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Catalytic asymmetric construction of planarly and centrally chiral [2.2]paracyclophanes by combining photochemical and cobalt-catalyzed desymmetrization†

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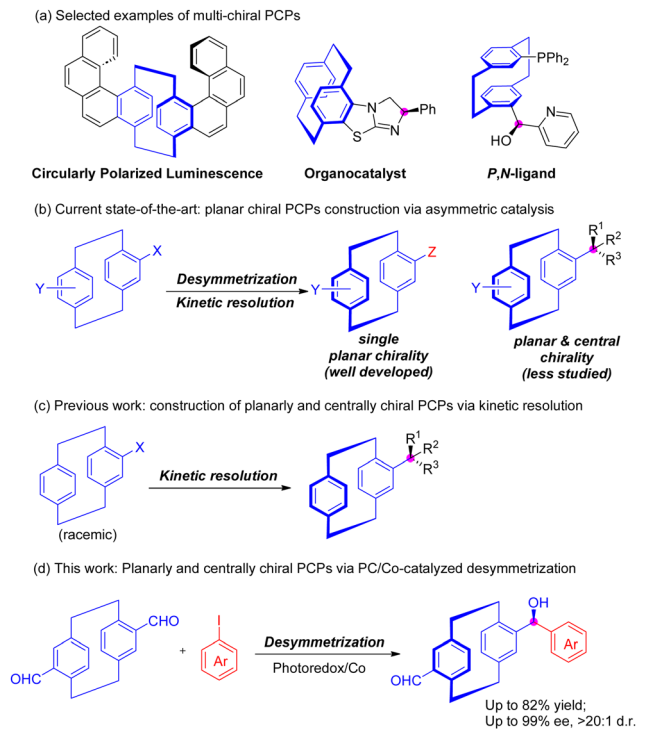
A direct single-step catalytic asymmetric synthesis of [2.2]paracyclophanes (PCPs) bearing both planar and central chirality is reported *via* photochemical cobalt-catalyzed desymmetrization. This reaction proceeds efficiently under mild conditions and exhibits broad functional group tolerance with high stereoselectivities, thus providing a platform for the synthesis of valuable multi-chiral PCPs.

The [2.2]paracyclophanes (PCPs), featuring stable planar chirality and a unique, sterically congested and configurationally distorted structure,[1] have found applications in various research fields, ranging from chiral functional materials[2] to ligand and catalyst design[3] (Scheme 1(a)). Although a practical synthetic route was achieved by Cram and Steinberg in 1951,[4] the current strategies for introducing such planar chirality remain limited. Traditional approaches to access optically pure PCPs mainly rely on time-consuming, small-scale chiral chromatography separation or complicated chemical resolution.[5] Undoubtedly, the catalytic enantioselective synthesis represents an ideal method, in which valuable PCPs in their enantiopure forms can be afforded effectively and straightforwardly.[6] In this regard, structurally diverse enantioenriched PCPs have been achieved through kinetic resolution (KR) strategy[7,8] or catalytic desymmetrization[9,10] (Scheme 1(b)). Very recently, Xu and co-workers developed an enantioconvergent alkynylation of a strained dehydro[2,2]paracyclophane intermediate by asymmetric copper(I) catalysis.[11] Despite these elegant advances, the catalytic synthesis of functionalized PCP derivatives with multiple stereogenic elements in a single step lags far behind. Conversely, introducing additional chiral elements into planar chiral PCPs provides an opportunity to incorporate new properties, thus expanding the potential utility of PCPs.[12] However, the synthesis of multi-chiral PCPs with excellent diastereo- and enantioselectivities remains unexplored and highly challenging. Current approaches for constructing such motifs mainly focus on KR strategy,[13] despite its inherent limitation of 50% theoretical yield as well as limited reaction scope (Scheme 1(c)). Therefore,



Scheme 1 Background and catalytic asymmetric synthesis of planar chiral PCPs: (a) selected examples of multi-chiral PCPs; (b) current state-of-the-art: planar chiral PCPs construction *via* asymmetric catalysis; (c) previous work: construction of planarly and centrally chiral PCPs *via* kinetic resolution; (d) this work: planarly and centrally chiral PCPs *via* PC/Co-catalyzed desymmetrization.

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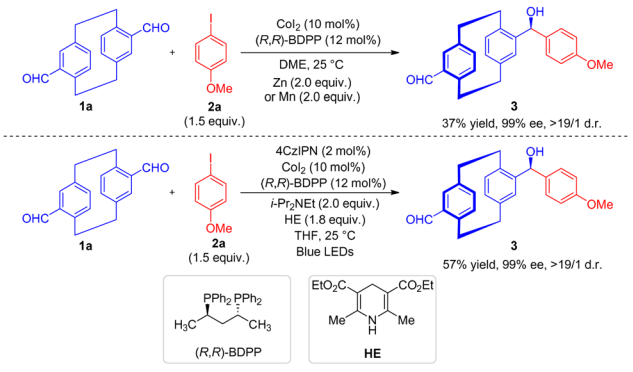
developing novel synthetic protocols for the formation of structurally diverse enantioenriched PCPs, particularly with high yield and broad substrate scope, is highly desirable and significant.

Recently, transition-metal-catalyzed asymmetric reductive addition has evolved into an efficient protocol for constructing enantiopure secondary alcohols.[14] This reductive protocol employs aryl halides directly as the coupling partners, thus avoiding the use of sensitive organometallic nucleophiles. Different kinds of chiral elements, including both axial and central chirality, have been achieved. In sharp contrast, asymmetric reductive addition to synthesize planar chiral PCPs has not been attempted. Herein, inspired by the pioneering studies, we report a highly diastereoselective and enantioselective construction of planarly and centrally chiral PCPs *via* the selective functionalization of prochiral aldehydes (Scheme 1(d)). It should be noted that while we were finalizing our study, Xiao's group reported a similar photoinduced cobalt-catalyzed desymmetrization reaction.[15]

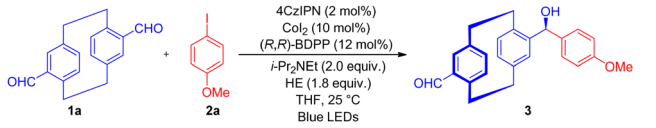
At the outset of our study, the *pseudo-para*-diformyl PCP **1a** and 4-iodoanisole (**2a**) were selected as the model substrates in the presence of CoI_2 (10 mol%) and (*R*,*R*)-BDPP (12 mol%). Several metals, such as zinc and manganese powder, were tested in the preliminary experiments (Scheme 2). The desired product was obtained in 37% yield with 99% ee and >19/1 d.r. Pleasingly, switching the classical metal reductive strategy to photoreduction using Hantzsch ester (HE) as an organic reductant and 4CzIPN as the photocatalyst greatly improved the yield to 57% while maintaining the enantioselectivity and diastereoselectivity.

Inspired by these promising results, a systematic optimization of the photoreductive desymmetrization was further conducted (Table 1. For details, see ESI†). Other chiral ligands, such as (*R*)-BINAP and (*R*,*R*)-DIOP, were also examined, but neither of them afforded the expected product (entry 1). It was shown that solvents have a great impact on the reaction efficiency. In general, ethereal solvents proved to be effective in this asymmetric photoreductive addition reaction. Of note, the optimal yield was obtained when 1,2-dimethyl ether (DME)



Scheme 2 Preliminary results of cobalt-catalyzed reductive addition.[a] [a]Yield and d.r. were determined by ^{1}H NMR analysis of the crude mixture, employing CH_2Br_2 as an internal standard; ee was determined by chiral-phase HPLC analysis.

Table 1 Optimization of reaction conditions[a]



Entry	Variations from the above conditions	Yield[b] (%)	ee[c] (%)
1	(*R*)-BINAP, or (*R*,*R*)-DIOP instead of (*R*,*R*)-BDPP	N.D.	—
2	Toluene instead of THF	58%	99%
3	DME instead of THF	72%	99%
4	1,4-dioxane instead of THF	62%	99%
5[d]	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ instead of 4CzIPN	76% (72%)[e]	99%
6[d]	Ir(ppy) instead of 4CzIPN	37%	99%

[a] Reactions were conducted with **1a** (0.1 mmol), **2a** (1.5 equiv.), CoI_2 (10 mol%), (*R*,*R*)-BDPP (12 mol%), 4CzIPN (2 mol%), i-Pr_2NEt (2 equiv.), and Hantzsch ester (1.8 equiv.) in 2 mL THF at room temperature under the irradiation of 10 W blue LEDs for 12–36 h. In all cases, dr > 19/1. N.D.: not detected. [b] Determined by ^{1}H NMR analysis of the crude mixture employing CH_2Br_2 as an internal standard. [c] ee was determined by chiral-phase HPLC analysis. [d] DME was used as solvent. [e] Isolated yield.

was used as the solvent and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as the photocatalyst, giving the product **3** in 72% isolated yield, 99% ee, and >19/1 d.r. (entry 5). Control experiments revealed that the presence of Hantzsch ester, photocatalyst, base, and visible light was indispensable for this desymmetrization.

Under the established reaction conditions, the scope of various aryl iodides with **1a** was then investigated (Table 2). In general, aromatic iodides containing electronically diverse substituents were all well tolerated under the photoreductive conditions, affording the corresponding enantioenriched products in good yields and excellent stereoselectivities. Regardless of the substitution pattern of the aryl ring (*ortho*, *meta*, or *para*) used in the reaction, the corresponding products (**3–18**) were obtained in good yields (41%–82% yield) and high enantioselectivities and diastereoselectivities. Remarkably, the reaction proceeded smoothly with a broad range of functional groups, including halides (**5–6**, **14–15**), diphenylamine (**8**), thioether (**9**), nitrile (**11**, **17**) and ester (**12**, **16**), which provide attachment sites for further functionalization. The relative configuration was unambiguously determined by X-ray diffraction analysis of **15**. Disubstituted aryl groups (**18–19**) as well as a naphthyl ring (**20**) were also compatible. Moreover, the reaction performed satisfactorily with diverse heteroaromatic systems. Of note, even unprotected heteroaromatic substituents, such as indole (**22**) and carbazole (**23**), bearing free hydrogen in the substrates, could directly participate in the reaction, thus further demonstrating the robustness and excellent functional group tolerance of the developed methodology. In addition, we were delighted to find that the reaction could also proceed smoothly with an array of optoelectronic material intermediates (**25–28**), which could have potential applications in the field of chiral functional materials.

To further evaluate our method, *pseudo-gem*-diformyl PCP **1b** was next studied, first with 4-iodoanisole (**2a**) under the optimized reaction conditions (Table 3). However, the desired product was not observed in this case. Slight modification of

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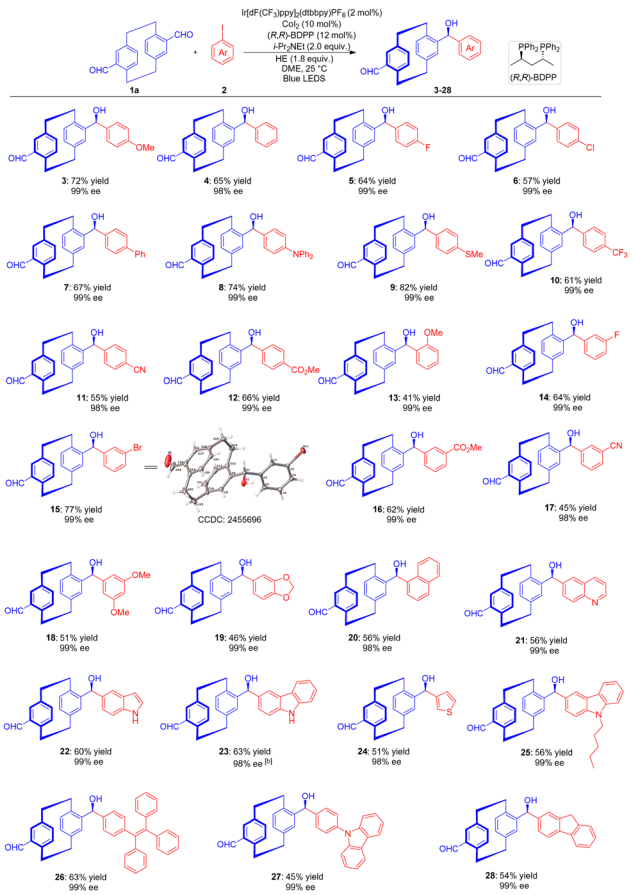
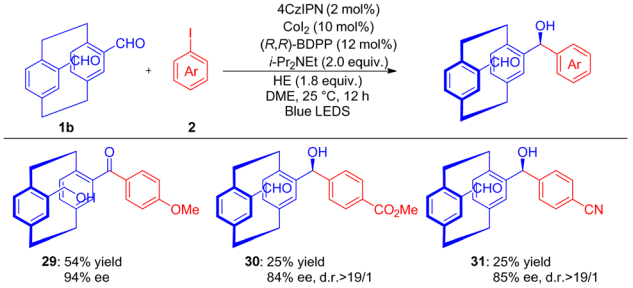
Table 2 Scope of aromatic iodides[a]



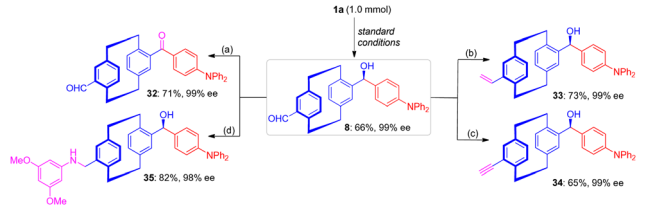
[a] Reactions were conducted on a 0.1 mmol scale. Isolated yield; ee determined by chiral HPLC analysis; d.r. ratio determined by ^{1}H NMR analysis. In all cases, d.r. > 19/1. [b] ee was determined by converting **23** to **25**.

the reaction conditions led to the formation of compound **29**, which is characterized by both a hydroxymethyl group and a carbonyl moiety. The unexpected product presumably arises from undesired side reactions due to the spatially close *pseudo-gem* aldehyde groups.[10a,15] It is interesting to find that the desired reductive addition products could be detected when

Table 3 Attempts with *pseudo-gem*-diformyl PCP **1b**[a]



[a] Reactions were conducted with **1a** (0.1 mmol), **2** (1.5 equiv.) under the above conditions.

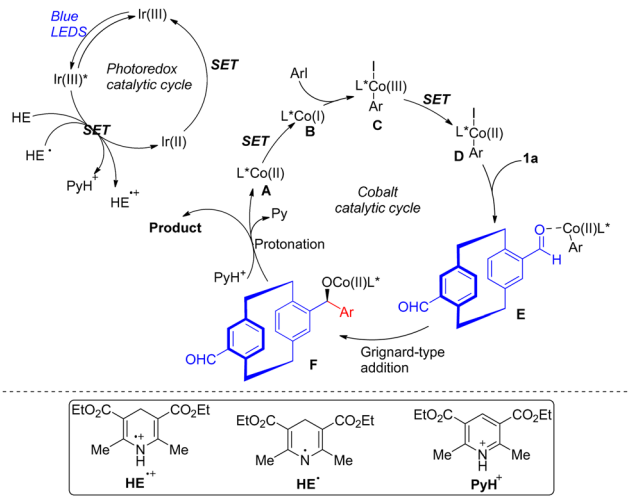


Scheme 3 Synthetic transformations of **8**. For detailed reaction conditions, see (ESI†).

electron-withdrawing groups were installed onto the aromatic iodides. However, lower yields (25%) and lower enantioselectivities (84%) were obtained, together with undesired side products.

Diverse synthetic transformations were attempted to reveal the synthetic potential of the obtained products (Scheme 3). The presence of formyl and hydroxy groups in the products provides opportunities to expand the molecular diversity. For instance, the hydroxyl group could be oxidized with Dess–Martin periodinane (DMP), delivering the planar chiral ketone **32** in 71% yield. Planar chiral alkene **33** and alkyne **34** could be easily accessed through Wittig reaction and Seyferth-Gilbert homologation, respectively. In addition, a benzylic amine **35** could be formed *via* a reductive amination process. Of important note, enantioselectivity was essentially maintained in all cases.

Based on the previous reports,[14a,c,d] the possible catalytic cycles were proposed (Scheme 4). First, the reduction of photo-excited catalyst Ir(III)* [$E^{red}_{1/2}$(*Ir(III)/Ir(II)) = 1.21 V *vs.* SCE][16] by Hantzsch ester (HE) [$E^{ox}_{1/2}$(HE/HE$^{\bullet+}$) = 0.51 V *vs.* Fc][17] gives rise to the corresponding Ir(II), which then reduces the Co(II) complex **A** *via* a single-electron transfer (SET) process, generating the Co(I) species **B**. **B** undergoes oxidative addition with ArI to form the aryl Co(III) intermediate **C**, which could be reduced *via* SET to form the Co(II) intermediate **D**. After coordination with the aldehyde, a highly stereoselective Grignard-type addition to the carbonyl carbon might occur, which then is followed



Scheme 4 Proposed reaction mechanism.

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by protonation to deliver the chiral product, while regenerating the Co(II) complex A to close the cobalt catalytic cycle.

In summary, a single-step synthesis of [2.2]paracyclophane derivatives with both planar and central chirality was achieved by photocobalt-catalyzed asymmetric reductive addition reaction using a desymmetrization strategy. This protocol features mild reaction conditions, good functional group tolerance, and excellent enantioselectivity and diastereoselectivity. The utility of this methodology was further demonstrated in different transformations, leading to a broad range of multi-chiral PCPs. Further catalytic synthesis of varied planar chiral frameworks and the exploration of their potential applications in material science and asymmetric catalysis are currently under way in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and in the ESI.†

Notes and references

1 (*a*) Z. Hassan, E. Spuling, D. M. Knoll, J. Lahann and S. Brase, *Chem. Soc. Rev.*, 2018, **47**, 6947; (*b*) Z. Hassan, E. Spuling, D. M. Knoll and S. Brase, *Angew. Chem., Int. Ed.*, 2020, **59**, 2156.
2 (*a*) J.-M. Teng, D.-W. Zhang and C.-F. Chen, *ChemPhotoChem*, 2022, **6**, e202100228; (*b*) S. Felder, M.-L. Delcourt, D. Contant, R. Rodríguez, L. Favereau, J. Crassous, L. Micouin and E. Benedetti, *J. Mater. Chem. C*, 2023, **11**, 2053; (*c*) W. Liu, H. Li, Y. Huo, Q. Yao and W. Duan, *Molecules*, 2023, **28**, 2891; (*d*) M. Gong, L. Yuan, Y.-X. Zheng and W.-H. Zheng, *Adv. Funct. Mater.*, 2024, **34**, 2314205; (*e*) Z. Hassan, *Adv. Funct. Mater.*, 2024, **34**, 2311828; (*f*) J. He, Y. Fan, Z. Lian, S. Guo, Y. Wang and H. Jiang, *Adv. Opt. Mater.*, 2024, **12**, 2302221; (*g*) S. Wu, S. Felder, J. Brom, F. Pointillart, O. Maury, L. Micouin and E. Benedetti, *Adv. Opt. Mater.*, 2024, **12**, 2400934.
3 (*a*) S. E. Gibson and J. D. Knight, *Org. Biomol. Chem.*, 2003, **1**, 1256; (*b*) D. K. Whelligan and C. Bolm, *J. Org. Chem.*, 2006, **71**, 4609; (*c*) C. Beemelmanns, R. Husmann, D. K. Whelligan, S. Özçubukçu and C. Bolm, *Eur. J. Org. Chem.*, 2012, 3373; (*d*) D. Enders, M. Ludwig and G. Raabe, *Chirality*, 2012, **24**, 215; (*e*) S. Kitagaki, T. Ueda and C. Mukai, *Chem. Commun.*, 2013, **49**, 4030; (*f*) E. Xie, S. Huang and X. Lin, *Org. Lett.*, 2019, **21**, 3682; (*g*) Z.-H. Zhu, Y.-X. Ding, B. Wu and Y.-G. Zhou, *Chem. Sci.*, 2020, **11**, 10220; (*h*) J. Wang, Q.-X. Xie, X. Li, C.-B. Yu and Y.-G. Zhou, *Chin. J. Chem.*, 2024, **42**, 705.
4 (*a*) C. J. Brown and A. C. Farthing, *Nature*, 1949, **164**, 915; (*b*) D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, 1971, **4**, 204; (*c*) D. J. Cram and H. Steinberg, *J. Am. Chem. Soc.*, 1951, **73**, 5691.
5 G. J. Rowlands, *Org. Biomol. Chem.*, 2008, **6**, 1527.
6 K. Zhu, L. Yang, Y. Yang, Y. Wu and F. Zhang, *Chin. Chem. Lett.*, 2025, **36**, 110678.
7 J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5.
8 (*a*) K. Rossen, P. J. Pye, A. Maliakal and R. P. Volante, *J. Org. Chem.*, 1997, **62**, 6462; (*b*) M. L. Delcourt, S. Turcaud, E. Benedetti and L. Micouin, *Adv. Synth. Catal.*, 2016, **358**, 1213; (*c*) K. Mori, H. Kishi and T. Akiyama, *Synthesis*, 2017, 365; (*d*) M.-L. Delcourt, S. Felder, S. Turcaud, C. H. Pollok, C. Merten, L. Micouin and E. Benedetti, *J. Org. Chem.*, 2019, **84**, 5369; (*e*) D. Weinzierl and M. Waser, *Beilstein J. Org. Chem.*, 2021, **17**, 800; (*f*) S. Yu, H. Bao, D. Zhang and X. Yang, *Nat. Commun.*, 2023, **14**, 5239; (*g*) F.-R. Huang, M.-Y. Teng, H. Qiu, Q.-J. Yao and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2025, **64**, e202506465; (*h*) Q. Liu, K. Teng, Y. Zhang, Y. Lv, Y. R. Chi and Z. Jin, *Angew. Chem., Int. Ed.*, 2024, **63**, e202406386; (*i*) Y. Lv, C. Mou, Q. Liu, L. Shu, Y. Cai, X. Lv, Z. Jin and Y. R. Chi, *Org. Lett.*, 2024, **26**, 1584.
9 (*a*) X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou and J. Zhou, *Chem. Rev.*, 2016, **116**, 7330; (*b*) C. Nájera, F. Foubelo, J. M. Sansano and M. Yus, *Tetrahedron*, 2022, **106–107**, 132629; (*c*) Y. Xu, T.-Y. Zhai, Z. Xu and L.-W. Ye, *Trends Chem.*, 2022, **4**, 191; (*d*) P. Xu, F. Zhou, L. Zhu and J. Zhou, *Nat. Synth.*, 2023, **2**, 1020.
10 (*a*) M.-L. Delcourt, S. Felder, E. Benedetti and L. Micouin, *ACS Catal.*, 2018, **8**, 6612; (*b*) V. Dočekal, F. Kouckỳ, I. Císařová and J. Veselỳ, *Nat. Commun.*, 2024, **15**, 3090; (*c*) Z. Wu, S. Fang, J. He, J. Che, Z. Liu, X. Wei, Z. Su and T. Wang, *Angew. Chem., Int. Ed.*, 2025, **64**, e202423702.
11 X. Zhang, Y. Zhou, Z. X. Yu, C. H. Tung and Z. Xu, *Angew. Chem., Int. Ed.*, 2025, **64**, e202420667.
12 A. Gaucherand, E. Yen-Pon, A. Domain, A. Bourhis, J. Rodriguez and D. Bonne, *Chem. Soc. Rev.*, 2024, **53**, 11165.
13 (*a*) P. Dorizon, C. Martin, J.-C. Daran, J.-C. Fiaud and H. B. Kagan, *Tetrahedron: Asymmetry*, 2001, **12**, 2625; (*b*) Y. Zhao, H. Wang, B. Wu and Y.-G. Zhou, *Org. Chem. Front.*, 2019, **6**, 3956; (*c*) Y. Zhao, X. Q. Wang, Y. J. Yu and Y. G. Zhou, *J. Org. Chem.*, 2021, **86**, 1262; (*d*) C. Zippel, Z. Hassan, A. Q. Parsa, J. Hohmann and S. Bräse, *Adv. Synth. Catal.*, 2021, **363**, 2861; (*e*) Y. Zhao, Y.-X. Ding, B. Wu and Y.-G. Zhou, *J. Org. Chem.*, 2021, **86**, 10788.
14 (*a*) X. Jiang, H. Jiang, Q. Yang, Y. Cheng, L.-Q. Lu, J. A. Tunge and W.-J. Xiao, *J. Am. Chem. Soc.*, 2022, **144**, 8347; (*b*) Z. Zhu, J. Xiao, M. Li and Z. Shi, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201370; (*c*) H. Jiang, X.-K. He, X. Jiang, W. Zhao, L.-Q. Lu, Y. Cheng and W.-J. Xiao, *J. Am. Chem. Soc.*, 2023, **145**, 6944; (*d*) T. Liang, Y. Wu, J. Sun, M. Li, H. Zhao, J. Zhang, G. Zheng and Q. Zhang, *Chin. J. Chem.*, 2023, **41**, 3253; (*e*) L. Hu, J. Le Blanc Lele Fosso, R. Guillot, M. Mellah and E. Schulz, *Chem. – Eur. J.*, 2024, **30**, e202403432; (*f*) C. Lin, J. Zhang, Z. Sun, Y. Guo, Q. Chong, Z. Zhang and F. Meng, *Angew. Chem., Int. Ed.*, 2024, **63**, e202405290.
15 S. Q. Liu, W. Xiong, J. C. Huang, X. Jiang, W. Xu, Z. Zhang, Y. Cheng, L. Q. Lu, K. Gao and W. J. Xiao, *Nat. Commun.*, 2025, **16**, 4012.
16 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322.
17 X.-Q. Zhu, H.-R. Li, Q. Li, T. Ai, J.-Y. Lu, Y. Yang and J.-P. Cheng, *Chem. – Eur. J.*, 2003, **9**, 871.

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