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# Organocatalytic atroposelective fluorooxindole addition to coumarin Michael acceptors†

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**Organocatalytic atropisomeric synthesis with fluorinated oxindoles and 4-halo-3-nitrocoumarins gives congested structures displaying a Csp<sup>2</sup>–Csp<sup>3</sup> chirality axis and an adjacent tetrasubstituted stereogenic carbon center with good yields, up to 97% ee and 41 : 1 dr. The scalable dehalogenative C–C bond formation is achieved under mild conditions with a commercially available urea catalyst.**

The widespread interest in fluorinated organic compounds stems at least in part from their favorable lipophilicity, bioavailability and metabolic stability, which among other advantageous properties have been widely recognized and pursued in the drug development realm. The general demand for new fluorinated compounds with ever-increasing molecular complexity has been a steady driving force in the intense search of synthetic methods that can address this need and conquer new chemical space.<sup>1–3</sup> Today, a large pool of fluorinated building blocks is readily available but the small size and high electronegativity of fluorine continue to render stereocontrolled C–C bond formation challenging, in particular when highly substituted stereocenters or more than one element of chirality needs to be introduced.<sup>4–7</sup> The discovery of Maxipost and analogues thereof<sup>8–10</sup> has inspired numerous drug development initiatives and a surge of catalytic asymmetric protocols that use fluorooxindoles to produce new structures with potential medicinal use.<sup>11–24</sup> Like oxindoles, coumarins are known for their wide-ranging biological activities and therapeutic value, for example, as antimicrobial, anticoagulant, anti-inflammatory and anticancer agents.<sup>25</sup> It is not surprising that chiral drugs combining these two prevalent pharmacophores have also evolved as promising leads with various medical applications. New synthetic methods that generate such hybrid scaffolds

have therefore emerged and become remarkably sought-after in recent years.<sup>26–30</sup>

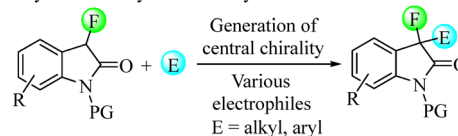
While the focus on medicinally relevant scaffolds in asymmetric catalysis follows the obvious rationale to generate promising libraries of future drug candidates, many research groups have begun to pay increasing attention to the construction of complex molecules exhibiting not only central but also axial, planar or helical chirality.<sup>31</sup> To this end, the steadily growing significance of axially chiral drugs<sup>32</sup> has initiated numerous efforts that have significantly expanded the breadth of atroposelective catalysis and an impressive variety of fascinating atropisomeric architectures can nowadays be accessed.<sup>33–49</sup>

By contrast, examples of atropisomerselective synthesis including either oxindole or coumarin molecules to forge a chiral axis are very rare.<sup>50</sup> We now wish to report an organocatalytic method that generates atropisomeric fluorooxindole-coumarin hybrids exhibiting an adjacent tetrasubstituted stereogenic carbon center. This reaction uses a commercially available urea catalyst to achieve stereocontrolled construction of axial and central chirality in congested, multifunctional structures that are obtained in high enantiomeric and diastereomeric ratios and good yields at room temperature (Scheme 1).

At the onset of this study we chose to explore the possibility of asymmetric C–C bond formation with *N*-methyl-3-fluorooxindole,

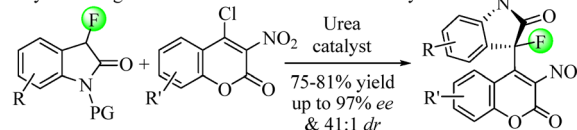
## Previous work (refs 11–17, 19–24):

Asymmetric alkylation and arylation of fluorooxindoles



## This work:

Asymmetric generation of central and axial chirality



Scheme 1 Asymmetric synthesis with fluorooxindoles.

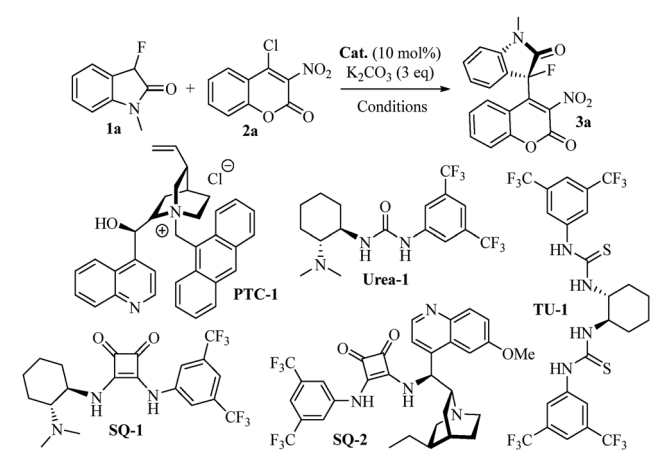
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Table 1 Optimization study



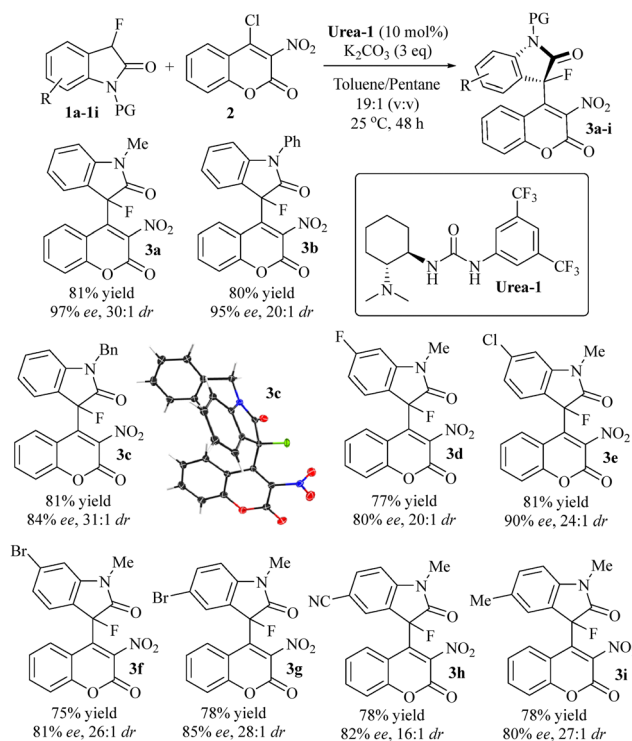
| Entry | Time (h) | Temp. (°C) | Solvent                | Catalyst | Conv. (%) | dr   | ee   |
|-------|----------|------------|------------------------|----------|-----------|------|------|
| 1     | 24       | 25         | Toluene                | PTC-1    | 17        | 20:1 | 0    |
| 2     | 24       | 25         | Toluene                | TU-1     | 3         | 20:1 | n.d. |
| 3     | 24       | 25         | Dichloromethane        | SQ-1     | 83        | 20:1 | 80   |
| 4     | 24       | 25         | Dichloromethane        | SQ-2     | 39        | 20:1 | 83   |
| 5     | 48       | -40        | Dichloromethane        | SQ-2     | 38        | 20:1 | 60   |
| 6     | 24       | 25         | Toluene                | Urea-1   | 99        | 20:1 | 79   |
| 7     | 24       | 25         | Mesitylene             | Urea-1   | 45        | 20:1 | 81   |
| 8     | 24       | 25         | Chlorobenzene          | Urea-1   | 79        | 20:1 | 77   |
| 9     | 48       | -40        | Xylene                 | Urea-1   | 73        | 20:1 | 80   |
| 10    | 24       | 25         | Trifluorotoluene       | Urea-1   | 37        | 20:1 | 72   |
| 11    | 24       | 25         | Dichloromethane        | Urea-1   | 83        | 20:1 | 70   |
| 12    | 24       | 25         | Toluene/ether (15:1)   | Urea-1   | 99        | 20:1 | 71   |
| 13    | 72       | -40        | Toluene/ether (15:1)   | Urea-1   | 50        | 20:1 | 75   |
| 14    | 24       | 25         | Toluene/pentane (19:1) | Urea-1   | 82        | 20:1 | 97   |
| 15    | 48       | 25         | Toluene/pentane (19:1) | Urea-1   | 99        | 30:1 | 97   |

Reaction conditions: *N*-methyl-3-fluoro-2-oxindole (0.09 mmol), 4-chloro-3-nitrocoumarin (0.1 mmol), potassium carbonate (3 eq.) and 10 mol% of the catalyst were dissolved in 0.8 mL of the indicated solvent. Conversion determined by  $^1\text{H}$  NMR spectroscopy. dr determined by  $^{19}\text{F}$  NMR spectroscopy. ee determined by chiral HPLC. n.d. = not determined.

**1a**, and 4-chloro-3-nitrocoumarin, **2a**, in the presence of various organocatalysts. Extensive screening of 15 different chiral urea, thiourea, squaramide and phase-transfer catalysts in several solvents at varying temperatures revealed that the axially chiral structure **3a** can be obtained with high conversion and high diastereomeric ratios while ee's varied substantially (Table 1 and ESI†). Our initial attempts with phase-transfer catalysts like **PTC-1** were disappointing showing slow conversion to racemic **3a** albeit with high diastereoselectivity (entry 1). We therefore resorted to urea, thiourea and squaramide catalysts to exploit activation of the coumarin electrophile *via* hydrogen bonding with the nitro group. This proved successful and we observed smooth reaction to the desired product which was obtained in 20:1 dr and with promising enantiomeric excess, in particular when **SQ-1** and **Urea-1** were used (entries 3 and 6). We then tested a variety of low polarity solvents and combinations thereof in the presence of commercially available **Urea-1** (entries 7–15) and found that the use of 10 mol% of this catalyst in a toluene/pentane solvent mixture allows formation of a chiral axis and a chiral center with excellent enantio- and diastereoselectivity at room temperature after 48 hours (entry 15). It is noteworthy that the organocatalytic

reaction typically requires 1–2 days for completion but the long reaction times do not favor formation of by-products. Interestingly, a decrease in the reaction temperature to  $-40^\circ\text{C}$  only slightly improved ee's while the conversion to **3a** was still incomplete after 72 hours (compare entries 12 and 13).

Having developed an optimized protocol, we continued with the evaluation of the reaction scope by testing the suitability of different fluorooxindoles using stoichiometric amounts of the coumarin and 10 mol% of **Urea-1** in a toluene/pentane solution at room temperature. We were pleased to find that **3a** was formed in 81% yields, 97% ee and 30:1 dr (Scheme 2). Excellent results were also obtained with *N*-phenyl and *N*-benzyl fluorooxindoles and we isolated **3b** and **3c**, respectively, in similar yields, 84–95% ee and high dr's. However, the reaction with unprotected oxindole resulted in low yields due to by-product formation and the use of *N*-Boc-3-fluorooxindole gave racemic product. The presence of fluoride, chloride and bromide substituents at C-5 in the oxindole ring is well tolerated. The corresponding atropisomers **3d–f** were produced in 75–81% yield and up to 90% ee and 26:1 diastereomeric ratio. Finally, three fluorooxindoles carrying a bromide, cyano or methyl substituent at position-6 were employed in the same protocol which gave the corresponding atropisomeric fluorooxindole-coumarin hybrids **3g–i** in comparable yields and stereoselectivities. The reaction can be performed at larger scale without erosion of the yield and enantioselectivity while the diastereomeric ratio is

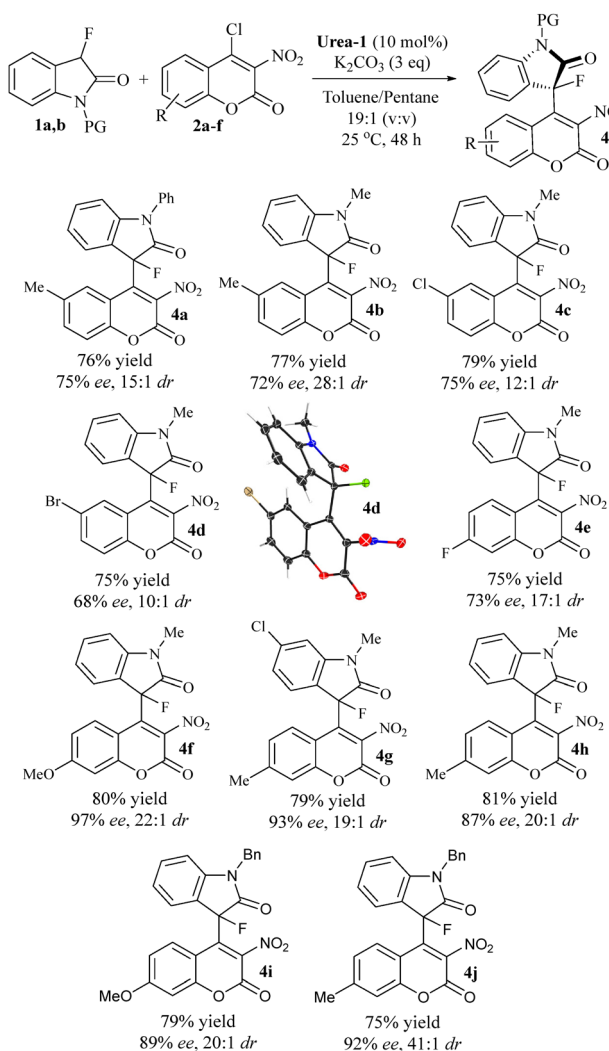


**Scheme 2** Atroposelective catalysis with different fluorooxindoles. General conditions: fluorooxindole (0.09 mmol), coumarin (0.1 mmol),  $\text{K}_2\text{CO}_3$  (0.27 mmol), and **Urea-1** (10 mol%) were stirred in anhydrous toluene/pentane (0.4 mL, 19:1 v/v) under nitrogen at  $25^\circ\text{C}$  for 48 hours. See ESI† for details.



reduced but still very high. In fact, a 10 times increase of the reaction scale gave **3a** in 82% yield, 98% ee, and 24 : 1 dr (see ESI†).

Next, the coumarin scaffold was varied and several derivatives were employed in the urea catalyzed reaction (Scheme 3). Accordingly, we prepared chlorocoumarins exhibiting substituents at the C-6 or C-7 positions and identified noticeable effects on the stereoselectivities. Incorporation of a methyl or halogen moiety at C-6 did not compromise the product formation but both ee and dr values were slightly lower in most cases. Compound **4a–4d** were isolated in good yields ranging from 75 to 79% which is very close to the results discussed above, however, ee's decreased to 68–75% and the diastereomeric ratios varied substantially between 10:1 and 28:1. Interestingly, better results were obtained with coumarins carrying a methyl or methoxy group at C-7. Although the fluoride **4e** was produced in only 73% ee and 17:1 dr, we found that the formation of the atropisomers **4f–j** occurred with excellent central and axial chirality control resulting in 87–93% ee and diastereomeric ratios between 19:1 and 41:1.

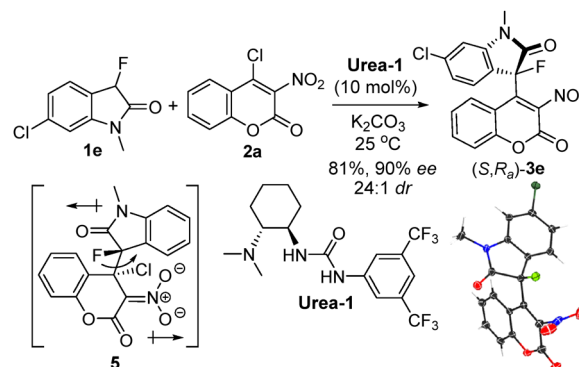


**Scheme 3** Atroposelective catalysis with different coumarins. General conditions: see Scheme 2 and ESI,† for details.

The atropisomeric scaffold of these oxindole-coumarin adducts is very crowded and does not show any sign of diastereomerization *via* rotation about the chiral axis even at increased temperatures. Chiral HPLC analysis of a sample of **3b** exhibiting 95% ee and 20:1 dr did not show any change in its stereochemical composition after heating in refluxing acetonitrile for 7 hours. The presence of the nitro group is considered important to provide sufficient steric hindrance to rotation about the chiral axis but it also is essential to the coumarin reactivity and the stereoselectivity of the reaction. Replacement with a formyl or a trifluoroacetyl group led to decreased asymmetric induction, *i.e.* significantly reduced enantio- and diastereoselectivity, and lower yields due to incomplete conversion as well as competing 1,2-addition of the fluorooxindole enolate to the aldehyde.

We found that some compounds display a high propensity to form racemic crystals even when the enantiomeric excess is higher than 90%. The single crystals of **3c** and **4d** obtained by layering of a dichloromethane solution with pentane were indeed racemic (see ESI†). This tendency offers practical means to increase the enantiopurity of the atropisomers by crystallization and removal of racemic precipitate (see ESI,† for several examples) but it rendered the determination of the absolute configuration of the asymmetric reaction product challenging. After many attempts with several compounds, we were able to increase the enantiopurity of **3e** to 95% ee and grew an enantiopure single crystal by slow evaporation of a dichloromethane solution. X-ray crystallography together with chiral HPLC analysis of this crystal revealed that the major enantiomer formed is (*S,R<sub>a</sub>*)-**3e** (Scheme 4 and ESI†). Interestingly, the C–F bond is in the same plane as the neighboring nitro group while the oxindole and coumarin rings point in almost perpendicular directions.

The stereochemical outcome of the **Urea-1** catalyzed reaction is in agreement with a *Si*-face attack of the fluorooxindole enolate on the 4-chlorocoumarin *Re*-face which was expected as this approach minimizes the overall dipole moments of the two substrates. The corresponding intermediate **5** exhibiting two halogenated tetrasubstituted stereocenters then undergoes chloride elimination and counterclockwise rotation of the oxindole moiety to adopt the favored and crystallographically verified axially chiral conformation with the C–F bond and the nitro group residing in a synperiplanar orientation.



**Scheme 4** X-ray structure of **3e** and proposed intermediate **5**.

In summary, we have introduced an organocatalytic atropisomeric synthesis protocol that produces unprecedented fluorooxindole-coumarin hybrid structures displaying a stable chirality axis and an adjacent tetrasubstituted stereogenic carbon center. The reaction proceeds with good yields, up to 97% ee and 41:1 dr, can be scaled up, and tolerates various substituents in the oxindole and coumarin rings. The urea catalyst used is commercially available and the starting materials are readily prepared following known literature protocols. The products are thermally stable to atropisomerization and no sign of rotation about the highly congested chiral Csp<sup>2</sup>–Csp<sup>3</sup> axis was observed after heating at 80 °C for 7 hours. It is expected that this reaction will attract increasing attention to the development of other catalytic atropisomeric methods that achieve stereocontrolled formation of multifunctional scaffolds with two or more different elements of chirality.

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## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

The authors declare no competing financial interest.

## Notes and references

- 1 K. Müller and C. Faeh, *Diederich Sci.*, 2007, **317**, 1881.
- 2 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422.
- 3 B. R. Smith, C. M. Eastman and J. Njardarson, *J. Med. Chem.*, 2014, **57**, 9764.
- 4 A. M. Cook and C. Wolf, *Angew. Chem., Int. Ed.*, 2016, **55**, 2929.
- 5 R. Ding and C. Wolf, *Org. Lett.*, 2018, **20**, 892.
- 6 R. Ding and Z. A. De Los Santos, *ACS Catal.*, 2019, **9**, 2169.
- 7 A. Sripada and C. Wolf, *J. Org. Chem.*, 2022, **87**, 11880.
- 8 V. K. Gribkoff, J. E. Starrett, S. L. Dworetzky, P. Hewawasam, C. G. Boissard, D. A. Cook, S. W. Frantz, K. Heman, J. R. Hibbard, K. Huston, G. Johnson, B. S. Krishnan, G. G. Kinney, L. A. Lombardo, N. A. Meanwell, P. B. Molinoff, R. A. Myers, S. L. Moon, A. Ortiz, L. Pajor, R. L. Pieschl, D. J. Post-Munson, L. J. Signor, N. Srinivas, M. T. Taber, G. Thalody, J. T. Trojnecki, H. Wiener, K. Yeleswaram and S. W. Yeola, *Nat. Med.*, 2001, **7**, 471.
- 9 P. Hewawasam, V. K. Gribkoff, Y. Pendri, S. I. Dworetzky, N. A. Meanwell, E. Martinez, C. G. Boissard, D. J. Post-Munson, J. T. Trojnecki, K. Yeleswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone and J. E. Starrett Jr., *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1023.
- 10 P. L. N. Ranganath and A. V. Narsaiah, *J. Fluorine Chem.*, 2023, **268**, 110134.
- 11 T. Wang, D. L. Hoon and Y. Lu, *Chem. Commun.*, 2015, **51**, 10186.
- 12 X. Chen, Y. Li, J. Zhao, B. Zheng, Q. Lu and X. Ren, *Adv. Synth. Catal.*, 2017, **359**, 3057.
- 13 Y. Zhu, H. Mei, J. Han, V. A. Soloshonok, J. Zhou and Y. Pan, *J. Org. Chem.*, 2017, **82**, 13663.
- 14 Y. Jin, M. Chen, S. Ge and J. F. Hartwig, *Org. Lett.*, 2017, **19**, 1390.
- 15 S. Paladhi, S. Y. Park, J. W. Yang and C. E. Song, *Org. Lett.*, 2017, **19**, 5336.
- 16 K. Balaraman and C. Wolf, *Angew. Chem., Int. Ed.*, 2017, **56**, 1390.
- 17 Y. Zhu, Y. Mao, H. Mei, Y. Pan, J. Han, V. A. Soloshonok and T. Hayashi, *Chem. – Eur. J.*, 2018, **24**, 8994.
- 18 S. Hajra, A. Hazra and P. Mandal, *Org. Lett.*, 2018, **20**, 6471.
- 19 J. Zhao, Y. Li, L.-Y. Chen and X. Ren, *J. Org. Chem.*, 2019, **84**, 5099.
- 20 B.-Y. Li, Y. Lin and D.-M. Du, *J. Org. Chem.*, 2019, **84**, 11752.
- 21 Z.-B. Qiu, L.-Y. Chen, J. Ji, X. Ren and Y. Li, *J. Fluorine Chem.*, 2020, **236**, 109594.
- 22 T. W. Butcher, W. M. Amberg and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2022, **61**, e202112251.
- 23 Y.-L. Liu, X.-P. Wang, J. Wei and Y. Li, *Org. Biomol. Chem.*, 2022, **20**, 538.
- 24 M. Bouda, J. A. Bertke and C. Wolf, *J. Org. Chem.*, 2024, **89**, 6100.
- 25 A. Khursheed and V. Jain, *J. Nat. Prod.*, 2021, **11**, 648.
- 26 B. Zhou, Z. Luo and Y. Li, *Chem. – Eur. J.*, 2013, **19**, 4428.
- 27 K. Parthasarathy, C. Praveen, J. C. Jeyaveeran and A. A. M. Prince, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 4310.
- 28 C.-W. Lei, C.-B. Zhang, Z.-H. Wang, K.-X. Xie, J.-Q. Zhao, M.-Q. Zhou, X.-M. Zhang, X.-Y. Xua and W.-C. Yuan, *Org. Chem. Front.*, 2020, **7**, 499.
- 29 C.-W. Lei, C.-B. Zhang, Z.-H. Wang, K.-X. Xie, J.-Q. Zhao, M.-Q. Zhou, X.-M. Zhang, X.-Y. Xua and W.-C. Yuan, *Org. Biomol. Chem.*, 2020, **18**, 845.
- 30 V. P. R. Gajulapalli, N. Kumarswamyreddy, K. Lokesh and V. Kesavan, *ChemistrySelect*, 2021, **6**, 7855.
- 31 H.-H. Zhang, T.-Z. Li, S.-J. Liu and F. Shi, *Angew. Chem., Int. Ed.*, 2024, **63**, e202311053.
- 32 S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller and P. J. Edwards, *J. Med. Chem.*, 2011, **54**, 7005.
- 33 L. Wang, S. Li, M. Blümel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**, 11110.
- 34 K. Yamanomoto, K. Yamamoto, S. Yoshida, S. Sato and T. Akiyama, *Chem. Commun.*, 2024, **60**, 582.
- 35 Y. Yang, C. Wu, J. Xing and X. Dou, *J. Am. Chem. Soc.*, 2024, **146**, 6283.
- 36 Z. Zhang, M. M. Simon, S. Yu, S. Li, X. Chen, S. Cattani, X. Hong and L. Ackermann, *J. Am. Chem. Soc.*, 2024, **146**, 9172.
- 37 B. Ye, L. Su, K. Zheng, S. Gao and J. Liu, *Angew. Chem., Int. Ed.*, 2025, **64**, e202413949.
- 38 D. Xu, G. Zhou, B. Liu, S. Jia, Y. Liu and H. Yan, *Angew. Chem., Int. Ed.*, 2025, **64**, e202416873; C. Ma, F. Sheng, H. Wang, S. Deng, Y. Zhang, Y. Jiao, W. Tan and F. Shi, *J. Am. Chem. Soc.*, 2020, **142**, 15686.
- 39 W. Zhan, J. Hu, X. Chen, G. Luo and X. Song, *Chem. Commun.*, 2024, **60**, 14984.
- 40 S. He, B. Shen, L. Zuo, S. Xiang, H. Liu, P. Yu and B. Tan, *J. Am. Chem. Soc.*, 2024, **146**, 19137.
- 41 C. Weng, L. Liu, M. Sun, X. Lu, X. Hong, L. Ye and B. Zhou, *Angew. Chem., Int. Ed.*, 2024, e202418254.
- 42 X. Tang, Y. Tang, J. Peng, H. Du, L. Huang, J. Jiahui Gao, S. Liu, D. Wang, W. Wang, L. Gao, Y. Lan and Z. Song, *J. Am. Chem. Soc.*, 2024, **146**, 26639.
- 43 Y. Xiao, Z. Zhao, E. Irran and M. Oestreich, *Angew. Chem., Int. Ed.*, 2024, **63**, e202414005.
- 44 Y. Gao, Z. Liu, S. Tian, Y. Min, X. Li, Y. Chen, X. Hong, W. Zhang and L. Wang, *Angew. Chem., Int. Ed.*, 2024, e202418888.
- 45 Y. Du, Q. Lu, Y. Cui, K. Wu, Y. Wang, Y. Zhang, Z. Zhao, J. Hou and Q. Cai, *Angew. Chem., Int. Ed.*, 2024, e202421060.
- 46 Y. Wang, W. Liu, T. Li, Y. Lu, Y. Yu, H. Liu, M. Liu, P. Li, P. Qian, H. Tang, J. Guan, L. Ye and L. Li, *J. Am. Chem. Soc.*, 2024, **146**, 33804.
- 47 J. Zhang, Y. Zhang and Y. Huang, *Angew. Chem., Int. Ed.*, 2025, **64**, e202413102.
- 48 B. Ye, L. Su, K. Zheng, S. Gao and J. Liu, *Angew. Chem., Int. Ed.*, 2025, **64**, e202413949.
- 49 D. Xu, G. Zhou, B. Liu, S. Jia, Y. Liu and H. Yan, *Angew. Chem., Int. Ed.*, 2025, **64**, e202416873.
- 50 C. Ma, F. Sheng, H. Wang, S. Deng, Y. Zhang, Y. Jiao, W. Tan and F. Shi, *J. Am. Chem. Soc.*, 2020, **142**, 15686.

