



Cite this: *Org. Biomol. Chem.*, 2025, **23**, 7935

Received 19th June 2025,
Accepted 11th August 2025

DOI: 10.1039/d5ob01000d

rsc.li/obc

Synthesis of axially chiral 5,5'-substituted 2,2'-bipyridine ligands and their application in palladium-catalyzed asymmetric oxidative [2 + 2] annulation

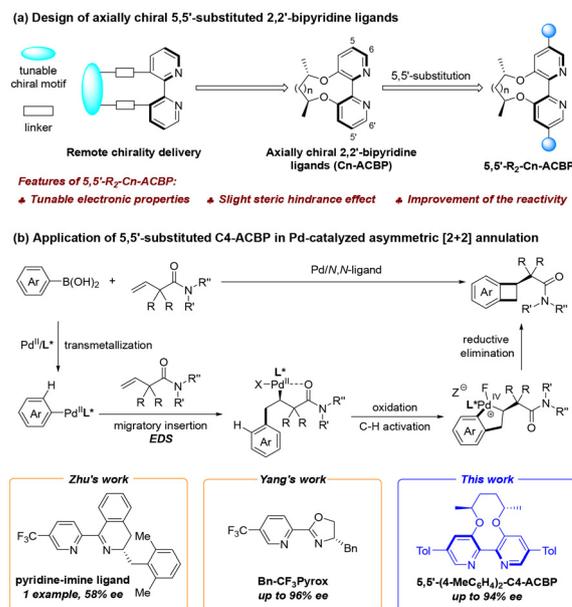
Kai Xue,^{a,b} Jian Chen,^a Yu-Qing Bai,^a Bo Wu *^a and Yong-Gui Zhou *^{a,c}

A series of axially chiral 5,5'-substituted 2,2'-bipyridine ligands featuring tunable properties have been synthesized. These ligands have been successfully applied to palladium-catalyzed asymmetric oxidative [2 + 2] annulation of arylboronic acids and alkenes, providing a diverse range of chiral benzocyclobutenes in excellent enantioselectivities with a broad substrate scope.

In modern synthetic chemistry, the innovation of novel chiral ligands has been a crucial area of asymmetric catalysis.¹ Owing to their robust stability and easy functionalization, chiral *N,N*-ligands have occupied a predominant position in enantioselective synthesis.^{1a,2} Among the various types of chiral *N,N*-ligands, chiral 2,2'-bipyridine ligands have served as some of the notable representatives. Since the first development of chiral monoalkyl-substituted 2,2'-bipyridine ligands by Botteghi's group in 1984,³ a diverse series of chiral 2,2'-bipyridine ligands have been designed and extensively applied in the last four decades.^{4–6} These privileged chiral ligands consist of centrally-chiral bipyridine ligands,⁴ planarly-chiral bipyridine ligands,⁵ and axially-chiral bipyridine ligands.⁶ In 2015, our group developed axially chiral 2,2'-bipyridine ligands (abbreviated as Cn-ACBP) through the remote chirality delivery strategy (Scheme 1a).^{6a} These axially chiral ligands have been successfully utilized in versatile transition metal-catalyzed asymmetric reactions, including palladium-catalyzed enantioselective C–H functionalization of indoles^{6a} and pyrroles,^{6b} O–H insertion reaction of phenols,^{6a} intramolecular C(sp³)–H insertion of donor–donor carbenes,^{6c} arylation of *N*-tosylarylimines,^{6d} cyclization of aniline-tethered alkynyl cyclohexadienones,^{6e} and so on.^{6f–i} Although our axially chiral 2,2'-bipyridine ligands have displayed superior performance in asymmetric catalysis, the exploration of more tunable and appli-

cable axially chiral 2,2'-bipyridine ligands is still in demand. Conventionally, the introduction of substituents to the 6,6'-positions of 2,2'-bipyridine ligands would cause remarkable steric hindrance to the transition metal center and reduce the reactivity. In order to overcome this obstacle, we envisioned developing axially chiral 5,5'-substituted 2,2'-bipyridine ligands (abbreviated as 5,5'-R₂-Cn-ACBP), which would fine-tune the electronic properties by regulating different substituents and exhibit slight steric hindrance effects simultaneously to ensure high reactivity and stereoselectivity (Scheme 1a).

Benzocyclobutenes have emerged as vital structural motifs in natural products and bioactive molecules.⁷ Due to the significant importance of benzocyclobutenes, considerable attention has been paid to them and various synthetic methods



Scheme 1 Axially chiral 5,5'-substituted 2,2'-bipyridine ligands enabled palladium-catalyzed asymmetric oxidative [2 + 2] annulation.

^aState Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China. E-mail: bowu@dicp.ac.cn, ygzhou@dicp.ac.cn

^bUniversity of Chinese Academy of Sciences, Beijing 100049, P. R. China

^cState Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China



have been developed.^{8,9} Recently, palladium-catalyzed oxidative [2 + 2] annulation has been a useful and straightforward protocol to construct benzocyclobutenes.¹⁰ In 2022, Zhu and coworkers disclosed an elegant synthesis of functionalized benzocyclobutenes *via* palladium-catalyzed oxidative [2 + 2] annulation of arylboronic acids with alkenes using an achiral 2,2'-bipyridine as a ligand.¹¹ They also reported a single catalytic asymmetric version of this reaction, delivering the target chiral benzocyclobutene product with 58% ee in the presence of a chiral pyridine-imine ligand. Last year, Yang's group realized a Pd/Pyrox-catalyzed asymmetric oxidative [2 + 2] annulation to afford a wide range of chiral benzocyclobutenes (Scheme 1b).¹² Based on the exceptional catalytic efficacy of chiral *N,N*-ligands in this reaction and the advantages of axially chiral 5,5'-substituted 2,2'-bipyridine ligands, we envisaged applying 5,5'-R₂-Cn-ACBP ligands in palladium-catalyzed asymmetric annulation to ensure both reactivity and enantioselectivity. Herein, we reported the synthesis of axially chiral 5,5'-substituted 2,2'-bipyridine ligands and their application in palladium-catalyzed asymmetric oxidative annulation of arylboronic acids with alkenes for the synthesis of benzocyclobutenes with excellent enantioselectivities (Scheme 1b).

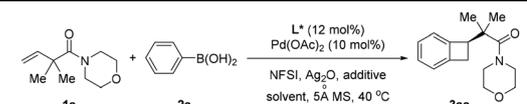
Axially chiral 5,5'-substituted 2,2'-bipyridine ligands were synthesized through the approach shown in Scheme 2. A wide range of 5,5'-R₂-Cn-ACBP ligands were conveniently synthesized through two steps from easily available chiral (2*R*,5*R*)-hexane-2,5-diyl dimethanesulfonate and variable 5-substituted 2-iodo-3-hydroxypyridines **S1** which can be obtained from 3-hydroxy-5-bromopyridine or 3-(benzyloxy)-5-bromopyridine *via* cross-coupling and iodination. Initiated by the S_N2 reaction and followed by Ullmann coupling, various 5,5'-R₂-Cn-ACBP ligands **L1–L10** bearing diverse alkyl and aryl substituents at 5,5'-positions were obtained in moderate 28–60% yields.

With the axially chiral 2,2'-bipyridine ligands in hand, we began our investigation on palladium-catalyzed asymmetric oxidative [2 + 2] annulations. Initially, 2,2-dimethyl-1-morpholinobut-3-en-1-one **1a** and phenylboronic acid **2a** were chosen as the model substrates to perform the reaction at 40 °C using

(*R*_a,*S*,*S*)-3,3'-(1,4-dimethylbutanedioxy)-2,2'-bipyridine (abbreviated as **C4-ACBP**) as a ligand and benzotrifluoride as solvent. Satisfyingly, the target product **3aa** was obtained in 38% yield with 82% ee (Table 1, entry 1). Further evaluation of solvents revealed that tetrahydrofuran (THF) afforded comparable results to benzotrifluoride (entry 2). 1,2-Dichloroethane (DCE) proved optimal, delivering product **3aa** in 40% yield with 95% ee (entry 3).

Afterwards, (*R*_a,*S*,*S*)-3,3'-(1,2-dimethylethylenedioxy)-2,2'-bipyridine (abbreviated as **C2-ACBP**) and (*R*_a,*S*,*S*)-3,3'-(1,3-dimethylpropanedioxy)-2,2'-bipyridine (abbreviated as **C3-ACBP**) ligands were evaluated. Compared with the **C4-ACBP** ligand, the **C2-ACBP** ligand diminished enantioselectivity, although slightly increased the yield (entry 4). The **C3-ACBP** ligand resulted in both diminished yield and enantioselectivity (entry 5). In order to further improve the yield and maintain the enantioselectivity, a number of 5,5'-R₂-C4-ACBP ligands bearing diverse substituents were screened. Ligands bearing alkyl groups **L1–L3** exhibited inferior results compared to **C4-ACBP** (entries 6–8). When the phenyl substituted ligand **L4** was utilized, the yield could be enhanced to 46% and the ee value was 90% (entry 9). Notably, **L5** bearing *p*-methylphenyl groups was the most efficient ligand, affording the desired product in 52% yield and 91% ee (entry 10). **L6–L9** containing aromatic substituents with different electronic properties behaved worse than **L5** (entries 11–14). **L10** with bulky groups reduced the

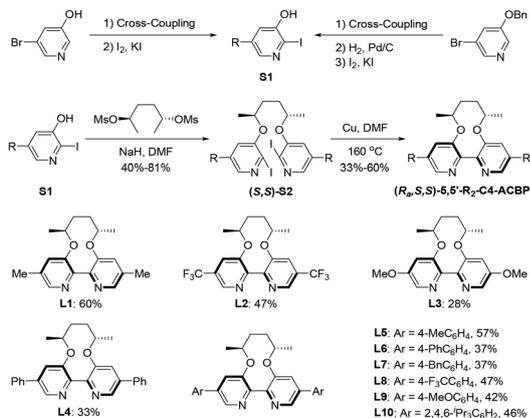
Table 1 Optimization of reaction conditions



Entry ^a	Solvent	L*	Yield ^b (%)	ee ^c (%)
1	PhCF ₃	C4-ACBP	38	82
2	THF	C4-ACBP	39	84
3	DCE	C4-ACBP	40	95
4	DCE	C2-ACBP	45	53
5	DCE	C3-ACBP	37	91
6	DCE	L1	39	93
7	DCE	L2	33	83
8	DCE	L3	37	92
9	DCE	L4	46	90
10	DCE	L5	52	91
11	DCE	L6	47	80
12	DCE	L7	40	89
13	DCE	L8	48	92
14	DCE	L9	41	91
15	DCE	L10	40	93
16 ^d	DCE	L5	56	89
17 ^e	DCE	L5	49	93
18 ^f	DCE	L5	65 ^g	91

^a Reaction conditions: **1a** (0.10 mmol), phenylboronic acid **2a** (0.20 mmol), Pd(OAc)₂ (10 mol%), L* (12 mol%), NFSI (1.3 equiv.), Ag₂O (1.0 equiv.), 5 Å MS (30 mg), solvent (1.0 mL), 40 °C, 22 hours.

^b The yield was measured by analysis of ¹H NMR spectra, using diphenyl acetonitrile as the internal standard. ^c Determined by chiral HPLC. ^d AgOTf (20 mol%) was added. ^e AgSbF₆ (30 mol%) was added. ^f The reaction was conducted on a 0.30 mmol scale; **L5** (10 mol%), AgOTf (20 mol%) and AgSbF₆ (30 mol%) were added; 3 h. ^g Isolated yield.

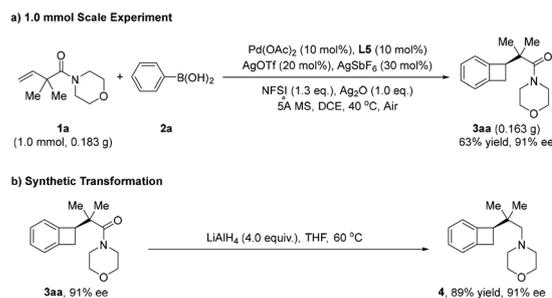


Scheme 2 Synthesis of axially chiral 5,5'-substituted 2,2'-bipyridine ligands.



yield of the reaction (entry 15). Since silver salt additives play a crucial role in palladium-catalyzed C–H activation,¹³ the investigation of silver salt additives was conducted. It was found that the addition of AgOTf could improve the yield of the reaction but slightly decreased the enantioselectivity (entry 16). The addition of AgSbF₆ could improve the enantioselectivity to 93%, but reduced the yield to 49% (entry 17). To achieve a better yield and enantioselectivity at the same time, the combination of AgOTf and AgSbF₆ was adopted (see the SI for details). When both AgOTf and AgSbF₆ were added and the loading of ligand **L5** was reduced to 10 mol%, the enantiomeric excess of **3aa** was maintained at 91% with a significant improvement of yield to 65% (entry 18).

Upon establishing the reliable reaction conditions, we explored the substrate scope of this enantioselective [2 + 2] annulation by varying alkenes **1** and arylboronic acids **2** (Scheme 3). First, we investigated the arylboronic acid components. 4-Alkyl substituted arylboronic acids furnished the benzocyclobutenes **3ab–3ae** in moderate yields with 87%–92% ee values. 4-Phenyl substituted arylboronic acid **2f** was accommodated. Arylboronic acids with electron-withdrawing substituents were appropriate reaction partners. (4-Formylphenyl)boronic acid **2g** and (4-acetylphenyl)boronic acid **2h** and smoothly underwent the annulation with 94% and 89% ee values. (4-(Methoxycarbonyl)phenyl)boronic acid **2i** afforded desirable benzocyclobutene with excellent 93% enantioselectivity. (4-(Trimethylsilyl)phenyl)boronic acid **2j** was also tolerated, giving good enantioselectivity and a moderate yield. When arylboronic acids bearing a halogen at the 4-position were used, the corresponding benzocyclobutenes (**3ak–3am**)



Scheme 4 Experiment on a 1.0 mmol scale and synthetic transformation.

were obtained in moderate yields and excellent enantioselectivities using Pd(OPiv)₂ and **L4** as the catalyst. 3-Substituted (**2n**, **2o**) and 3,5-disubstituted (**2p**) arylboronic acids were suitable for the asymmetric reaction, affording the desired products **3an–3ap** with good enantioselectivities. Moreover, a range of alkenes **1** were examined with phenylboronic acid. The amide moiety in alkene **1** derived from piperidine (**1b**) and linear amides (**1c–1e**) were tolerated. Finally, the alkene with a cyclic *gem*-disubstituted group (**1f**) could also afford the corresponding benzocyclobutene in a moderate yield with 92% ee.

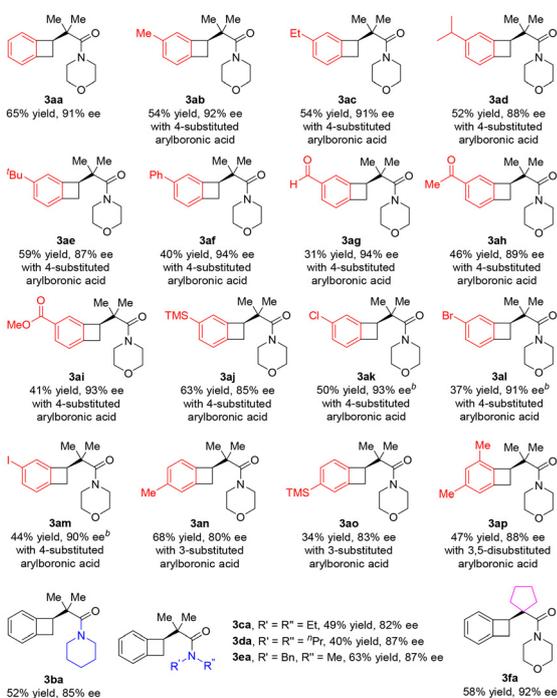
To demonstrate the scalability of the strategy, a 1.0 mmol scale experiment was performed to provide the desirable chiral product **3aa** in 63% yield with 91% ee, which is consistent with the result of a 0.30 mmol scale (Scheme 4a). Then product **3aa** underwent reduction with LiAlH₄ to give a chiral amine in 89% yield and 91% ee (Scheme 4b).

Conclusions

In conclusion, we successfully synthesized a class of axially chiral 5,5'-substituted 2,2'-bipyridine ligands, featuring tunable properties. These ligands would finely regulate the electronic characteristics by introducing different substituents to 5,5'-positions and slightly affect the steric hindrance. These ligands were applied in palladium-catalyzed oxidative [2 + 2] annulation of arylboronic acids and alkenes to afford chiral benzocyclobutenes in excellent enantioselectivities. These results suggested the promising potential of axially chiral ligands as a useful class of chiral *N,N*-ligands. Further explorations on the application of these ligands in asymmetric catalysis are ongoing in our laboratory.

Author contributions

Kai Xue: methodology, investigation and writing – review & editing. Jian Chen: validation. Yu-Qing Bai: validation. Bo Wu: conceptualization, validation, supervision, and writing – review & editing. Yong-Gui Zhou: conceptualization, validation, supervision, and writing – review & editing.



Scheme 3 Substrate scope: alkenes **1** and arylboronic acids **2**.



Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this communication have been included as part of the SI: experimental procedures, synthesis of ligands, characterization data, and copies of the ^1H , ^{13}C , ^{19}F NMR spectra of all new compounds are included. See DOI: <https://doi.org/10.1039/d5ob01000d>.

Acknowledgements

Financial support from the National Key Research and Development Program of China (2023YFA1507500), National Natural Science Foundation of China (22171260), Natural Science Foundation of Liaoning Province (2023-MS-009) and Dalian Institute of Chemical Physics (DICP I202404, I202241) is acknowledged.

References

- (a) L. M. Stanley and M. P. Sibi, *Privileged Chiral Ligands and Catalysts*, John Wiley & Sons, Ltd, 2011, pp. 171–219; (b) T. P. Yoon and E. N. Jacobsen, *Science*, 2003, **299**, 1691.
- (a) F. Fache, E. Schulz, M. L. Tommasino and M. Lemaire, *Chem. Rev.*, 2000, **100**, 2159; (b) N. C. Fletcher, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1831; (c) H.-L. Kwong, H.-L. Yeung, C.-T. Yeung, W.-S. Lee, C.-S. Lee and W.-L. Wong, *Coord. Chem. Rev.*, 2007, **251**, 2188; (d) G. Yang and W. Zhang, *Chem. Soc. Rev.*, 2018, **47**, 1783; (e) R. Connon, B. Roche, B. V. Rokade and P. J. Guiry, *Chem. Rev.*, 2021, **121**, 6373.
- C. Botteghi, G. Caccia, G. Chelucci and F. Soccolini, *J. Org. Chem.*, 1984, **49**, 4290.
- (a) G. Chelucci and R. P. Thummel, *Chem. Rev.*, 2002, **102**, 3129; (b) K. Ito and T. Katsuki, *Synlett*, 1993, 638; (c) D. Lötscher, S. Rupprecht, H. Stoeckli-Evans and A. von Zelewsky, *Tetrahedron: Asymmetry*, 2000, **11**, 4341; (d) A. V. Malkov, M. Bella, V. Langer and P. Kočovský, *Org. Lett.*, 2000, **2**, 3047; (e) A. V. Malkov, D. Pernazza, M. Bell, M. Bella, A. Massa, F. Teplý, P. Meghani and P. Kočovský, *J. Org. Chem.*, 2003, **68**, 4727; (f) T. Kitanosono, L. Zhu, C. Liu, P. Xu and S. Kobayashi, *J. Am. Chem. Soc.*, 2015, **137**, 15422; (g) S. Lauzon, H. Keipour, V. Gandon and T. Ollevier, *Org. Lett.*, 2017, **19**, 6324; (h) T. Kitanosono, P. Xu and S. Kobayashi, *Science*, 2018, **362**, 311; (i) T. Kitanosono, T. Hisada, Y. Yamashita and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2021, **60**, 3407; (j) S. Lauzon, L. Caron and T. Ollevier, *Org. Chem. Front.*, 2021, **8**, 2242; (k) P. S. Riehl, A. D. Richardson, T. Sakamoto, J. P. Reid and C. S. Schindler, *Chem. Sci.*, 2021, **12**, 14133; (l) Y. Ouyang, M. Zhan, J. Zhou, J. Jiao, H. Hu, Y. M. A. Yamada and P. Li, *Chin. J. Chem.*, 2019, **37**, 807; (m) S. Zhang, S. Perveen, Y. Ouyang, L. Xu, T. Yu, M. Zhao, L. Wang, P. Song and P. Li, *Angew. Chem., Int. Ed.*, 2022, **61**, e202117843; (n) S. Perveen, S. Zhang, L. Wang, P. Song, Y. Ouyang, J. Jiao, X.-H. Duan and P. Li, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212108; (o) L. Wang, T. Li, S. Perveen, S. Zhang, X. Wang, Y. Ouyang and P. Li, *Angew. Chem., Int. Ed.*, 2022, **61**, e202213943.
- (a) R. Rios, J. Liang, M. M.-C. Lo and G. C. Fu, *Chem. Commun.*, 2000, 377; (b) G. C. Fu, *Acc. Chem. Res.*, 2006, **39**, 853.
- (a) X. Gao, B. Wu, W.-X. Huang, M.-W. Chen and Y.-G. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 11956; (b) H.-Q. Shen, C. Liu, J. Zhou and Y.-G. Zhou, *Org. Chem. Front.*, 2018, **5**, 611; (c) W. Li, H. Zhang, K. Chen, H. Jiang, J. Sun and S. Zhu, *Chem. Sci.*, 2022, **13**, 12396; (d) X. Gao, B. Wu, Z. Yan and Y.-G. Zhou, *Org. Biomol. Chem.*, 2016, **14**, 55; (e) J. Chen, X. Han and X. Lu, *Angew. Chem., Int. Ed.*, 2017, **56**, 14698; (f) X. Gao, B. Wu, Z. Yan and Y.-G. Zhou, *Org. Biomol. Chem.*, 2016, **14**, 8237; (g) Q.-Q. Zhou, F.-D. Lu, D. Liu, L.-Q. Lu and W.-J. Xiao, *Org. Chem. Front.*, 2018, **5**, 3098; (h) K. Dong, T. Wu, M. Wang and L. Lin, *Angew. Chem., Int. Ed.*, 2024, **63**, e202411158; (i) H. Yang, X. Sun, Z. Chen, C. Jiang, L. Duan, J. Zhao and Z. Gu, *Angew. Chem., Int. Ed.*, 2025, **64**, e202416839.
- (a) G. Mehta and S. Kotha, *Tetrahedron*, 2001, **57**, 625; (b) B. Yang and S. Gao, *Chem. Soc. Rev.*, 2018, **47**, 7926; (c) I. Kouno, T. Komori and T. Kawasaki, *Tetrahedron Lett.*, 1973, **14**, 4569; (d) V. H. Rawal and M. P. Cava, *Tetrahedron Lett.*, 1983, **24**, 5581; (e) R. A. Kirchhoff and K. J. Bruza, *Prog. Polym. Sci.*, 1993, **18**, 85; (f) H.-H. Ko, C.-N. Lin and S.-Z. Yang, *Helv. Chim. Acta*, 2000, **83**, 3000; (g) M. A. Psotka and J. R. Teerlink, *Circulation*, 2016, **133**, 2066.
- (a) I. L. Klundt, *Chem. Rev.*, 1970, **70**, 471; (b) A. K. Sadana, R. K. Saini and W. E. Billups, *Chem. Rev.*, 2003, **103**, 1539; (c) R. Davenport, M. Silvi, A. Noble, Z. Hosni, N. Fey and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2020, **59**, 6525.
- (a) G. Dyker, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 103; (b) O. Baudoin, A. Herrbach and F. Guéritte, *Angew. Chem., Int. Ed.*, 2003, **42**, 5736; (c) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot and O. Baudoin, *J. Am. Chem. Soc.*, 2008, **130**, 15157; (d) S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou and O. Baudoin, *J. Am. Chem. Soc.*, 2010, **132**, 10706; (e) C. E. Kefalidis, M. Davi, P. M. Holstein, E. Clot and O. Baudoin, *J. Org. Chem.*, 2014, **79**, 11903; (f) Z. Wu, D. Ma, B. Zhou, X. Ji, X. Ma, X. Wang and Y. Zhang, *Angew. Chem., Int. Ed.*, 2017, **56**, 12288; (g) J. Ye, Z. Shi, T. Sperger, Y. Yasukawa, C. Kingston, F. Schoenebeck and M. Lautens, *Nat. Chem.*, 2017, **9**, 361; (h) P. A. Provencher, J. F. Hoskin, J. J. Wong, X. Chen, J.-Q. Yu, K. N. Houk and E. J. Sorensen, *J. Am. Chem. Soc.*, 2021, **143**, 20035; (i) W.-X. Wei, Y. Li, Y.-T. Wen, M. Li, X.-S. Li, C.-T. Wang, H.-C. Liu, Y. Xia, B.-S. Zhang, R.-Q. Jiao and Y.-M. Liang, *J. Am. Chem. Soc.*, 2021, **143**, 7868.



- 10 (a) S. Kotha, K. Lahiri and Y. Tangella, *Asian J. Org. Chem.*, 2021, **10**, 3166; (b) M. Catellani, G. P. Chiusoli and S. Ricotti, *J. Organomet. Chem.*, 1985, **296**, c11; (c) M. Catellani and L. Ferioli, *Synthesis*, 1996, 769; (d) D. I. Chai, P. Thansandote and M. Lautens, *Chem. – Eur. J.*, 2011, **17**, 8175; (e) X. Wu and J. Zhou, *Chem. Commun.*, 2013, **49**, 11035; (f) T. Nanjo, C. Tsukano and Y. Takemoto, *Chem. Pharm. Bull.*, 2016, **64**, 1384; (g) P. Annamalai, H.-C. Hsiao, S. Raju, Y.-H. Fu, P.-L. Chen, J.-C. Horng, Y.-H. Liu and S.-C. Chuang, *Org. Lett.*, 2019, **21**, 1182; (h) J.-M. Yang, Y.-K. Lin, T. Sheng, L. Hu, X.-P. Cai and J.-Q. Yu, *Science*, 2023, **380**, 639.
- 11 T. Fujii, S. Gallarati, C. Corminboeuf, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2022, **144**, 8920.
- 12 P. K. Pramanick, S. Zhao, H.-T. Ji, X. Chen and G. Yang, *Angew. Chem., Int. Ed.*, 2025, **64**, e202415927.
- 13 For Pd–Ag heterobimetallic intermediate species in C–H activation, see: (a) R. L. de Carvalho, E. B. T. Diogo, S. L. Homölle, S. Dana, E. N. da Silva Júnior and L. Ackermann, *Chem. Soc. Rev.*, 2023, **52**, 6359; (b) K. L. Bay, Y.-F. Yang and K. N. Houk, *J. Organomet. Chem.*, 2018, **864**, 19; (c) T. Bhattacharya, S. Dutta and D. Maiti, *ACS Catal.*, 2021, **11**, 9702; (d) S. Ghosh, S. Shilpa, C. Athira and R. B. Sunoj, *Top. Catal.*, 2022, **65**, 141.

