of applications in biology and materials technology, but the development of efficient synthesis of these valuable scaffolds is still in great demand. Herein, we describe a highly efficient iridium catalyzed asymmetric C–H alkylation reaction that provides a range of new distal biaxial atropisomers with excellent yields (up to 99%) and stereoselectivity (up to 99% ee and essentially one isomer). Based on this unprecedented strategy, a polycyclic skeleton with five successive chiral centers as well as C–C and C–N (or N–N) two distal chiral axes was created successfully in mild circumstances. In addition, the optically pure products bearing fluorophores show circular polarized luminescence (CPL) properties, being potential candidate materials for CPL applications.

Introduction

Atropisomers are common structural motifs in natural products,¹ chiral catalysts,² and functional materials.³ Due to their significant importance, a lot of investigations have been conducted on the enantioselective synthesis of these compounds, especially the biaryls, which are the most representative atropisomers with a single chiral axis.⁴ But it is noteworthy that atropisomers containing chiral diaxes, particularly when the position of chiral axes is at quite a distance,⁵ also demonstrate unique features and applications in the disciplines of drug development,⁶ materials research,⁷ catalysis⁸ and ligand design⁹ (Scheme 1a). Nevertheless, due to the spatial interaction of various chiral axes, distal biaxial atropisomers have more challenges in diastereoselective and enantioselective control. Up to now, only a few examples of the efficient asymmetric construction of distal biaxial atropisomers have been reported. In 2019, Yan and co-workers have demonstrated a highly diastereo- and enantio-selective organocatalytic strategy for the synthesis of molecules featuring helicenes and two distal stereogenic axes¹⁰ *via* the corresponding VQM intermediate (Scheme 1b).¹¹ In 2020, Bonne and co-workers reported a bidirectional enantioselective synthesis of bis-benzofuran

atropisomeric oligoarenes containing two distal C–C stereogenic axes, which were obtained by a two-fold central-to-axial chirality conversion upon oxidative aromatization (Scheme 1b).¹² In the same year, Shibata and co-workers reported a cycloisomerization strategy closely related to (2 + 2 + 2) cycloaddition for the enantioselective synthesis of unichiral and distal biaxial chiral polycyclic hydrocarbons (PAHs) (Scheme 1b).¹³ Despite the effectiveness of the reported reaction modes, there are still plenty of challenges to overcome in the development of new methods for the synthesis of distal-axes chiral molecules.

In recent decades, transition metal-catalyzed C–H activation reactions involving the (dynamic) kinetic resolution or desymmetrization process for the construction of atropisomers have attracted great prominence as a potent tactic.¹⁴ Compared with traditional coupling reactions, this approach exhibits good atom economy, high synthetic efficiency, and significantly widens the range of substrates. The utilization of C–H activation for the synthesis of uniaxial chiral compounds has so far produced impressive results,¹⁵ but the synthesis of multiaxial chirality still presents a significant difficulty, and little progress has been made until recently. Lassaletta,¹⁶ He,¹⁷ Ackermann¹⁸ and our group¹⁹ successfully accomplished the molecules with excellent axial and central chirality; Wencel-Delord and Colobert,²⁰ Zhou,²¹ Niu²² and Shi²³ respectively succeeded in the formation of enantiopure vicinal 1,2-diaxes compounds; and most recently, our group²⁴ reported highly atroposelective construction of 1,3-diaxes compounds *via* C–H activation; in addition, the synthesis of chiral 1,4-diaxes compound utilizing two fold C–H activation strategy was reported by Shi and co-workers²⁵ (Scheme 1c). These works mainly focus on transition metals such as Pd, Rh, Co, Cu, Ru, *etc.*, using sequential control

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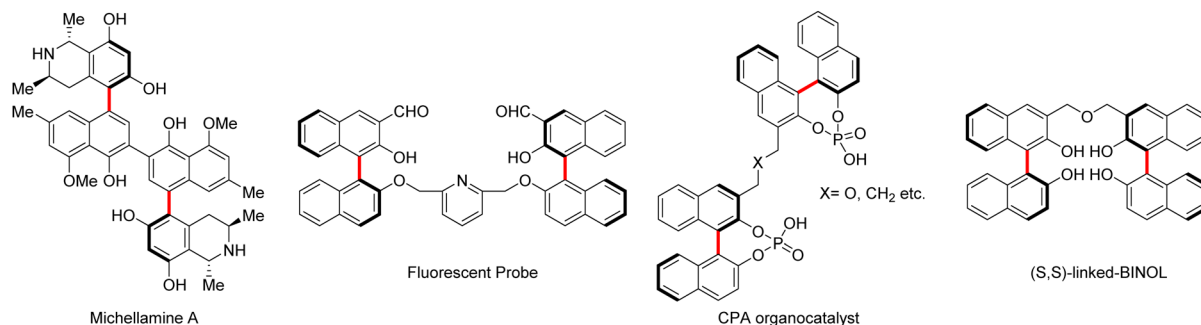
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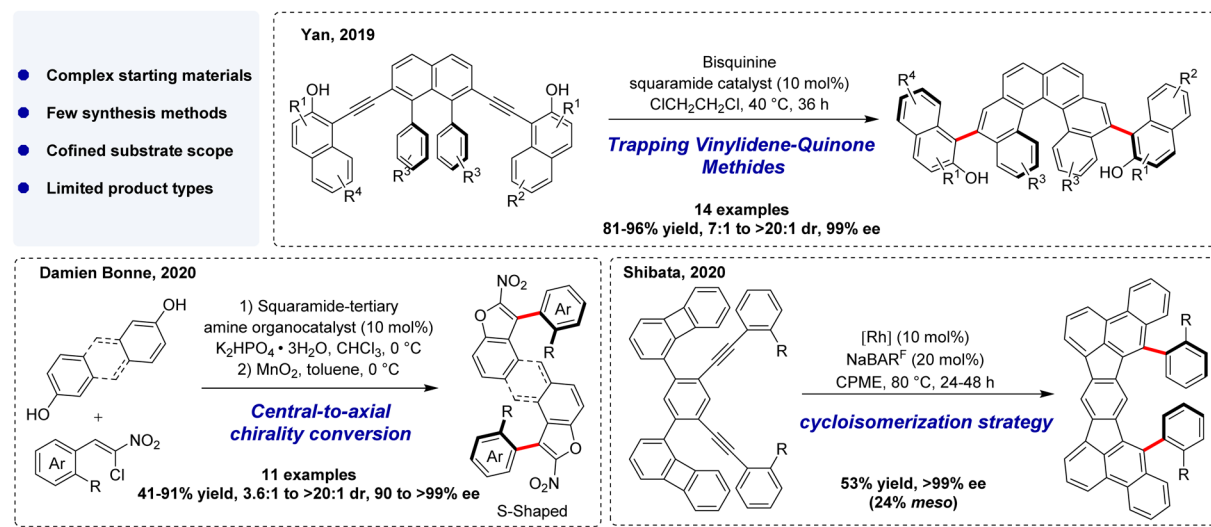
‡ The authors have contributed equally.



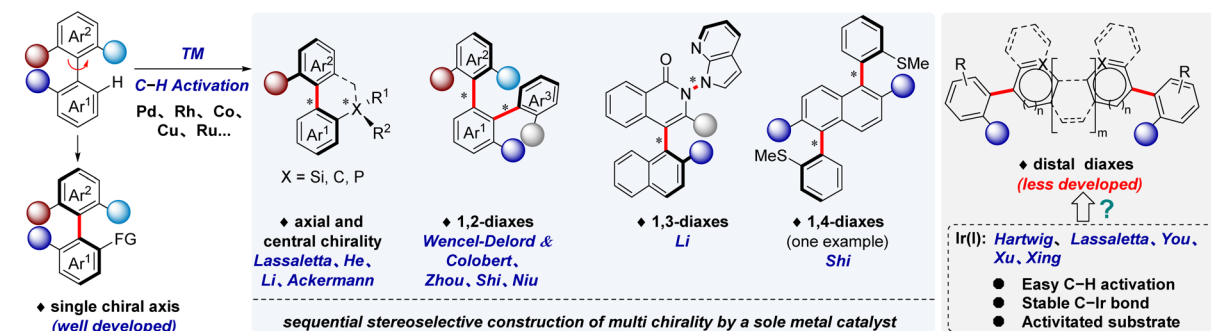
(a) Representative atropisomers with distal diaxes



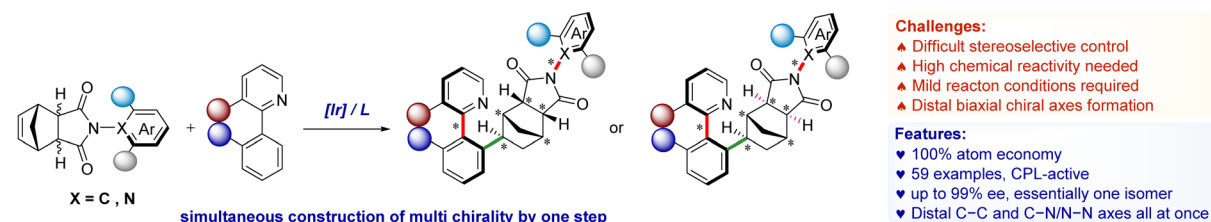
(b) Previous works in the synthesis of distal biaxial atropisomers



(c) General strategy for the construction of atropisomers through transition metal-catalyzed C-H activation



(d) This work: Transition metal-catalyzed C-H alkylation in combination with desymmetrization strategy for the synthesis of distal biaxial atropisomers



Scheme 1 Background for the development of current work.

to complete the construction of multiple chiral axes or chiral centers. However, this approach makes it more challenging to simultaneously control the enantioselectivity and diastereoselectivity of the products, particularly when the multiple

chiral axes are distally distributed. Consequently, there is an urgent need to find solutions to these problems.

Recently, as a potent tool for the activation of C-H bonds,²⁶ iridium(i) complexes have garnered a lot of interest in the realm



of the enantioselective synthesis of atropisomers. The synthesis of axially chiral scaffolds is made possible by the reaction of the stable C–Ir bond with activated substrate, which guarantees a smooth reaction and leads to a more effective response. Notably, some elegant works have been reported by Hartwig,²⁷ Lassaletta,^{16,28} Xu,²⁹ You,³⁰ and Xing.³¹ Despite the significant progress in this research area, however, these reports focus on the construction of atropisomers featuring one stereogenic axis, atroposelective synthesis of distal biaxial atropisomers *via* C–H activation remains underexplored. This probably due to (1) the great difficulty in assembling multiple distal stereogenic axes with a high degree of enantioselective control and (2) the high steric requirements of the substrates needed to stop the rotation of multiple distal stereogenic axes reducing their chemical reactivity. Recently, our interest was drawn to the ability of *N*-aryl maleimide derivative as a Diels–Alder adduct from cyclopentadiene and maleimide with a prochiral C–N axis,³² which can desymmetrally build a C–N axis chiral scaffold. Inspired by this, we wondered if a new distal biaxial chiral molecule with both C–C and C–N (or N–N) axes could be generated with a *N*-aryl maleimide derivative and heterobiaryl as precursor materials using an iridium(i) catalyzed C–H activation in combination with desymmetrization strategy (Scheme 1d). Herein, we describe the details of this study towards distal biaxial chiral compounds by iridium catalyzed asymmetric C–H alkylation.

Results and discussion

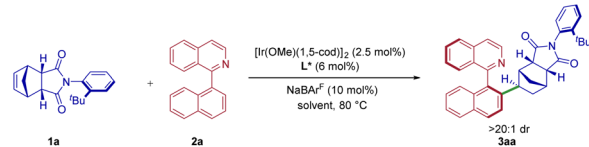
Reaction optimization

To explore the proposed construction of new distal biaxial atropisomers, preliminary studies were carried out using *N*-aryl 5-norbornene-*endo-cis*-2,3-dicarboximides **1a** and naphthylisoquinoline **2a** as the model substrates. The reaction parameters, including catalyst, ligand, solvent, and temperature, were carefully optimized (see the ESI† for more details). First, ligands **L1**–**L6**, which were previously used in the asymmetric C–H functionalization reactions, were investigated, and proven to be a significant influence on this transformation (Table 1, entries 1–6). Although none of the screening ligands gave satisfactory results, the attempt of **L2** gave **3aa** with excellent enantioselectivity albeit with low yield (Table 1, entry 2). To further improve the yield, we evaluated the influence of other critical reaction parameters, such as the solvent (Table 1, entries 7–13). We found that toluene was the best choice for this iridium catalyzed asymmetric C–H alkylation (Table 1, entry 11). After considerable optimization (Table 1), a combination of [Ir(OMe)(1,5-cod)]₂ (2.5 mol%), **L2** (6 mol%) and 10 mol% NaBAR^F (Ar^F = 3,5-CF₃-C₆H₃) in toluene at 80 °C for 24 h afforded the best results, giving rise to distal biaxial atropisomer **3aa** in quantitative yield with 97% ee and high diastereoselectivity (>20 : 1 dr).

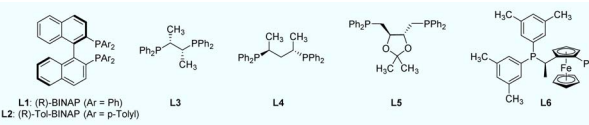
Reaction scope

With the optimal conditions in hand, we subsequently examined the iridium catalyzed asymmetric C–H alkylation reactions of a series of *N*-aryl maleimide derivatives **1** with various

Table 1 Summary of selected optimization of reaction conditions^a



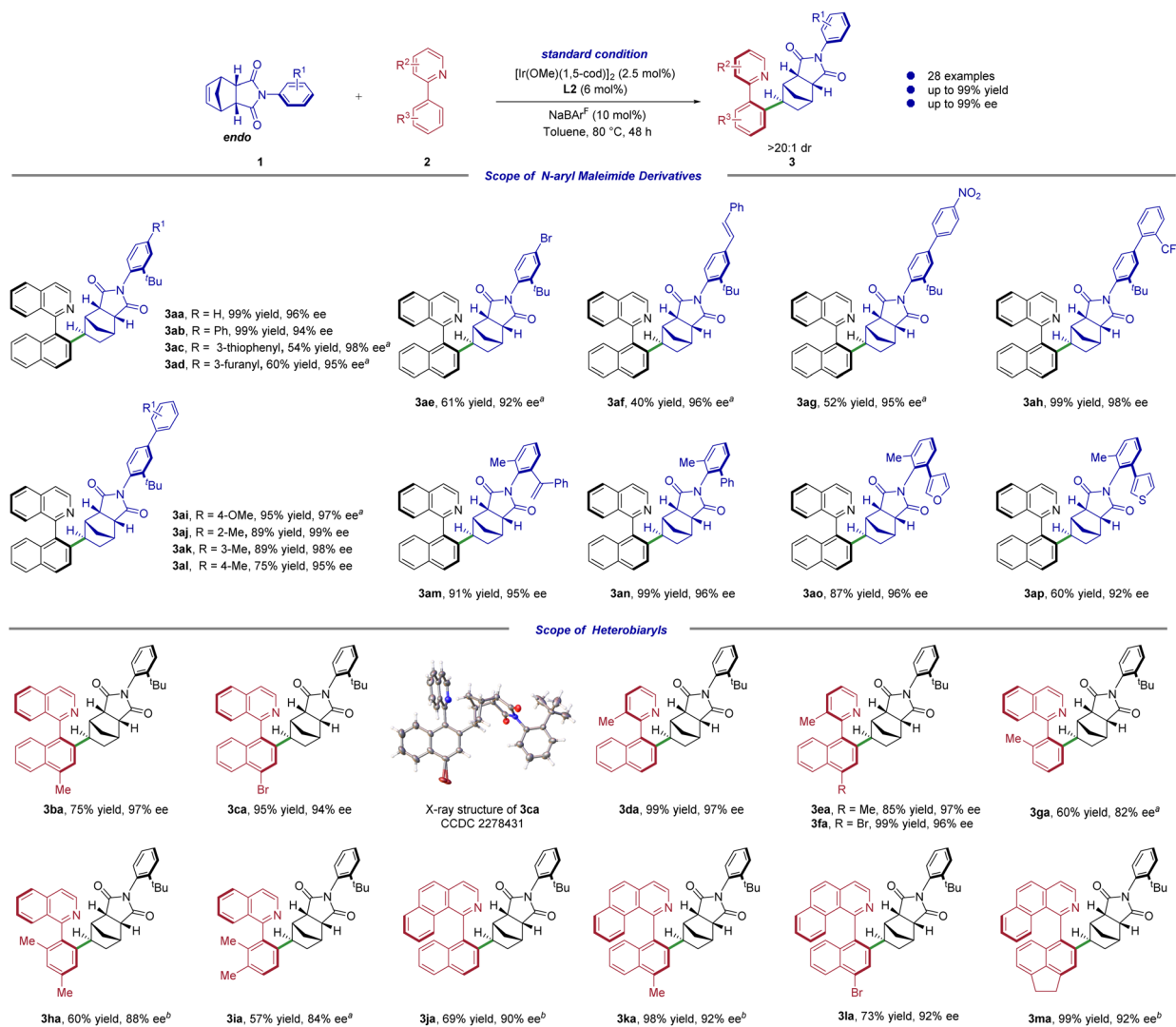
| Entry | Ligand | Solvent | Yield ^b (%) | ee ^c (%) |
|-------|-----------|-------------|------------------------|---------------------|
| 1 | L1 | 1,4-Dioxane | 15 | 89 |
| 2 | L2 | 1,4-Dioxane | 11 | 96 |
| 3 | L3 | 1,4-Dioxane | 9 | 73 |
| 4 | L4 | 1,4-Dioxane | >99 | 36 |
| 5 | L5 | 1,4-Dioxane | 71 | 18 |
| 6 | L6 | 1,4-Dioxane | 26 | 22 |
| 7 | L2 | Xylene | 98 | 97 |
| 8 | L2 | DCE | 76 | 96 |
| 9 | L2 | MTBE | >99 | 96 |
| 10 | L2 | DCM | 72 | 95 |
| 11 | L2 | Toluene | >99 | 97 |
| 12 | L2 | THF | 37 | 95 |
| 13 | L2 | Ph-F | >99 | 96 |



^a Reaction condition: **1a** (0.05 mmol), **2a** (0.06 mmol), [Ir(OMe)(1,5-cod)]₂ (2.5 mol%), **L** (10 mol%), NaBAR^F (10 mol%) in solvent (1.0 mL) at 80 °C under N₂ for 24 h. ^b Yield was detected by ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard. ^c Determined by chiral high performance chromatography (HPLC) analysis. DCE: 1,2-dichloroethane. MTBE: methyl *tert*-butyl ether.

heterobiaryls **2** by using the desymmetrization strategy (Scheme 2). To our delight, the reaction took place without a hitch under the usual reaction circumstances, though it took a little longer time to react. A range of substituents on the phenyl ring of *N*-aryl maleimide derivatives were well tolerated, resulting in the desired products in excellent yields and enantioselectivities. No matter whether the benzene ring is charged with an electron-donating group or an electron-withdrawing group, the product could be obtained in good reactivity with high enantioselectivity (Scheme 2, **3aa**–**3al**). However, when the substituents are functional groups like furan, thiophene, bromo, alkenyl, and nitro, the yields of the products are significantly decreased and the reactions need to be heated up to 110 °C to produce moderate yields (Scheme 2, **3ac**–**3ag**, 40–61% yields, 92–98% ee). Notably, when the strong electron-withdrawing trifluoromethyl group is attached to the benzene ring, high yield and ee value can be obtained (Scheme 2, **3ah**, 99% yield, 98% ee). To evaluate the remote control of distal axial chirality, the substrates scope of bulky *ortho*-substituents on the *N*-aryl groups was also tested. Delightfully, when the *N*-aryl *ortho*-substituents were replaced from *tert*-butyl to other bulky site blocking groups like phenyl, heteroaryl and α -phenylethenyl, the reactions still proceeded with moderate to good yields and excellent enantioselectivities (Scheme 2, **3am**–**3ap**, 60–99% yields, 92–96% ee).





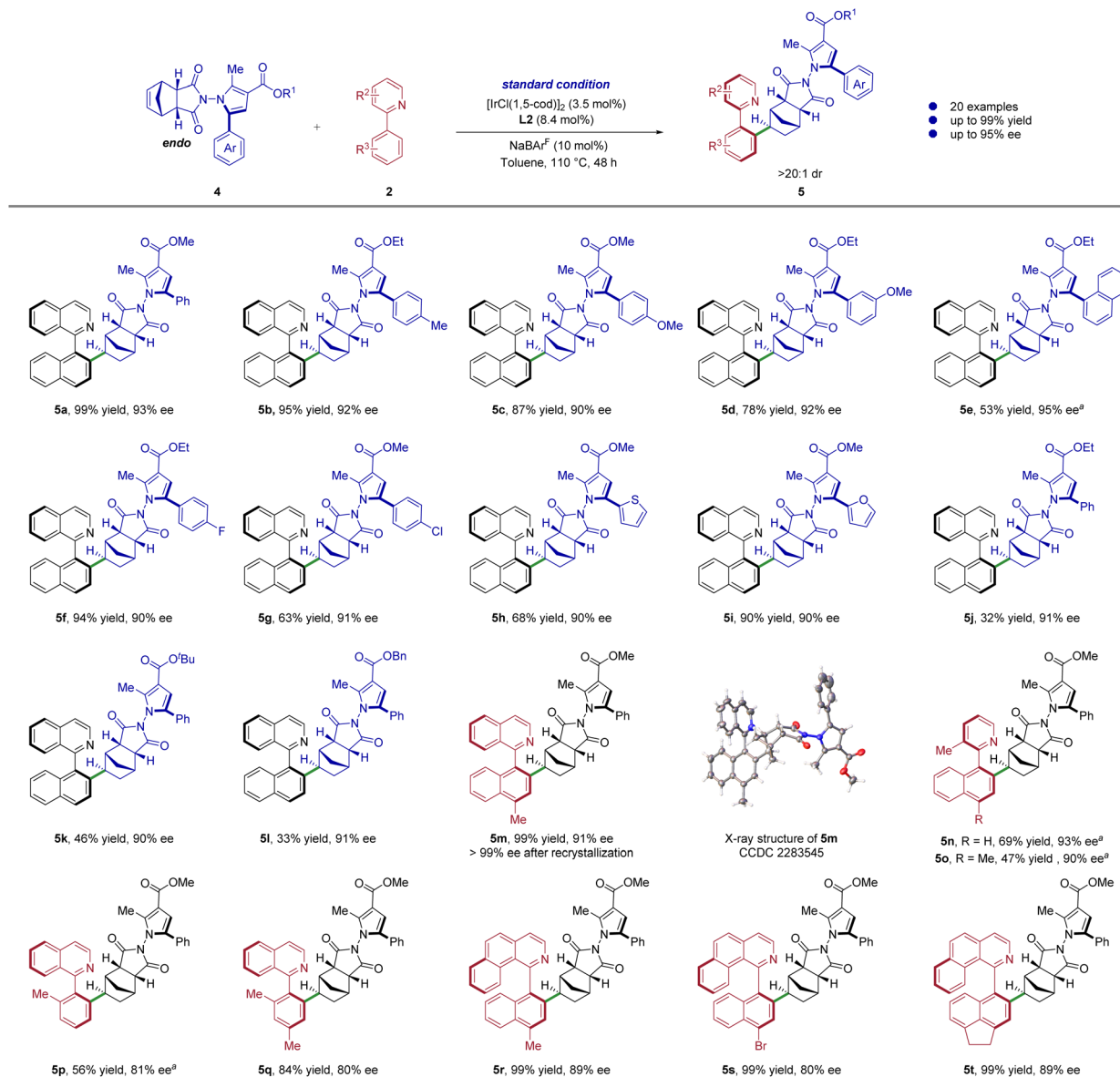
Scheme 2 Reaction scope of C–C and C–N atropisomers. Standard conditions: **1** (0.1 mmol), **2** (0.12 mmol), $[\text{Ir}(\text{OMe})(1,5\text{-cod})_2]$ (2.5 mol%), L2 (6 mol%), NaBAR^{F} (10 mol%) in toluene (2.0 mL) at 80 °C under N_2 for 48 h, isolated yield. Enantiomeric excess (ee) values were determined by chiral HPLC analysis. ^a110 °C, 48 h. ^b80 °C, 96 h.

We next investigated the scope of the heterobiaryl substrates. As shown in Scheme 2, an array of heterobiaryls was well tolerated, and the desired distal biaxial chiral products **3ba–3ma** were isolated in good yields (up to 99%) with excellent enantioselective control (up to 97% ee). However, substrates with a methyl group on the *ortho* position of phenyl ring showed relatively low reaction efficiency (**3ga–3ia**). Products **3ga–3ia** were obtained in only moderate yields even at higher temperature or longer reaction time. Satisfactorily, this procedure could successfully be extended to aryl benzo[*h*]isoquinolines^{15c,33} with methyl, bromo group on the naphthalene ring, delivering the corresponding products **3ja–3ma** in moderate to excellent yields and enantioselectivities (69–99% yields, 90–92% ee). The relative and absolute configuration of **3ca** was determined by single crystal X-ray analysis, and those of other products were assigned by analogy.

Following that, the formation of C–C and N–N atropisomers was investigated to show the wide application of this

asymmetric catalytic system even more (Scheme 3). Prochiral substrates with a N–N axis have been effectively synthesized based on related studies.³⁴ To our delight, under the optimum reaction conditions, the N–N prochiral pyrrole substrates were applicable with this reaction, affording the corresponding products with adequate efficiency and great enantioselectivity (**5a–5t**). The C5-substituents on the pyrrole ring were first examined. Pleasingly, the reactions of various aryl-substituted pyrroles proceeded smoothly to give the desired products in moderate to excellent yields and enantioselectivities (**5a–5g**, 53–99% yields, 90–95% ee). The substrate with heterocycles on the pyrrole fragment can also adapt to this reaction system (**5h–5i**, 68–90% yields, 90% ee). Moreover, the substrates bearing an ethyl, *tert*-butyl, benzyl substituted ester group at the 3-position of pyrrole were well compatible in this reaction, although there has been a decrease in reactivity (**5j–5l**, 32–46% yields, 90–91% ee). In addition, the N–N prochiral pyrrole substrates can also react with different types of heterobiaryls to deliver the expected





Scheme 3 Reaction scope of C–C and N–N atropisomers. Standard conditions: **4** (0.1 mmol), **2** (0.12 mmol), $[\text{IrCl}(1,5\text{-cod})_2]$ (3.5 mol%), L2 (8.4 mol%), NaBARF (10 mol%) in toluene (2.0 mL) at 110 °C under N_2 for 48 h, isolated yield. Enantiomeric excess (ee) values were determined by chiral HPLC analysis. ^a110 °C, 96 h.

products in moderate to excellent yields and enantioselectivities (**5m–5t**, 47–99% yields, 80–93% ee), greatly expanding the range of substrates. The absolute configuration of product **5m** was determined by single-crystal X-ray diffraction analysis, and those of other products were assigned by analogy.

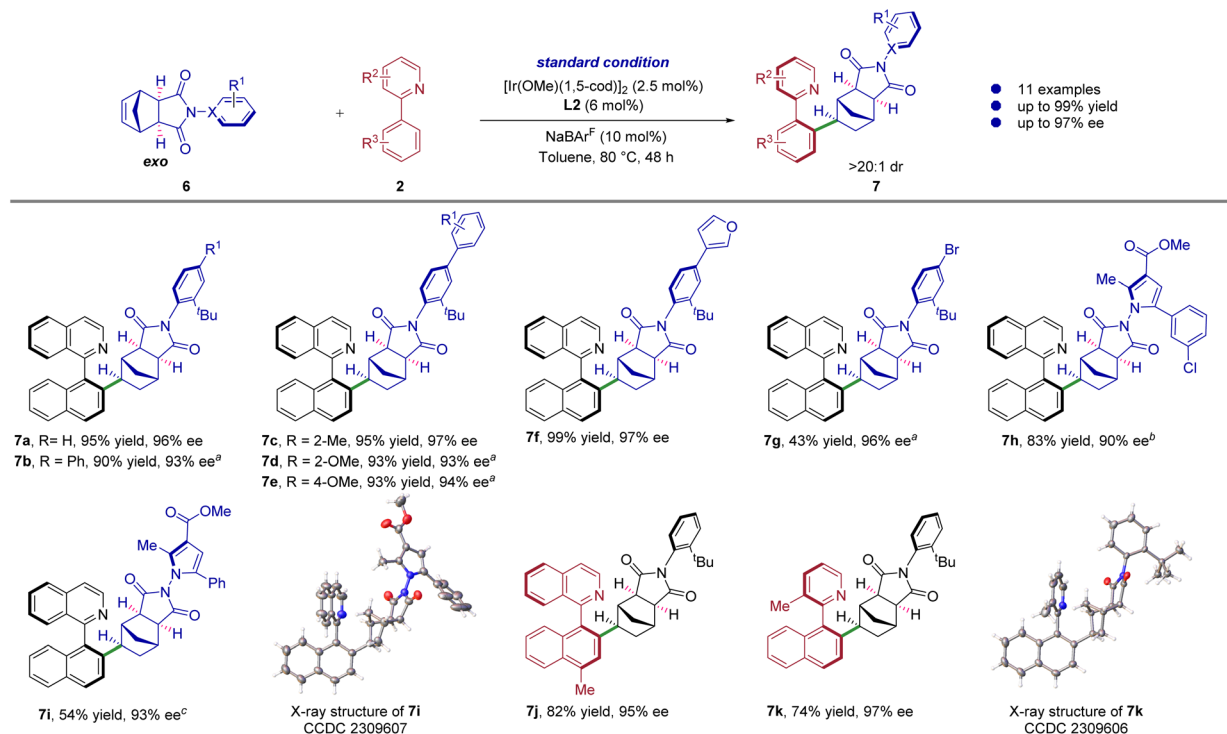
Furthermore, we tested the reactivity of the more challenging *exo* substrate in this scenario. Compared with *endo* substrates, *exo* substrates formed polychiral control centers that were more distant and difficult to react during the catalytic reaction, which greatly affected the yields and enantioselectivities of the products. Remarkably, the matching compounds were successfully obtained from the attempts conducted under regular conditions (Scheme 4). Various C–N axes derivatives of *N*-aryl malimide successfully reacted with heterobiaryls **2**, accommodating a range of electron-donating and electron-

withdrawing groups, resulting in good enantioselectivities and yields (**7a–7g**, 43–99% yields, 93–97% ee). Surprisingly, the *exo* pre-chiral substrates possessing the N–N axis, were also compatible with the reaction, as demonstrated by two representative examples (**7h–7i**, 54–83% yields, 90–93% ee). Furthermore, the study revealed that different types of heteroaryl derivatives could react with the *exo* substrates (**7j–7k**, 74–82% yields, 95–97% ee). The absolute configuration of products **7i** and **7k** was determined through single-crystal X-ray diffraction analysis, while the configurations of other products were assigned by analogy.

Gram scale reaction and synthetic transformations

In order to evaluate the scalability of the current method, a gram scale reaction of **1a** with **2a** was conducted. To our

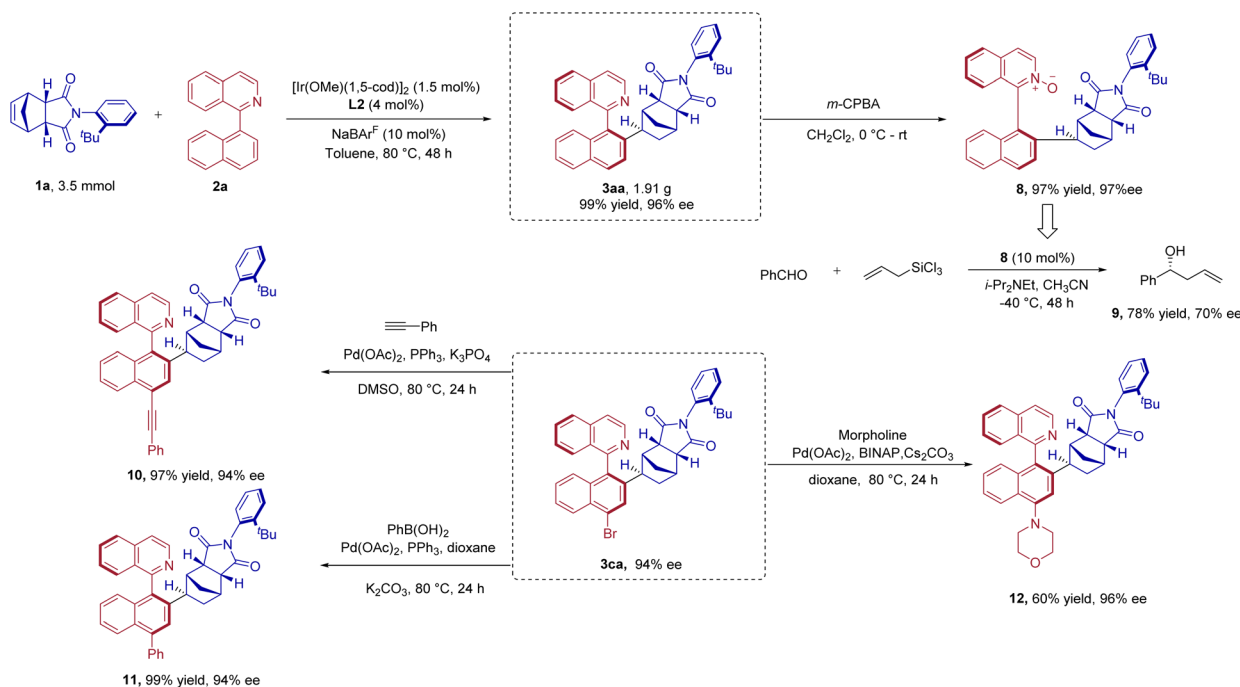




Scheme 4 Scopes of compounds 7. Standard conditions: **6** (0.1 mmol), **2** (0.12 mmol), $[\text{Ir}(\text{OMe})(1,5\text{-cod})]_2$ (2.5 mol%), L2 (6 mol%), NaBARF (10 mol%) in toluene (2.0 mL) at 80 °C under N₂ for 48 h. ^a110 °C, 48 h. ^b $[\text{IrCl}(\text{1,5-cod})]_2$ (3.5 mol%), L2 (8.4 mol%), 110 °C, 48 h. ^c $[\text{IrCl}(\text{1,5-cod})]_2$ (3.5 mol%), L2 (8.4 mol%), 110 °C, 96 h. Isolated yield. Enantiomeric excess (ee) values were determined by chiral HPLC analysis.

delight, with the catalyst loading reduced to 1.5 mol% based on the ligand used, the desired product **3aa** was isolated in 99% yield (1.91 g) and 96% ee (Scheme 5). Several transformations were then carried out to demonstrate the synthetic utility of the

products obtained above. First, **3aa** could be efficiently oxidized to *N*-oxide **8** in 97% yield and 97% ee, without losing its enantioselectivity (Scheme 5). Additionally, it was discovered that chiral *N*-oxide **8** was a potential catalyst for the asymmetric



Scheme 5 Gram scale reaction and synthetic transformations.



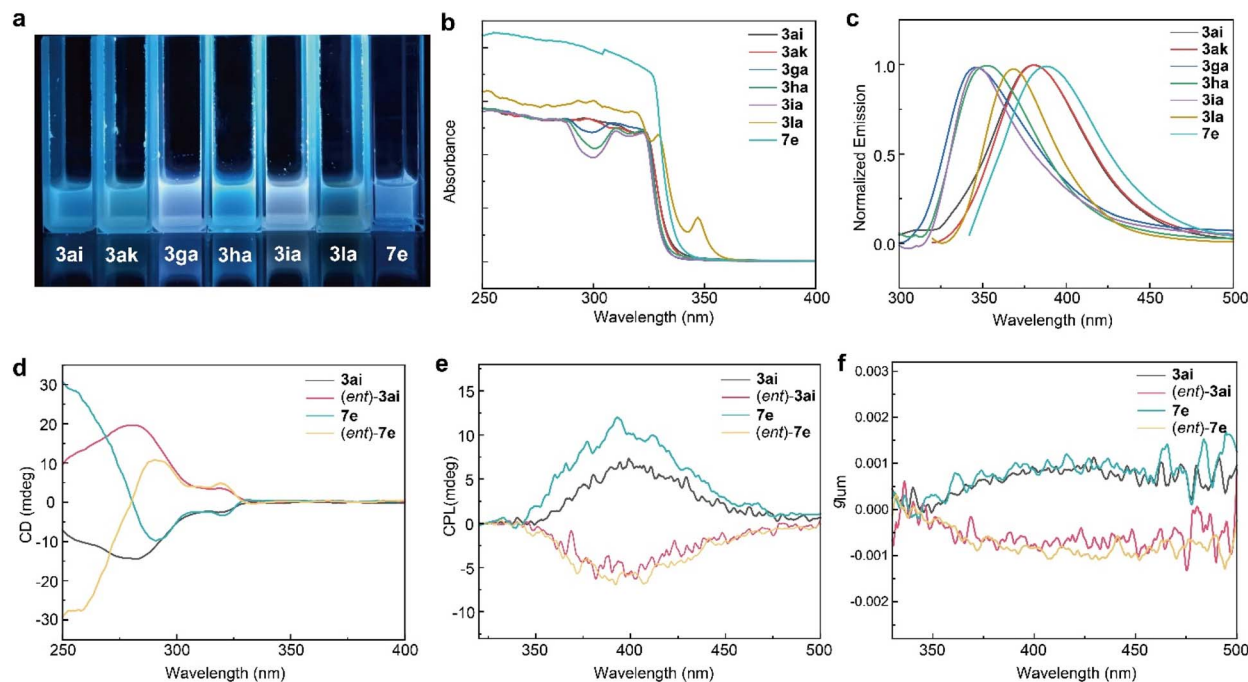


Fig. 1 (a) Fluorescence images of selected distal biaxial atropisomers ($\lambda_{\text{ex}} = 365$ nm). (b) Absorption spectra of selected compounds in CH_2Cl_2 (10^{-3} M). (c) Emission spectra of selected compounds in CH_2Cl_2 (10^{-3} M). (d) CD (circular dichroism) spectra of **3ai**, **7e**, and their enantiomers in CH_2Cl_2 (10^{-3} M) at room temperature. (e) CPL (circular polarized luminescence) spectra of **3ai**, **7e**, and their enantiomers in CH_2Cl_2 (10^{-3} M) at room temperature, excited at 280 nm. (f) g_{lum} (luminescence dissymmetry factor) values–wavelength curve for **3ai**, **7e**, and their enantiomers.

allylation of aromatic aldehyde with allyltrichlorosilane, and product **9** was produced in 78% yield with 70% ee (Scheme 5).³⁵ Second, **3ca** was converted into a variety of functionalized derivatives **10**, **11**, and **12** through several easy-to-run coupling reactions (Scheme 5).

Photophysical properties of products

We further investigated the photophysical properties of several selected products to illustrate their perspectives as chiral functional materials. Under UV light irradiation (365 nm), all solutions revealed luminescence phenomena (Fig. 1a). First, the UV/vis spectra of **3ai**, **3ak**, **3ga**, **3ha**, **3ia**, **3la** and **7e** in CH_2Cl_2 (10^{-3} M) were obtained. All absorption spectra exhibited structured absorption bands, and their absorption maxima were observed at similar wavelengths (308–327 nm, Fig. 1b). Next, the electronic emission spectra (Fig. 1c) of these compounds in CH_2Cl_2 (10^{-3} M) were acquired. These compounds display similar fluorescent spectra (344–388 nm) when excited. A remarkable red-shift was observed in **3ai**, **3ak**, **3la** and **7e** for both the absorption and emission maxima, maybe due to the extended π -conjugated system. Then, the chiroptical properties of the distal biaxial atropisomers **3ai**, **7e** and their enantiomers were examined using circular dichroism (CD) and circular polarized luminescence (CPL) spectroscopies. The CD spectra of **7e** and (*ent*)-**7e** was a mirror image and displayed clear Cotton effects at around 290 nm and 319 nm (Fig. 1d). To our delight, **3ai**, **7e** and their enantiomers in CH_2Cl_2 solution are CPL-active, displaying clear mirror images at 400 nm (Fig. 1e). The luminescence dissymmetry factor (g_{lum})

was 1.1×10^{-3} for **7e** and -1.0×10^{-3} for (*ent*)-**7e** respectively, measured at emission maxima (Fig. 1f).

Conclusions

In conclusion, we developed an efficient and direct Ir(I)-catalyzed asymmetric C–H alkylation procedure to synthesize a unique distal biaxial chiral molecule with high yield and excellent enantioselectivity through the desymmetrization strategy. The various transformations of the products greatly expanded the diversity of the related distal biaxial atropisomers.

According to tests, the resulting series of compounds have good optical properties to be employed as potential chiral organic light-emitting materials in the future. This method also provides a unique approach for creating brand-new distal multi-axial atropisomers.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or its ESI†].

Author contributions

X. Hu and Y. Zhao developed and conducted the reactions. T. He and W. Jia guided the characterization of photophysical properties. C. Niu, F. Liu and Y. Mu prepared some starting materials. X. Li and Z.-Q. Rong directed the project and wrote



the manuscript with input from all authors. All authors analysed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) J. Clayden, W. J. Moran, P. J. Edwards and S. R. LaPlante, *Angew. Chem., Int. Ed.*, 2009, **48**, 6398; (b) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (c) J. E. Smyth, N. M. Butler and P. A. Keller, *Nat. Prod. Rep.*, 2015, **32**, 1562; (d) B. K. Lombe, D. Feineis and G. Bringmann, *Nat. Prod. Rep.*, 2019, **36**, 1513.
- (a) R. Noyori and H. Takaya, *Acc. Chem. Res.*, 1990, **23**, 345; (b) Y. Chen, S. Yekta and A. K. Yudin, *Chem. Rev.*, 2003, **103**, 3155; (c) M. Terada, *Chem. Commun.*, 2008, **35**, 4097; (d) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486; (e) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047; (f) T. Akiyama and K. Mori, *Chem. Rev.*, 2015, **115**, 9277; (g) W. Fu and W. Tang, *ACS Catal.*, 2016, **6**, 4814; (h) Q. Yue, B. Liu, G. Liao and B.-F. Shi, *ACS Catal.*, 2022, **12**, 9359.
- (a) L. Pu, *Acc. Chem. Res.*, 2012, **45**, 150; (b) D.-W. Zhang, M. Li and C.-F. Chen, *Chem. Soc. Rev.*, 2020, **49**, 1331.
- (a) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem., Int. Ed.*, 2005, **44**, 5384; (b) O. Baudoin, *Eur. J. Org. Chem.*, 2005, **2005**, 4223; (c) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (d) J. Wencel-Delord, A. Panossian, F. R. Leroux and F. Colobert, *Chem. Soc. Rev.*, 2015, **44**, 3418; (e) E. Kumarasamy, R. Raghunathan, M. P. Sibi and J. Sivaguru, *Chem. Rev.*, 2015, **115**, 11239; (f) Y. N. Ma, S. X. Li and S. D. Yang, *Acc. Chem. Res.*, 2017, **50**, 1480; (g) C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.*, 2017, **117**, 8908; (h) B. Zilate, A. Castrogiovanni and C. Sparr, *ACS Catal.*, 2018, **8**, 2981; (i) G. Liao, T. Zhou, Q.-J. Yao and B.-F. Shi, *Chem. Commun.*, 2019, **55**, 8514; (j) A. J. Metrano and S. J. Miller, *Acc. Chem. Res.*, 2019, **52**, 199; (k) G. Liao, T. Zhang, Z.-K. Lin and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2020, **59**, 19773; (l) T.-Z. Li, S.-J. Liu, W. Tan and F. Shi, *Chem.-Eur. J.*, 2020, **26**, 15779; (m) J. K. Cheng, S.-H. Xiang, S. Li, L. Ye and B. Tan, *Chem. Rev.*, 2021, **121**, 4805; (n) Y.-J. Wu, G. Liao and B.-F. Shi, *Green Synth. Catal.*, 2022, **3**, 117; (o) G.-J. Mei, W. L. Koay, C.-Y. Guan and Y. Lu, *Chem*, 2022, **8**, 1855; (p) X.-F. Bai, Y.-M. Cui, J. Cao and L.-W. Xu, *Acc. Chem. Res.*, 2022, **55**, 2545; (q) J. K. Cheng, S.-H. Xiang and B. Tan, *Acc. Chem. Res.*, 2022, **55**, 2920.
- (a) X. Bao, J. Rodriguez and D. Bonne, *Angew. Chem., Int. Ed.*, 2020, **59**, 12623; (b) H.-H. Zhang, T.-Z. Li, S.-J. Liu and F. Shi, *Angew. Chem., Int. Ed.*, 2023, e202311053.
- (a) B. K. Lombe, D. Feineis and G. Bringmann, *Nat. Prod. Rep.*, 2019, **36**, 1513; (b) S. Fayez, J. Li, D. Feineis, L. A. Assi, M. Kaiser, R. Brun, M. A. Anany, H. Wajant and G. Bringmann, *J. Nat. Prod.*, 2019, **82**, 3033.
- (a) Y. L. Wu, F. Ferroni, S. Pieraccini, W. B. Schweizer, B. B. Frank, G. P. Spada and F. Diederich, *Org. Biomol. Chem.*, 2012, **10**, 8016; (b) Y. Y. Zhu, X. D. Wu, S.-X. Gu and L. Pu, *J. Am. Chem. Soc.*, 2019, **141**, 175; (c) K. Takaishi, K. Iwachido, R. Takehana, M. Uchiyama and T. Ema, *J. Am. Chem. Soc.*, 2019, **141**, 6185; (d) D.-W. Zhang, M. Li and C.-F. Chen, *Chem. Soc. Rev.*, 2020, **49**, 1331.
- R. Mitra and J. Niemeyer, *ChemCatChem*, 2018, **10**, 1221.
- M. Shibasaki and S. Matsunaga, *Chem. Soc. Rev.*, 2006, **35**, 269.
- S. Jia, S. Li, Y. Liu, W. Qin and H. Yan, *Angew. Chem., Int. Ed.*, 2019, **58**, 18496.
- W. Qin, Y. Liu and H. Yan, *Acc. Chem. Res.*, 2022, **55**, 2780.
- X. Bao, J. Rodriguez and D. Bonne, *Chem. Sci.*, 2020, **11**, 403.
- H. Takano, N. Shiozawa, Y. Imai, K. S. Kanyiva and T. Shibata, *J. Am. Chem. Soc.*, 2020, **142**, 4714.
- (a) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu and J.-Q. Yu, *Science*, 2018, **359**, eaao4798; (b) T. K. Achar, S. Maiti, S. Jana and D. Maiti, *ACS Catal.*, 2020, **10**, 13748; (c) C.-X. Liu, W.-W. Zhang, S.-Y. Yin, Q. Gu and S.-L. You, *J. Am. Chem. Soc.*, 2021, **143**, 14025; (d) X. Yu, Z.-Z. Zhang, J.-L. Niu and B.-F. Shi, *Org. Chem. Front.*, 2022, **9**, 1458; (e) M. Li and J. Wang, *Synthesis*, 2022, **54**, 4734; (f) S. Choppin and J. Wencel-Delord, *Acc. Chem. Res.*, 2023, **56**, 189; (g) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (h) G. Liao, T. Zhou, Q.-J. Yao and B.-F. Shi, *Chem. Commun.*, 2019, **55**, 8514.
- (a) C. He, M. Hou, Z. Zhu and Z. Gu, *ACS Catal.*, 2017, **7**, 5316; (b) H. Li, X. Yan, J. Zhang, W. Guo, J. Jiang and J. Wang, *Angew. Chem., Int. Ed.*, 2019, **58**, 6732; (c) Q. Wang, Z.-J. Cai, C.-X. Liu, Q. Gu and S.-L. You, *J. Am. Chem. Soc.*, 2019, **141**, 9504; (d) L. Jin, Q.-J. Yao, P.-P. Xie, Y. Li, B.-B. Zhan, Y.-Q. Han, X. Hong and B.-F. Shi, *Chem*, 2020, **6**, 497; (e) Z. Li, X. Wang, Y.-M. Cui, J.-H. Ma, L.-L. Fang, L.-L. Han, Q. Yang, Z. Xu and L.-W. Xu, *Chem.-Eur. J.*, 2021, **27**, 4336; (f) Q. Xu, H. Zhang, F.-B. Ge, X.-M. Wang, P. Zhang, C.-J. Lu and R.-R. Liu, *Org. Lett.*, 2022, **24**, 3138; (g) J. Zhang, J. Fan, Y. Wu, Z. Guo, J. Wu and M. Xie, *Org. Lett.*, 2022, **24**, 5143; (h) P. Hu, B. Liu, F. Wang, R. Mi, X.-X. Li and X. Li, *ACS Catal.*, 2022, **12**, 13884; (i) T. Uchikura, S. Kato, Y. Makino, M. J. Fujikawa, M. Yamanaka and T. Akiyama, *J. Am. Chem. Soc.*, 2023, **145**, 15906; (j) L.-C. Xu, J. Frey, X. Hou, S.-Q. Zhang, Y.-Y. Li, J. C. A. Oliveira, S.-W. Li, L. Ackermann and X. Hong, *Nat. Synth.*, 2023, **2**, 321; (k) J.-J. Li, J.-H. Zhao,



- H.-C. Shen, K. Wu, X. Kuang, P. Wang and J.-Q. Yu, *Chem*, 2023, **9**, 1452.
- 16 A. Romero-Arenas, V. Hornillos, J. Iglesias-Sigüenza, R. Fernández, J. López-Serrano, A. Ros and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2020, **142**, 2628.
- 17 Y. Guo, M.-M. Liu, X. Zhu, L. Zhu and C. He, *Angew. Chem., Int. Ed.*, 2021, **60**, 13887.
- 18 (a) Y. Li, Y.-C. Liou, J. C. A. Oliveira and L. Ackermann, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212595; (b) T. von Münchow, S. Dana, Y. Xu, B. Yuan and L. Ackermann, *Science*, 2023, **379**, 1036; (c) Z. J. Zhang, S. W. Li, J. C. A. Oliveira, Y. Li, X. Chen, S. Q. Zhang, L. C. Xu, T. Rogge, X. Hong and L. Ackermann, *Nat. Commun.*, 2023, **14**, 3149.
- 19 (a) F. Wang, J. Jing, Y. Zhao, X. Zhu, X.-P. Zhang, L. Zhao, P. Hu, W.-Q. Deng and X. Li, *Angew. Chem., Int. Ed.*, 2021, **60**, 16628; (b) J. Wang, H. Chen, L. Kong, F. Wang, Y. Lan and X. Li, *ACS Catal.*, 2021, **11**, 9151; (c) R. Mi, Z. Ding, S. Yu, R. H. Crabtree and X. Li, *J. Am. Chem. Soc.*, 2023, **145**, 8150.
- 20 (a) Q. Dherbassy, J.-P. Djukic, J. Wencel-Delord and F. Colobert, *Angew. Chem., Int. Ed.*, 2018, **57**, 4668; (b) Q. Dherbassy, J. Wencel-Delord and F. Colobert, *Tetrahedron*, 2018, **74**, 6205.
- 21 (a) Q. Gao, C. Wu, S. Deng, L. Li, Z.-S. Liu, Y. Hua, J. Ye, C. Liu, H.-G. Cheng, H. Cong, Y. Jiao and Q. Zhou, *J. Am. Chem. Soc.*, 2021, **143**, 7253; (b) Z.-S. Liu, P.-P. Xie, Y. Hua, C. Wu, Y. Ma, J. Chen, H.-G. Cheng, X. Hong and Q. Zhou, *Chem*, 2021, **7**, 1917.
- 22 X.-J. Si, D. Yang, M.-C. Sun, D. Wei, M.-P. Song and J.-L. Niu, *Nat. Synth.*, 2022, **1**, 709.
- 23 B.-J. Wang, G.-X. Xu, Z.-W. Huang, X. Wu, X. Hong, Q.-J. Yao and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208912.
- 24 Y. Wang, X. Zhu, D. Pan, J. Jing, F. Wang, R. Mi, G. Huang and X. Li, *Nat. Commun.*, 2023, **14**, 4661.
- 25 G. Liao, T. Zhang, L. Jin, B.-J. Wang, C.-K. Xu, Y. Lan, Y. Zhao and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115221.
- 26 (a) S. Pan and T. Shibata, *ACS Catal.*, 2013, **3**, 704; (b) Ł. Woźniak, J.-F. Tan, Q.-H. Nguyen, A. M. du Vigné, V. Smal, Y.-X. Cao and N. Cramer, *Chem. Rev.*, 2020, **120**, 10516; (c) D. F. Fernández, J. L. Mascareñas and F. López, *Chem. Soc. Rev.*, 2020, **49**, 7378.
- 27 C. S. Sevov and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 2116.
- 28 P. Vázquez-Domínguez, A. Romero-Arenas, R. Fernández, J. M. Lassaletta and A. Ros, *ACS Catal.*, 2023, **13**, 42.
- 29 H. Zhao, L. Chen, C. Xia and S. Xu, *Asian J. Org. Chem.*, 2023, **12**, e202200695.
- 30 (a) Q. Zhou, S.-Y. Yin, D.-S. Zheng, W.-W. Zhang, S.-Z. Zhang, Q. Gu and S.-L. You, *Synlett*, 2023, **34**, 1442; (b) S.-Y. Yin, Q. Zhou, C.-X. Liu, Q. Gu and S.-L. You, *Angew. Chem., Int. Ed.*, 2023, **62**, e202305067.
- 31 (a) M. Xiong, F. Chen, Y. Shu, X. Wu, J. Tang, F. Yang and D. Xing, *Org. Lett.*, 2023, **25**, 5703; (b) M. Xiong, Z. Yan, S.-C. Chen, J. Tang, F. Yang and D. Xing, *ACS Catal.*, 2024, **14**, 7243.
- 32 (a) W.-L. Duan, Y. Imazaki, R. Shintani and T. Hayashi, *Tetrahedron*, 2007, **63**, 8529; (b) N. Di Iorio, P. Righi, A. Mazzanti, M. Mancinelli, A. Ciogli and G. Bencivenni, *J. Am. Chem. Soc.*, 2014, **136**, 10250; (c) J. Zhang, Y. Zhang, L. Lin, Q. Yao, X. Liu and X. Feng, *Chem. Commun.*, 2015, **51**, 10554; (d) F. Eudier, P. Righi, A. Mazzanti, A. Ciogli and G. Bencivenni, *Org. Lett.*, 2015, **17**, 1728; (e) L. Zhang, S.-H. Xiang, J. J. Wang, J. Xiao, J.-Q. Wang and B. Tan, *Nat. Commun.*, 2019, **10**, 566; (f) X.-W. Gu, Y.-L. Sun, J.-L. Xie, X.-B. Wang, Z. Xu, G.-W. Yin, L. Li, K.-F. Yang and L.-W. Xu, *Nat. Commun.*, 2020, **11**, 2904; (g) S. Barik, S. Shee, S. Das, R. G. Gonnade, G. Jindal, S. Mukherjee and A. T. Biju, *Angew. Chem., Int. Ed.*, 2021, **60**, 12264; (h) F. Sung, T. Wang, G.-J. Cheng and X. Fang, *ACS Catal.*, 2021, **11**, 7578; (i) J. Wang and X. Li, *Sci. China: Chem.*, 2023, **66**, 2046.
- 33 (a) J. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2014, **53**, 13244; (b) J. Zheng, W.-J. Cui, C. Zheng and S.-L. You, *J. Am. Chem. Soc.*, 2016, **138**, 5242; (c) S.-J. Wang, X. Wang, X. Xin, S. Zhang, H. Yang, M. W. Wong and S. Lu, *Nat. Commun.*, 2024, **15**, 518.
- 34 (a) G.-J. Mei, J. J. Wong, W. Zheng, A. A. Nangia, K. N. Houk and Y. Lu, *Chem*, 2021, **7**, 2743; (b) X.-M. Wang, P. Zhang, Q. Xu, C.-Q. Guo, D.-B. Zhang, C.-J. Lu and R.-R. Liu, *J. Am. Chem. Soc.*, 2021, **143**, 15005; (c) Y. Gao, L.-Y. Wang, T. Zhang, B.-M. Yang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2022, **61**, e202200371; (d) K.-W. Chen, Z.-H. Chen, S. Yang, S.-F. Wu, Y.-C. Zhang and F. Shi, *Angew. Chem., Int. Ed.*, 2022, **61**, e202116829; (e) P. Zhang, Q. Xu, X.-M. Wang, J. Feng, C.-J. Lu, Y. Li and R.-R. Liu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212101; (f) G. Centonze, C. Portolani, P. Righi and G. Bencivenni, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303966; (g) T.-Y. Song, R. Li, L. Huang, S. K. Jia and G. J. Mei, *Chin. J. Org. Chem.*, 2023, **43**, 1977; (h) Z.-H. Chen, T.-Z. Li, N.-Y. Wang, X.-F. Ma, S.-F. Ni, Y.-C. Zhang and F. Shi, *Angew. Chem., Int. Ed.*, 2023, **62**, e202300419.
- 35 Q. Wang, Z.-J. Cai, C.-X. Liu, Q. Gu and S.-L. You, *J. Am. Chem. Soc.*, 2019, **141**, 9504.

