ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue



Cite this: *Chem. Commun.*, 2025, **61**, 19036

Received 30th September 2025,
Accepted 15th October 2025

DOI: 10.1039/d5cc05636e

rsc.li/chemcomm



# N-Heterocyclic carbene-catalyzed asymmetric synthesis of bis-ferrocene derivatives bearing two stereogenic planes

Shiguang Li,[a] Jiang Wang,[a] Ya Lv,[a] Yonggui Robin Chi,[ab] Xiuhai Gan*[a] and Xingxing Wu*[a]

**The synthesis of ferrocene derivatives with dual planar chirality remains a significant challenge in asymmetric catalysis. This study presents an enantio- and diastereoselective N-heterocyclic carbene-catalyzed strategy to construct such compounds *via* a double desymmetrization reaction. Synthetic applications highlighted the versatility of these planar–planar chiral products in asymmetric synthesis as catalysts.**

Planar chiral metalocenes have received considerable interest due to their fantastic utilities as ligands for asymmetric synthesis.[1] The introduction of an additional chiral unit into the planar chiral metalocene ligand structure can bring a profound influence on its chelation properties, steric effect and chiral induction (Fig. 1a). For instance, JosiPhos is a bi-dentate phosphine ligand based on a planar chiral ferrocene backbone.[2] It bears an additional stereogenic center[3] on the branch, which orients its chelation effect to transition metals and enhances its steric effects for chiral inductions in asymmetric hydrogenations,[4] hydroacylations,[5] Michael additions[6] and Suzuki–Miyaura reactions.[7] The aminophosphine ligand bearing both a stereogenic plane and axis[8] has also found promising applications in the asymmetric allylic alkylation reactions.[9] The Shvo catalyst is a cyclopentadienone-ligated dimeric ruthenium complex and contains two stereogenic planes.[10] It represents one of the most active catalysts for the transfer hydrogenation reactions of carbonyls[11] and imines.[12] Therefore, the development of facile catalytic methods for enantio- and diastereoselective access to planar chiral molecules bearing multiple stereogenic units is appealing and significant.

Planar chiral molecules bearing additional stereogenic centers have frequently been prepared from enantio-pure starting materials (Fig. 1b, left side).[13] The directing group attached to the chiral center on the starting material could help introduce additional functional groups and give the planar–central chiral product through a diastereoselective directed *ortho*-metalation (DoM) process. Alternatively, enantio-enriched planar–central chiral molecules could be efficiently accessed through desymmetrization or kinetic resolution processes (Fig. 1b, right side).[14] Both transition-metal catalysts and organic catalysts could be used to promote the enantioselective reactions to simultaneously construct both the stereogenic plane and the stereogenic center from achiral or racemic starting materials.

Catalytic methods for the preparation of planar–axial chiral structures have been relatively less developed. Limited success

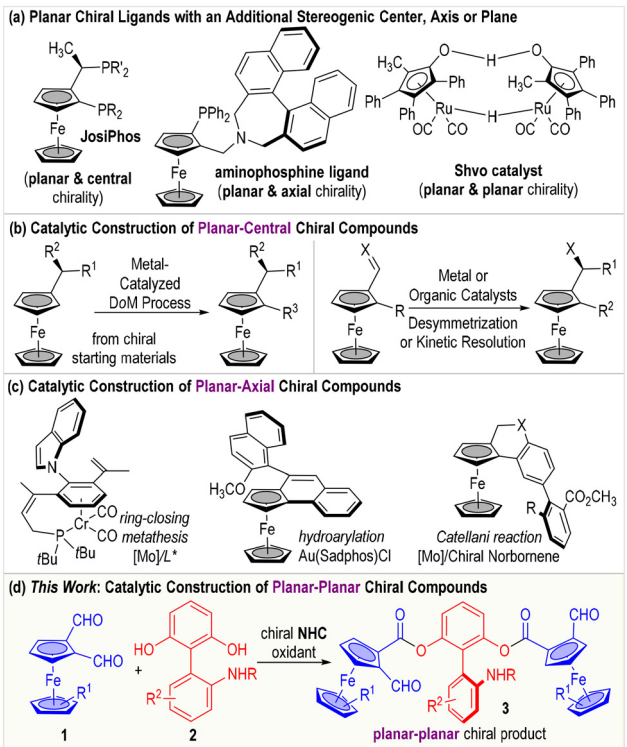



Fig. 1 Planar chiral molecules with an additional stereogenic center, axis or plane (a) and their catalytic synthetic methods (b–d).

[a] *State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China. E-mail: gxh200719@163.com, wuxx@gzu.edu.cn*

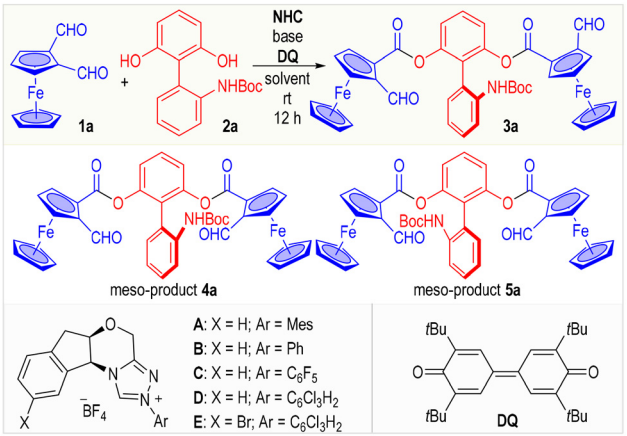
[b] *School of Chemistry, Chemical Engineering, and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore*

has been achieved with transition-metal-catalyzed asymmetric annulation reactions (Fig. 1c). For example, Kamikawa, Takahashi, Ogasawara and co-workers reported in 2015 a molybdenum-catalyzed asymmetric ring-closing olefin metathesis process for the preparation of arene-chromium complexes bearing both a stereogenic plane and axis.[15] Wu, Li, Zhang and co-workers disclosed in 2021 a gold-catalyzed enantio- and diastereoselective hydroarylation reaction for facile access to the chiral ferrocene derivative bearing an additional stereogenic axis.[16] Later, the groups of Liang/Liu/Li and Zhou/Cheng almost simultaneously developed the palladium/chiral norbornene co-catalyzed asymmetric Catellani reaction to achieve planar–axial chiral ferrocenes with excellent stereoselectivities.[17] In stark contrast, catalytic methods for the synthesis of chiral molecules bearing two stereogenic planes have remained rare.[18] Most of the planar–planar chiral molecules have either been prepared from enantio-pure starting materials or got resolved through chiral chromatography.[12]

Building upon our extensive interest in the catalyst-controlled preparation of planar-, axial- and heteroatom-stereogenic compounds,[19] we herein disclose an organocatalytic approach for facile access to ferrocene-derivatives bearing two stereogenic planes (Fig. 1d). Two molecules of the pro-chiral ferrocene-dicarbaldehyde **1** were desymmetrized to react with the bis-phenol substrate **2** under the catalysis of a chiral N-heterocyclic carbene (NHC)[20] catalyst in the presence of a stoichiometric amount of oxidant. The planar–planar chiral di-ester product **3** bearing two of the same ferrocene units was afforded in moderate to excellent yields with excellent enantio- and diastereoselectivities. Noteworthily, the formation of the *meso* by-products **4** and **5** could be suppressed under suitable catalytic conditions.

The double desymmetric esterification reaction between the ferrocene dicarbaldehyde **1a** and the 2-arylphenyl-1,3-diol **2a** was initially tested at room temperature using an indanol-derived NHC catalyst and the base of $Cs_2CO_3$ in the presence of a stoichiometric amount of **DQ** oxidant (Table 1). All the possible products **3a**, **4a** and **5a** could be observed from this catalytic process. In particular, the NHC catalysts **A** and **B** bearing electron-rich *N*-mesityl and *N*-phenyl substituents could give the product **3a** in moderate yields and enantioselectivities with poor diastereoselectivities (entries 1 and 2). The NHC catalyst **C** bearing an electron-deficient N-$C_6F_5$ group gave the target product **3a** in enhanced enantio- and diastereoselectivities (entry 3). Switching to NHC **D** bearing an N-$C_6Cl_3H_2$ group led to significant improvement in the product yield without erosion of the er or dr values (entry 4). Installing a bromo group onto the chiral indanol ring of the NHC catalyst could slightly increase the dr value of the product **3a** but with significant sacrificing of the yield and optical purity (entry 5). Therefore, the NHC catalyst **D** was selected for the evaluation of different bases and reaction solvents. To our delight, NaOAc was found to be effective in promoting the reaction enantioselectivity without obvious erosion on the product yield or dr value (entry 6). The organic bases we tested failed to improve the reaction outcome (entries 7 and 8). The reaction could proceed smoothly in a variety of organic solvents, although none of them could give better results than THF (entries 9 and 10). To our great delight, the target product **3a** could be afforded in an excellent yield, enantio- and diastereoselectivity when the reaction was carried out at a decreased temperature of −40 °C for 24 h (entry 12).

Table 1 Conditions optimization[a]




| Entry | NHC | Base | Solvent | Yield (%) | Er | Dr |
|---|---|---|---|---|---|---|
| 1 | **A** | $Cs_2CO_3$ | THF | 54 | 70 : 30 | 1 : 1 |
| 2 | **B** | $Cs_2CO_3$ | THF | 68 | 65 : 35 | 1 : 1 |
| 3 | **C** | $Cs_2CO_3$ | THF | 53 | 83 : 17 | 3 : 1 |
| 4 | **D** | $Cs_2CO_3$ | THF | 88 | 83 : 17 | 3 : 1 |
| 5 | **E** | $Cs_2CO_3$ | THF | 61 | 78 : 22 | 4 : 1 |
| 6 | **D** | NaOAc | THF | 85 | 87 : 13 | 3 : 1 |
| 7 | **D** | DBU | THF | 61 | 78 : 22 | 2 : 1 |
| 8 | **D** | DMAP | THF | 80 | 67 : 33 | 1 : 1 |
| 9 | **D** | NaOAc | DCM | 85 | 67 : 33 | 2 : 1 |
| 10 | **D** | NaOAc | MTBE | 81 | 87 : 13 | 3 : 1 |
| 11[b] | **D** | NaOAc | THF | 94 | 99 : 1 | 10 : 1 |
| 12[c] | **D** | NaOAc | THF | 93 | 99 : 1 | > 20 : 1 |

[a] Unless otherwise specified, the reactions were carried using **1a** (0.24 mmol), **2a** (0.10 mmol), **NHC** (0.02 mmol), base (0.02 mmol), **DQ** (0.24 mmol), and solvent (1.0 mL) at rt for 12 h. Yield was the combined isolated yield of **3a**, **4a** and **5a**. Er was the er value of **3a**. Dr was the ratio of **3a** : (**4a** + **5a**). [b] Reaction at −20 °C for 24 h. [c] Reaction at −40 °C for 24 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. MTBE = methyl *tert*-butyl ether.

Having identified the optimal catalytic conditions for the desymmetric double esterification reaction, we then examined the substrate scope using both the ferrocene dicarbaldehyde substrate **1** and the 2-arylphenyl-1,3-diol substrate **2** bearing different substituents (Fig. 2). The ferrocene dicarbaldehyde substrate **1** showed good tolerance to various substituents on the cyclopentadienyl ring. Linear, branched and cyclic alkyl groups could be introduced to the 1′-position of the ferrocene scaffold, with the target products afforded in good to excellent yields, enantio- and diastereoselectivities (*e.g.*, **3b** to **3i**). Aliphatic chains bearing a terminal aryl group could also be installed on the ferrocene 1′-position without much erosion of the reaction yield or stereoselectivities (*e.g.*, **3j** to **3m**). The 2-aryl group of the phenyl-1,3-diol substrate **2** could also tolerate diverse functional groups. For instance, methyl groups could be introduced to each position of the 2-aryl group of the substrate **2** to give the target products in good to excellent yields with excellent enantio- and diastereoselectivities (**3n** to **3p**, **3u**). Introducing halogen atoms to the 2-aryl group of the substrate **2** resulted in a slight drop in the reaction yields,

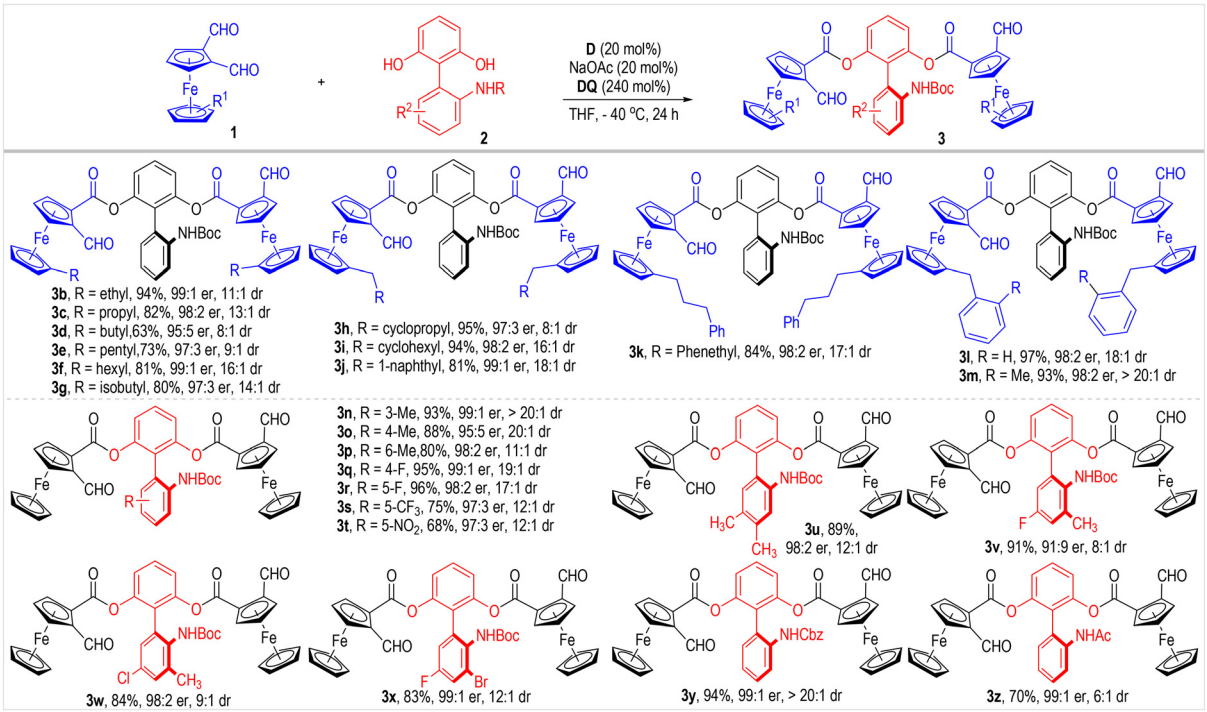



Fig. 2 Substrate scope. [a] Reaction conditions as stated in Table 1, entry 12. Combined isolated yield of **3**, and meso-byproducts **4**-**5**, er value of **3**, determined by chiral HPLC. Dr was the ratio of **3** : (**4** + **5**), determined by $^1$H NMR.

enantio- or diastereoselectivities (**3q** to **3r**, **3v** to **3x**). Strong electron-withdrawing groups on the 2-aryl group of the substrate **2** led to decreased product yields and stereoselectivities (**3s** to **3t**). The *N*-Boc group on the substrate **2** could be switched to the *N*-Cbz group without obvious erosion of the reaction outcome (**3y**). Replacing the *N*-Boc group with an *N*-acyl group resulted in a significant decrease in the reaction yield and diastereoselectivity, although the optical purity of the product was not affected (**3z**).

We were also very interested in the formation of the diastereomeric *meso*-products bearing two stereogenic ferrocene planes and a stereogenic C–C axis (*e.g.*, **4** and **5** in Table 1). In the *meso*-products, the two ferrocene motifs bear opposite planar chiralities. Therefore, we designed a step-wise protocol for the preparation of the *meso*-product **5a** (Fig. 3). We used an excess amount of the bisphenol substrate **2a** to react with the ferrocene dicarbaldehyde **1a** under the catalysis of the NHC **D** to give the enantio-pure monoester intermediate **6** in 63% yield and 3 : 1 diastereoselectivity. After that the NHC *ent*-**D** (bearing the opposite configuration to **D**) was adopted as the reaction catalyst for the enantioselective esterification between **6** and **1a.** After stirring for an additional 24 h the *meso*-product **5a** was obtained in 90% yield with 3 : 1 dr value.

The enantioselective double desymmetrization reaction between dicarbaldehyde **1a** and diol **2a** could be carried out at gram scale and the planar–planar chiral product **3a** could be afforded in good yield with excellent enantio- and diastereoselectivities (Fig. 4a). The two aldehyde groups on the compound **3a** could be reduced into alcohol groups to give the product **7** with little erosion of the optical purity. The aldehyde groups could also condense with a diol or a dithiol molecule to give the

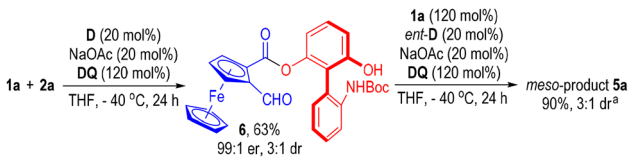



Fig. 3 Synthesis of the *meso* by-product **5a**. [a] The dr value of **5a** was the ratio of **5a** : (**3a** + **4a**), determined by $^1$H NMR.

planar chiral acetal **8** or the thioacetal **9** in good yields with excellent enantioselectivities. The Pinnick oxidation reaction of the aldehyde **3a** led to the formation of the planar chiral dicarboxylic acid **10** in a moderate yield, which could be further esterified with the phenol to give the di-ester product **11** in a good yield without much erosion of the enantioselectivity.

It was pleasing to find that the catalytically obtained multifunctional planar–planar chiral compounds can be adopted as promising ligands or catalysts in asymmetric synthesis (Fig. 4b). For example, the chiral dicarboxylic acid **10** could be used as the chiral ligand in the co-catalyzed asymmetric C($sp^3$)–H functionalization reaction between the thioamide **12** and the dioxazolone **13**, with the chiral product **14** afforded in a good yield and moderate optical purity (eqn (1)). The dicarbaldehyde compound **3a** could be used as an effective organic catalyst in the activation of the primary amine **15** for the enantioselective cycloaddition/dehydration reaction with the chalcone **16** to give the chiral pyrrolidine product **17** in a good yield and enantioselectivity as a single diastereomer (eqn (2)).

In summary, we have developed a chiral NHC-catalyzed enantio- and diastereoselective double desymmetrization

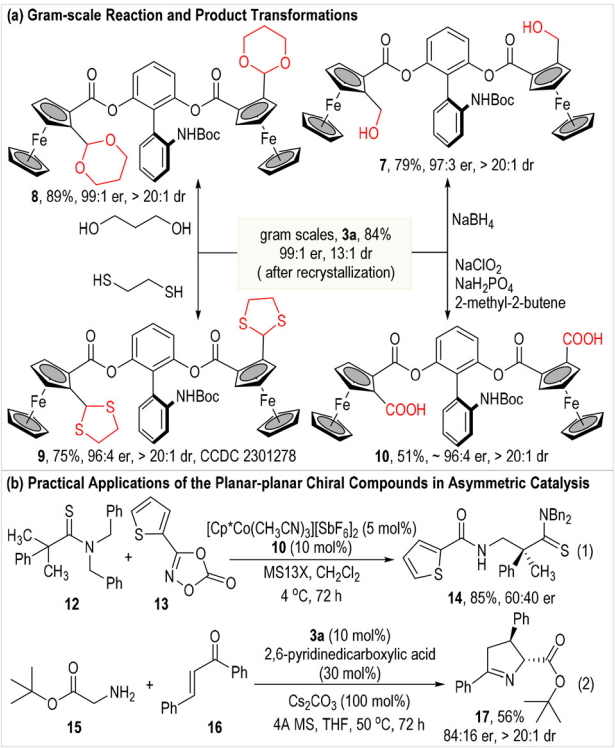



Fig. 4 Synthetic transformations of the planar–planar chiral products (a) and applications in asymmetric catalysis (b).

reaction of the ferrocene dicarbaldehydes with bis-phenols. The structurally complex dual planar chiral products were generally afforded in good to excellent yields and optical purities as single diastereomers, with diverse functional group tolerance. Ongoing studies aim to expand this strategy toward complex planar chiral architectures for asymmetric synthesis and agrochemical applications.

We acknowledge support from the National Key Research and Development Program of China (2022YFD1700300). National Natural Science Foundation of China (22371057, 32172459). The Central Government Guides Local Science and Technology Development Fund Projects [Qiankehezhongyindi (2024)007, (2023)001]. The Program of Major Scientific and Technological, Guizhou Province [Qiankehechengguo (2024)zhongda007]. Yongjiang Plan for Innovation and Entrepreneurship Leading Talent Project in the City of Nanning (2021005).

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: the full experimental details for the preparation of all new compounds, and their spectroscopic and chromatographic data generated in this study are provided. See DOI: **https://doi.org/10.1039/d5cc05636e**.

CCDC 2301278 contains the supplementary crystallographic data for this paper.[21]

## Notes and references

1 For selected examples, see: (*a*) L.-X. Dai, *et al.*, *Acc. Chem. Res.*, 2003, **36**, 659–667; (*b*) R. C. J. Atkinson, *et al.*, *Chem. Soc. Rev.*, 2004, **33**, 313–328; (*c*) G. C. Fu, *Acc. Chem. Res.*, 2006, **39**, 853–860; (*d*) H.-U. Blaser, *et al.*, *Acc. Chem. Res.*, 2007, **40**, 1240–1250; (*e*) Z. Zhang, *et al.*, *Chem. Rev.*, 2016, **116**, 14769–14827; (*f*) N. U. D. Reshi, *et al.*, *ACS Catal.*, 2021, **11**, 13809–13837; (*g*) A. Straube, *et al.*, *Chem. Rev.*, 2025, **125**, 3007–3058.
2 H. U. Blaser, *et al.*, *Top. Catal.*, 2002, **19**, 3–16.
3 H. Long, *et al.*, *Sci. China: Chem.*, 2024, **67**, 2199–2205.
4 (*a*) T. Ireland, *et al.*, *Angew. Chem., Int. Ed.*, 2008, **47**, 3666; (*b*) Q. Zhao, *et al.*, *Angew. Chem., Int. Ed.*, 2014, **53**, 8467–8470.
5 (*a*) K. G. M. Kou, *et al.*, *J. Am. Chem. Soc.*, 2014, **136**, 9471–9476; (*b*) Z. W. Chen, *et al.*, *Angew. Chem., Int. Ed.*, 2019, **58**, 4705–4709.
6 W. Mao, *et al.*, *Angew. Chem., Int. Ed.*, 2019, **58**, 10723–10726.
7 (*a*) J. Kim and S. H. Cho, *ACS Catal.*, 2019, **9**, 230–235; (*b*) W. Ji, *et al.*, *ACS Catal.*, 2020, **10**, 1548–1554.
8 M. Zhang, *et al.*, *Sci. China: Chem.*, 2025, **68**, 815–825.
9 A. Togni, *et al.*, *J. Am. Chem. Soc.*, 1994, **116**, 4062–4066.
10 B. L. Conley, *et al.*, Discovery, *Chem. Rev.*, 2010, **110**, 2294–2312.
11 N. V. Shvydkiy, *et al.*, *ChemCatChem*, 2019, **11**, 1602–1605.
12 X. Dou and T. Hayashi, *Adv. Synth. Catal.*, 2016, **358**, 1054–1058.
13 (*a*) B. J. Ueberbacher, *et al.*, *Chem. Commun.*, 2008, 3287–3289; (*b*) S. A. Herbert, *et al.*, *Org. Lett.*, 2013, **15**, 3334–3337; (*c*) R. K. Schmidt, *et al.*, *Chem. – Eur. J.*, 2016, **22**, 5376–5383.
14 (*a*) A.-N. R. Alba and R. Rios, *Molecules*, 2009, **14**, 4747–4757; (*b*) A. Latorre, *et al.*, *Chem. Commun.*, 2011, **47**, 8103–8105; (*c*) M. Akiyama, *et al.*, *Chem. Commun.*, 2014, **50**, 7893–7896; (*d*) R. Liu, *et al.*, *Adv. Synth. Catal.*, 2015, **357**, 3453–3457; (*e*) Y. Yang, *et al.*, *ACS Catal.*, 2023, **13**, 12464–12471.
15 K. Kamikawa, *et al.*, *Chem. – Eur. J.*, 2015, **21**, 4954–4957.
16 P.-C. Zhang, *et al.*, *Nat. Commun.*, 2021, **12**, 4609.
17 (*a*) Y. An, *et al.*, *Org. Lett.*, 2022, **24**, 7294–7299; (*b*) J. Ye, *et al.*, *JACS Au*, 2023, **3**, 384–390.
18 (*a*) R. Deng, *et al.*, *J. Am. Chem. Soc.*, 2014, **136**, 4472–4475; (*b*) B.-B. Xu, *et al.*, *ACS Catal.*, 2018, **8**, 11735–11740; (*c*) S. Shimizu, *et al.*, *Eur. J. Inorg. Chem.*, 2024, e202400492.
19 (*a*) X. Lv, *et al.*, *ACS Catal.*, 2022, **12**, 2706–2713; (*b*) Y. Deng, *et al.*, *ACS Catal.*, 2025, **15**, 6130–6140; (*c*) M. Liao, *et al.*, *Chem*, 2024, **10**, 1541–1552.
20 For selected examples, see: (*a*) D. M. Flanigan, *et al.*, *Chem. Rev.*, 2015, **115**, 9307–9387; (*b*) Y. Zhang, *et al.*, *Sci. China: Chem.*, 2024, **67**, 482–511; (*c*) A. Jialingbieke, *et al.*, *Sci. China: Chem.*, 2025, **68**, 1002–1008; (*d*) A. T. Biju, *N-Heterocyclic Carbenes in Organocatalysis*, Wiley-VCH, 2018.
21 CCDC 2301278: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2h7ns6**.