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Pd-catalyzed enantioselective access to hydrocarbazolones containing contiguous quaternary and tertiary stereocenters†

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The hydrocarbazole scaffold represents the core structure of numerous monoterpenoid indole alkaloids. The development of catalytic methods that provide efficient access to enantioenriched hydrocarbazole derivatives is central for the synthesis of these bioactive alkaloids. We report here a palladium-catalyzed enantioselective formal 5-*endo* arylative cyclization of enamines, facilitating the construction of hexahydrocarbazol-4-ones containing contiguous C4a-quaternary and C9a-tertiary stereocenters with high enantioselectivities (86.5 : 13.5–99 : 1 er) and diastereoselectivities (>20 : 1 dr). Notably, enaminone substrates bearing an α -allyl group undertake an arylation/Cope rearrangement cascade, offering a unique route to C1-substituted tetrahydrocarbazol-4-ones. A stereodivergent approach to all four stereoisomers of the quaternary/tertiary chiral center set is achieved by combining the catalyst with *Z/E* allyl substituents, yielding excellent enantioselectivity. The *N*-methyl group of the hydrocarbazolone products is readily removed under oxidation conditions. The utility of the method is demonstrated by the access to a variety of hydrocarbazole derivatives and the efficient syntheses of four *Aspidosperma* alkaloids/analogues, (+)-*N*-methyl aspidospermidine, (+)-C20-*epi-N*-methyl aspidospermidine, (+)-*N*-methyl fendleridine, and (+)-*N*-methyl limaspermidine from a hexahydrocarbazol-4-one in 3–5 steps.

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Introduction

Monoterpenoid indole alkaloids are known for their structural complexity and broad spectrum of biological activity.^{1,2} Extensive research has been dedicated to their enantioselective total synthesis, particularly focusing on the alkaloids from the *Aspidosperma* and *Kopsia* families (Scheme 1a).^{3–7} From a retrosynthetic perspective, the tetracyclic hydrocarbazole scaffold serves as a core structure for these complex alkaloids. Traditional synthetic strategies commonly targeted the enantioselective construction of tetrahydrocarbazol-4-ones containing a C3-all-carbon quaternary stereocenter, which corresponds to

C20 of the natural products (Scheme 1b, left).⁸ A number of sophisticated total syntheses have been successfully accomplished following this synthetic logic.^{9–14} Departing from these conventional strategies, alternative synthetic approaches have been developed that utilize the C4a-all-carbon quaternary stereocenter as a stereochemical linchpin. This strategy leverages hydrocarbazolone or hydrocarbazole intermediates (Scheme 1b, right), offering an efficient alternative and conceptually novel retrosynthetic disconnection pathway.^{15–20} As depicted in Scheme 1c, we considered hexahydrocarbazol-4-ones, constituting a tricyclic [6.5.6] framework with sterically congested contiguous stereocenters, to be one of the ideal intermediates for concise synthesis of aspidospermidine derivatives. By taking advantage of the carbonyl and the aminoethyl group on the quaternary center, a condensation cyclization can efficiently construct the E ring, which further allows for a modular installation of various substituents and stereochemical configurations at the C20 quaternary centers. However, asymmetric catalytic assembly of the quaternary center possessed in the C4a-position within the hydrocarbazol-4-one framework presents a significant challenge.^{21–26} This challenge increases in difficulty when the C ring incorporates functional groups necessary for streamlined synthetic elaboration. To our knowledge, however, there lacks catalytic methods capable of enantioselective access to hexahydrocarbazol-4-ones,^{27–29} even not mentioning its application in total synthesis.

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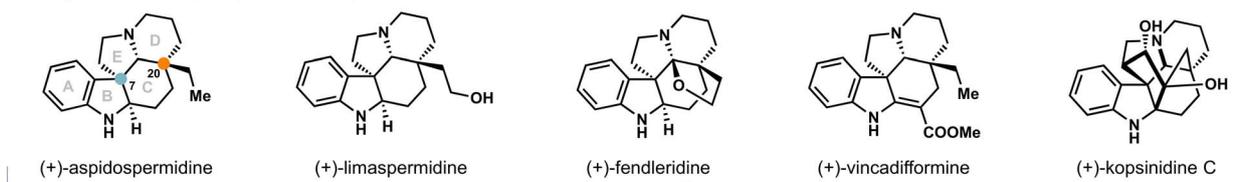
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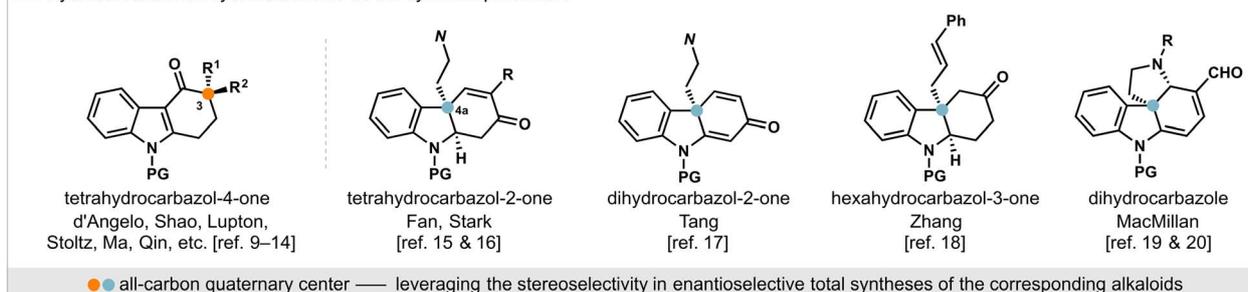
† Electronic supplementary information (ESI) available. CCDC 2363779 and 2407621. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4sc08215j>

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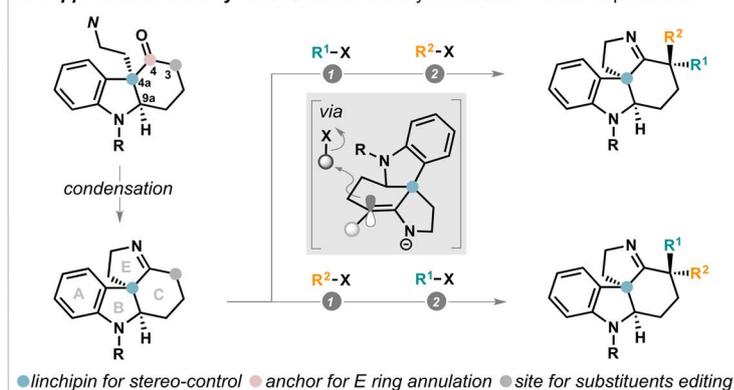


a. Representative *Aspidosperma* and *Kopsia* alkaloids

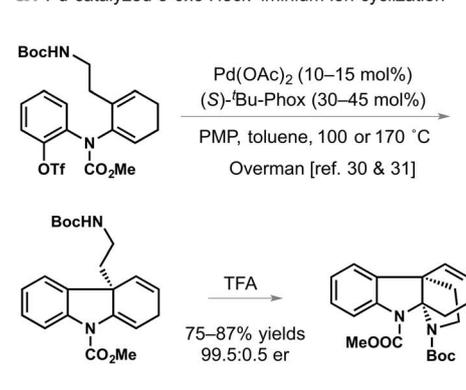
b. Hydrocarbazolones/hydrocarbazoles as the synthetic precursors



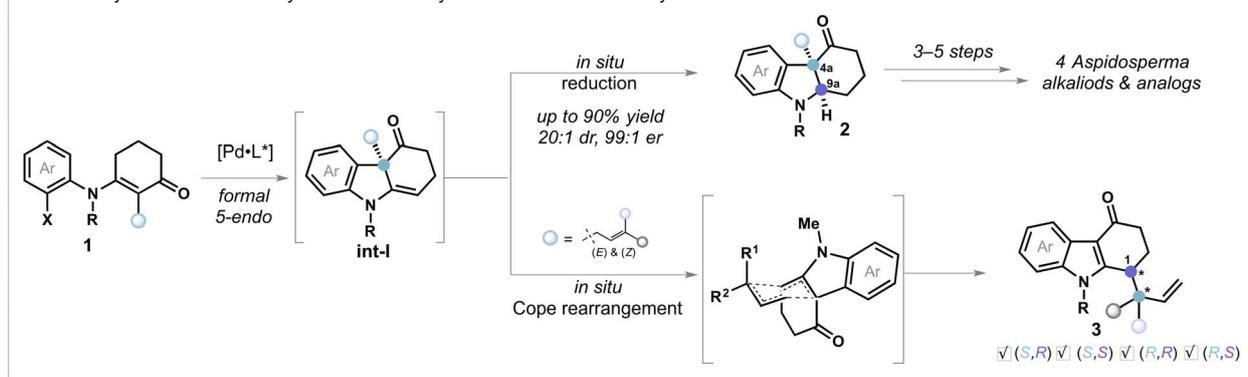
c. Approach enabled by this research: hexahydrocarbazol-4-ones as precursors



d. Pd-catalyzed 5-exo Heck–iminium ion cyclization



e. Pd-catalyzed formal 5-endo cyclization to hexahydrocarbazol-4-ones/tetrahydrocarbazol-4-ones



Scheme 1 Background and outline of this research.

Drawing inspiration from Overman's seminal work of 5-exo Heck cyclization of dieny aryl triflates (Scheme 1d),^{30–34} we devised a formal 5-endo arylyative cyclization of aryl enaminone **1** to construct hydrocarbazol-4-ones (Scheme 1e).^{35–38} Using this stereochemistry-enriched hydrocarbazolone as a platform, four complex alkaloids/analogues, (+)-*N*-methyl aspidospermidine,³⁹ (+)-C20-*epi-N*-methyl aspidospermidine, (+)-*N*-

methyl fendleridine,^{40,41} and (+)-*N*-methyl limaspermidine,⁴⁰ were synthesized in just 3–5 isolation steps. Additionally, we developed an arylation/Cope rearrangement cascade reaction using α -allyl-substituted enaminones as the substrates, allowing access to tetrahydrocarbazol-4-ones bearing contiguous quaternary and tertiary stereocenters. Indeed, enantioselective assembly of such stereochemical dyads is especially demanding



and represents the cutting edge of asymmetric catalysis.^{42–44} A stereodivergent approach to all four stereoisomers was achieved by judicious choice of chiral ligands and *Z/E* geometry of the allyl substituents.^{45–47}

Results and discussion

Reaction development

Our studies began with enaminone **1a'** as the model substrate to optimize the reaction conditions (Table 1, see Tables S1–S5† for additional details and the structures of ligands). The initial investigation of chiral ligands, including bisphosphines (**L1–L6**),⁴⁸ phosphoramidite (**L7**),⁴⁹ and phosphooxazoline (**L8**),⁵⁰ was carried out using TMG (1,1,3,3-tetramethylguanidine) as the base (entry 1). Among them, QuinoxP* (*S,S*)-**L4** showed the best enantioselectivity,⁵¹ albeit the yield was low (entry 2). Further optimization experiments highlighted the critical roles of the base in influencing the reactivity, and the use of Cs₂CO₃ was able to improve both the yield and enantioselectivity (entries 3–5, and Table S2†). Investigation of palladium precursors led us to find a significant enhancement in enantioselectivity using [Pd(allyl)Cl]₂ (entries 5–8 and Table S4†). During these experiments with **1a'** as the substrate, reductive deiodination was identified as the major side pathway, which limited the overall yield of the desired arylation product. This side reaction likely occurred because the rapid oxidative addition of palladium to the aryl iodide was not well-aligned with the subsequently slower cyclization step.⁵² To address this issue, we replaced the aryl iodide with an aryl bromide substrate **1a**, leading to an improved yield of 70% (entry 9). Ultimately, after further optimization of the enamine reduction step (Table S5†), we found that the addition of AcOH in MeCN could dramatically facilitate the reduction efficiency, affording product **2a** in 90% isolated yield with 98.5 : 1.5 er (standard conditions, entry 10).

Scope of the Pd-catalyzed asymmetric arylation cyclization to hexahydrocarbazol-4-ones

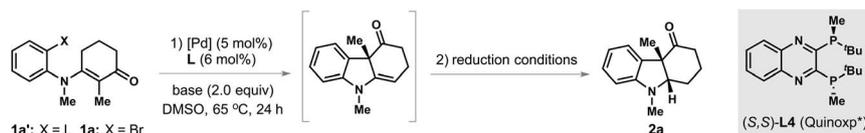
The substrate scope of this reaction was then explored (Scheme 2). Various substitutions on the aryl moiety of the substrates, including methyl (**2b**, **2e**), methoxy (**2c**, **2f**), fluoro (**2d**, **2g**), chloro (**2h**), and trifluoromethyl (**2i**), were successfully tolerated to deliver the products in 67–90% yields with 97.5 : 2.5–99 : 1 er. A substrate with a methyl substituent ortho to the nitrogen also proved feasible, affording the corresponding product **2k** in 75% yield with 99 : 1 er. Notably, the 3-methyl substituted substrate (**1j**) produced **2j** in a lower yield and reduced enantioselectivity due to the steric hindrance.^{35,38} The *N*-benzyl substrate **1l** was also compatible, providing **2l** in 82% yield with 96 : 4 er. Substituents at the α -position of the enaminone moiety were well-tolerated, furnishing ethyl, benzyl, and aminoethyl-substituted tetrahydrocarbazolones **2m–o** in good yields with high enantioselectivities.

Particularly noteworthy is the product **2o**, a key precursor in the total synthesis of *Aspidosperma* alkaloids as shown in Scheme 6. Additionally, an aryl substituted enaminone was feasible substrate, producing **2p** in 76% yield with 97 : 3 er. A gem-dimethyl-substituted enaminone was also examined, affording **2q** in 71% yield with 97 : 3 er.

Mechanistic consideration of the catalytic cycle

During the screening of reaction conditions, we found that no product was observed when Pd₂(dba)₃ was employed (Table 1, entry 7), which suggests that a complex directly formed from Pd(0) and **L4** is not likely to be the active catalyst. Previous report by Belyk disclosed that Pd(OAc)₂ and QuinoxP* **L4** in the presence of base could generate mono oxidized bisphosphine coordinated palladium(0) complex.⁵³ Inspired by this, we applied **L9** in combination with Pd₂(dba)₃ as the precatalyst, the

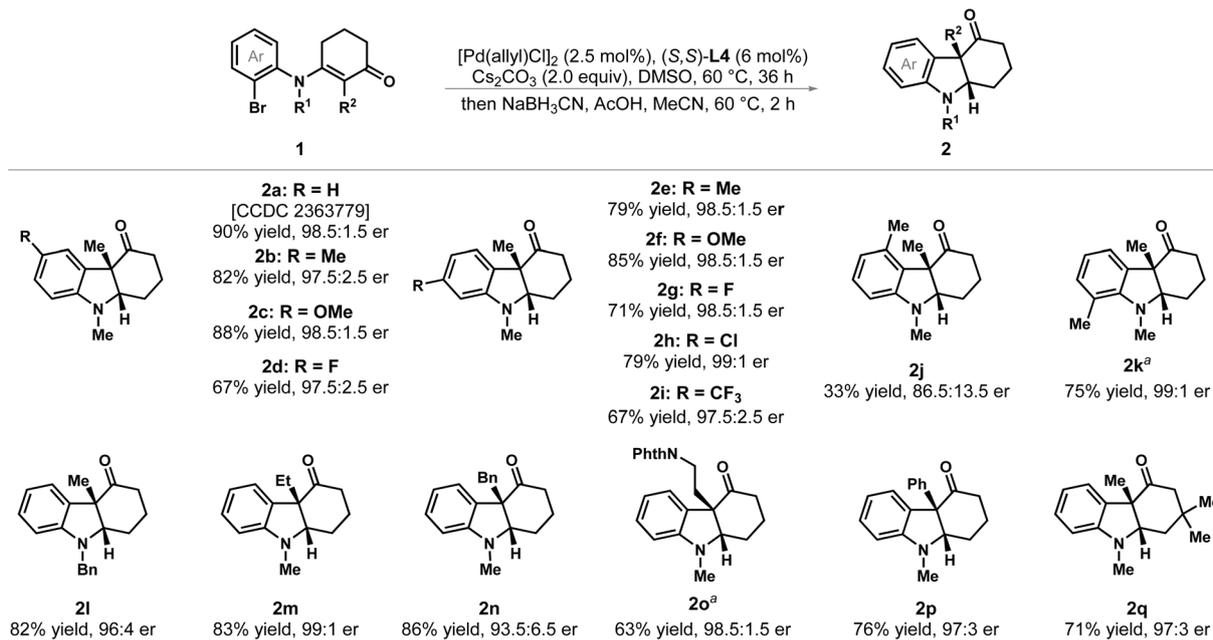
Table 1 Selected results of condition optimizations



Entry ^a	Ligand	[Pd]	Base	Sub	Reduction conditions	2a ^b (%)	er ^c of 2a
1	L1–L3 , L5–L8	Pd(OAc) ₂	TMG	1a'	NaBH ₃ CN, MeOH	<56	<56 : 44
2	L4	Pd(OAc) ₂	TMG	1a'	NaBH ₃ CN, MeOH	8	79.5 : 20.5
3	L4	Pd(OAc) ₂	TBD	1a'	NaBH ₃ CN, MeOH	12	79.5 : 20.5
4	L4	Pd(OAc) ₂	Na ₂ CO ₃	1a'	NaBH ₃ CN, MeOH	12	85 : 15
5	L4	Pd(OAc) ₂	Cs ₂ CO ₃	1a'	NaBH ₃ CN, MeOH	31	87 : 13
6	L4	Pd(MeCN) ₂ Cl ₂	Cs ₂ CO ₃	1a'	NaBH ₃ CN, MeOH	23	92 : 8
7	L4	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1a'	NaBH ₃ CN, MeOH	Trace	—
8	L4	[Pd(allyl)Cl] ₂	Cs ₂ CO ₃	1a'	NaBH ₃ CN, MeOH	33	97.5 : 2.5
9 ^d	L4	[Pd(allyl)Cl] ₂	Cs ₂ CO ₃	1a	NaBH ₃ CN, MeOH	70	98.5 : 1.5
10 ^d	L4	[Pd(allyl)Cl] ₂	Cs ₂ CO ₃	1a	NaBH ₃ CN, AcOH, MeCN	90	98.5 : 1.5

^a Conducted on 0.1 mmol scale with 2 equiv. of base for 24 h. ^b ¹H NMR yield (isolated yield). ^c Determined by HPLC (Chiralcel OJ-H). ^d At 60 °C for 36 h.





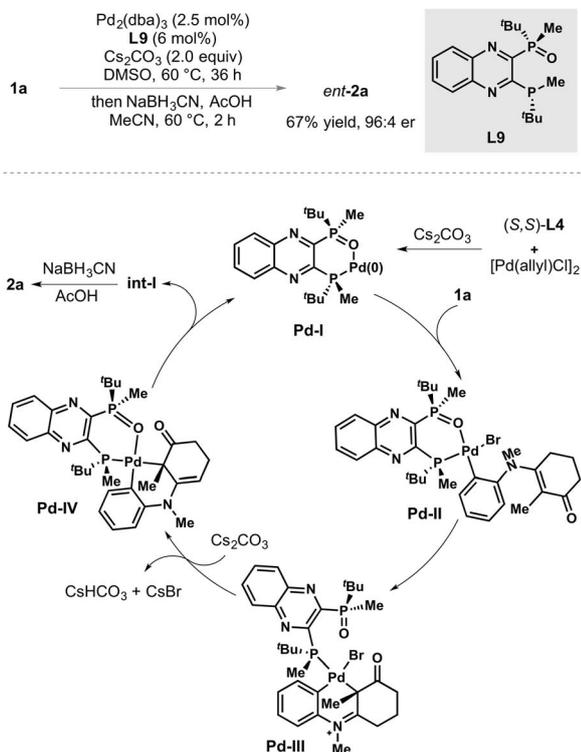
Scheme 2 Substrate scope of arylative cyclization/reduction. ^aWith 5 mol% of $[\text{Pd}(\text{allyl})\text{Cl}]_2$ and 12 mol% of (*S,S*)-L4.

reaction showed similar reactivity and enantioselectivity (Scheme 3, top). Based on this result and the Belyk's work, it is reasonable to propose that in our system, the active catalytic Pd(0) species **Pd-I** is generated *via* the reduction of $[\text{Pd}(\text{allyl})\text{Cl}]_2$ and (*S,S*)-L4. Next, a plausible catalytic cycle of the Pd-catalyzed arylative cyclization was provided (Scheme 3, bottom).³⁵ Oxidative addition of substrate **1a** with **Pd-I** forms aryl palladium(II)

species **Pd-II**, which subsequently generates iminium intermediate **Pd-III**. The deprotonation of iminium delivers enamine **Pd-IV** and followed by reductive elimination, intermediate **int-I** is produced while regenerating the catalytically active species **Pd-I**.

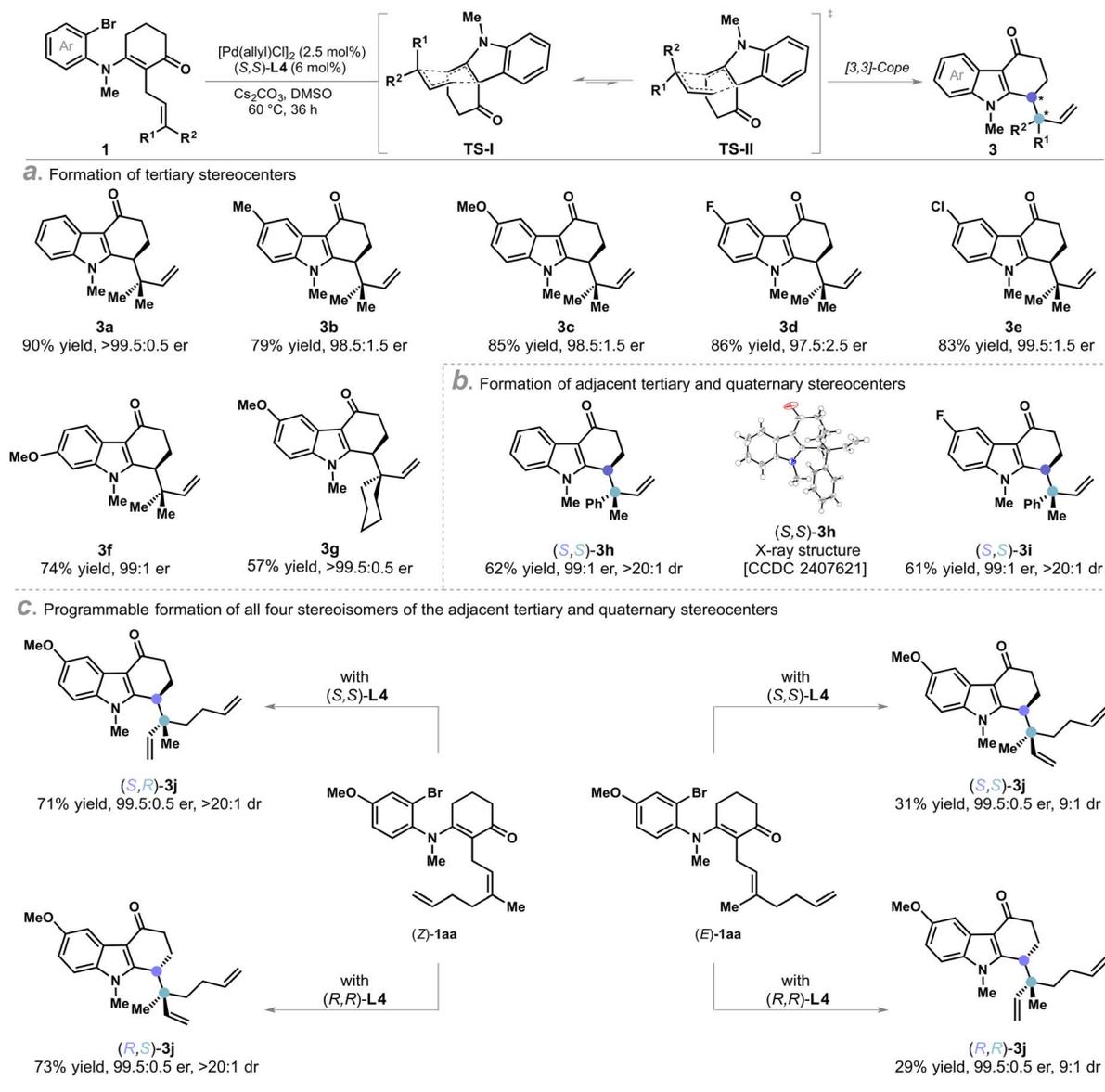
Scope of the Pd-catalyzed asymmetric arylative cyclization/Cope rearrangement cascade to tetrahydrocarbazol-4-ones

During the exploration of the reaction scope, a notable observation was an arylation/Cope rearrangement cascade when substrates bearing an α -allyl group were employed (Scheme 4). This reaction facilitated the formation of tetrahydrocarbazol-4-ones featuring a C1-tertiary chiral center adjacent to a bulky quaternary carbon substituent. The robustness of this method was demonstrated by the good yields and excellent enantioselectivities achieved across a range of substrates (**3a-g**). Remarkably, a new set of contiguous quaternary and tertiary stereocenters was assembled with perfect diastereoselectivities and enantioselectivities using tetrasubstituted allyl groups attaching two different substituents at the terminal carbon of the olefin (Scheme 4b). For instance, α -phenylbut-2-enyl enaminones (**1y** and **1z**) led to the formation of products **3h** and **3i** in good yields with excellent er and >20:1 dr. By programming the catalyst and geometry of the allyl group, we were able to assemble all the four stereoisomers of the products (Scheme 4c). Specifically, the combination of (*S,S*)-L4 with (*Z*)-allyl substituted enaminone, (*Z*)-**1aa**, delivered (*S,R*)-**3j** in 73% yield with 99.5:0.5 er and >20:1 dr; switching to (*E*)-allyl substituted enaminone, (*E*)-**1aa**, produced (*S,S*)-**3j** albeit in lower yield with reduced diastereoselectivity. The (*R,S*)-**3j** and (*R,R*)-**3j** were also obtained by the combination of (*R,R*)-L4 with (*Z*)-**1aa** and (*E*)-**1aa**, respectively. Previous mechanistic studies suggest that the stereospecific Cope rearrangement proceeds



Scheme 3 Plausible catalytic cycle.



Scheme 4 Substrate scope of α -arylation/Cope rearrangement cascade.

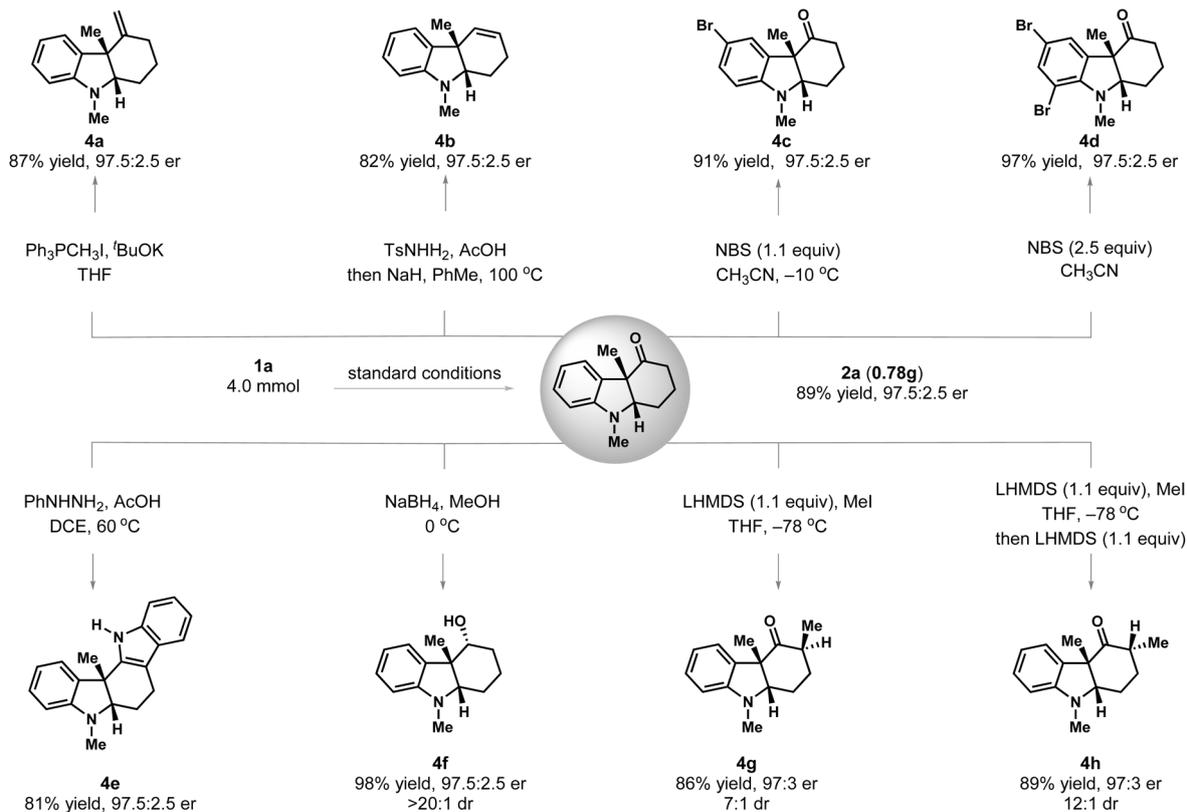
through a rigid chair-like transition state, which allows for precise control of diastereoselectivity.^{54–56} In our system, the aromatization of **TS-I** drives the rearrangement, enabling it to occur under relatively mild conditions compared to previously reported examples.^{57–59} The mechanistic rationale of the stereospecific rearrangement based on DFT calculations was included in the ESI (Scheme S1).[†] The diminished yields and diastereoselectivities observed for (*S,S*)-**3j** and (*R,R*)-**3j** can be attributed to their sterically hindered and energetically demanding transition states, which lead to allyl fragmentation as a side reaction in both cases.

Synthetic applications

The synthetic applications of the reaction were showcased (Scheme 5). A scale-up reaction produced **2a** (0.78 g) in 89% yield with 97.5 : 2.5 er. Treatment of **2a** with a Wittig reagent

resulted in exocyclic olefin **4a** in 87% yield. Under Bamford–Stevens reaction conditions,⁶⁰ tetrahydrocarbazole **4b** was obtained smoothly. Moreover, both mono- and bis-bromination of **2a** were successfully achieved, yielding **4c** and **4d**, respectively, by carefully controlling NBS loading and reaction temperature. The regioselectivity of this electrophilic substitution of **2a** in accordance with that observed in the bromination of *Aspidosperma* alkaloids.⁶¹ Subjecting **2a** to Fischer indole synthesis conditions furnished ring-fused indole **4e** in 81% yield. The arched shape of **2a**, with an 84.3° dihedral angle between the indoline and cyclohexanone planes caused by the contiguous stereocenters, provides an excellent stereocontrol for streamline manipulating toward the synthesis of complex molecules and natural products. Reduction of the carbonyl group with NaBH₄ delivered alcohol **4f** in quantitative yield with >20 : 1 dr. Diastereoselective α -alkylation of the carbonyl was achieved in 86%



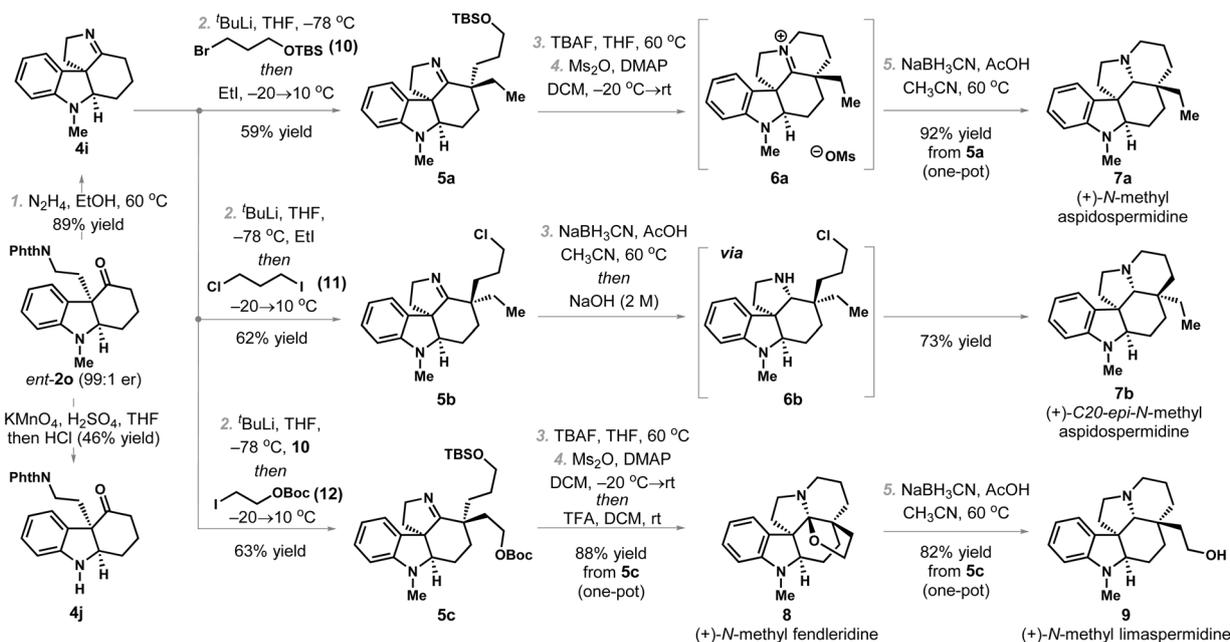


Scheme 5 Scale-up synthesis and product derivatization.

yield (4g). Notably, the α -stereocenter of carbonyl 4g can be inverted through a deprotonation/protonation process at -78°C , resulting in its diastereoisomer 4h in 89% yield.

Synthesis of *Aspidosperma* alkaloids and their analogs

The potential application of this method was further demonstrated by the access to complex alkaloids and their derivatives using *ent-2o* (99:1 er) as a common precursor (Scheme 6).

Scheme 6 Applications in the synthesis of *Aspidosperma* alkaloids/analogs.

Deprotection of the phthalimide group using hydrazine resulted in immediate condensation to form tetracyclic imine **4i** in 89% yield. By modulating the sequence of alkylation, both stereochemical configurations at the C20 quaternary center were accessible. For example, treatment of **4i** with 3.3 equivalents of ^tBuLi, followed by sequential addition of **10** and iodoethane, provided an intermediate **5a** with the same stereochemistry at C20 as the corresponding natural products. Similarly, both intermediates **5b** and **5c** were obtained using the appropriate alkylating reagents in 62% and 63% yields, respectively. The exceptionally high diastereoselectivity of the alkylation of **4i** might be associated with the torsional effects of planar conformational alignments of the 5–6 fused cyclohexamine.⁶² Subsequent deprotection of the TBS group of **5a**, followed by converting the resulting alcohol into a mesylate, led to spontaneous nucleophilic cyclization to form iminium ion **6a**.⁶³ Without further purification, reduction of the iminium with NaBH₃CN afforded the natural product (+)-*N*-methyl aspidospermidine **7a** in 5 total steps from *ent*-**2o** representing the shortest enantioselective total synthetic route reported to date.^{64–66} Starting from **5b**, reduction of the imine followed by *in situ* cyclization yielded (+)-C20-*epi-N*-methyl aspidospermidine **7b** in 73% yield in 3 steps from *ent*-**2o**. Our attention was then directed to the synthesis of fendleridine derivatives using **5c** as the synthetic precursor. Similar to our previous approaches, removal of the TBS group, followed by mesylation, intramolecular annulation, and C19-hemiaminal formation, resulted in the production of (+)-*N*-methyl fendleridine **8** in 88% yield.^{67–69} Further reduction of **8** under acidic conditions provided (+)-*N*-methyl limaspermidine **9** in 82% yield from **5c**.^{15,70,71} It should be emphasized that the *N*-methyl group of the hexahydrocarbazolone can be removed under the conditions developed by Fukuyama⁷² to afford **4j** in 46% yield, providing opportunities for the synthesis of other alkaloids of the *Aspidosperma* family.⁷³

Conclusions

In conclusion, we have developed a palladium-catalyzed enantioselective formal 5-*endo* cyclization of enamines to access hexahydrocarbazol-4-ones containing contiguous quaternary and tertiary stereocenters. Additionally, a catalytic arylation/Cope rearrangement cascade strategy has been established for α -allyl substituted enaminone substrates, achieving the stereodivergent assembly of adjacent quaternary and tertiary stereocenters. The method has proven applicable to the concise synthesis of four *Aspidosperma* alkaloids/analogs in just 3–5 steps from the hexahydrocarbazol-4-one *ent*-**2o**, highlighting the ability to control stereochemistry and efficiently build molecular complexity from a common intermediate accessed by our method. Further application of this reaction in the synthesis of other indole alkaloids is currently undergoing.

Data availability

All the data supporting this article have been included in the ESI.†

Author contributions

WBL conceptualized the project. HS and CLY conducted the experiments, analyzed the data, and wrote the manuscript. ZD carried out the initial optimization. PFS and YQZ performed experiments related to substrate synthesis and DFT studies. WBL and YCX revised the manuscript with input from all authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- V. DeLuca and W. G. W. Kurz, in *Phytochemicals in Plant Cell Cultures*, ed. F. Constabel and I. K. Vasil, Academic Press, San Diego, 1988, pp. 385–401.
- A. Brossi and X.-F. Pei, in *The Alkaloids: Chemistry and Biology*, ed. G. A. Cordell, Academic Press, San Diego, 1998, vol. 50, pp. 109–139.
- B. P. Pritchett and B. M. Stoltz, *Nat. Prod. Rep.*, 2018, **35**, 559–574.
- Y. Wang, F. Xie, B. Lin, M. Cheng and Y. Liu, *Chem. Eur J.*, 2018, **24**, 14302–14315.
- J. M. Saya, E. Ruijter and R. V. A. Orru, *Chem. Eur J.*, 2019, **25**, 8916–8935.
- N. Wang and X. Jiang, *Chem. Rec.*, 2021, **21**, 295–314.
- N. Wang, X. Xiao, C.-X. Liu, H. Yao, N. Huang and K. Zou, *Adv. Synth. Catal.*, 2022, **364**, 2479–2501.
- M. Usman, X.-D. Hu and W.-B. Liu, *Chin. J. Chem.*, 2020, **38**, 737–752.
- D. Desmaeele and J. d'Angelo, *J. Org. Chem.*, 1994, **59**, 2292–2303.
- Z. Li, S. Zhang, S. Wu, X. Shen, L. Zou, F. Wang, X. Li, F. Peng, H. Zhang and Z. Shao, *Angew. Chem., Int. Ed.*, 2013, **52**, 4117–4121.
- C. J. Gartshore and D. W. Lupton, *Angew. Chem., Int. Ed.*, 2013, **52**, 4113–4116.
- Y. Wei, D. Zhao and D. Ma, *Angew. Chem., Int. Ed.*, 2013, **52**, 12988–12991.
- L. Leng, X. Zhou, Q. Liao, F. Wang, H. Song, D. Zhang, X.-Y. Liu and Y. Qin, *Angew. Chem., Int. Ed.*, 2017, **56**, 3703–3707.



- 14 B. P. Pritchett, J. Kikuchi, Y. Numajiri and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2016, **55**, 13529–13532.
- 15 J.-Y. Du, C. Zeng, X.-J. Han, H. Qu, X.-H. Zhao, X.-T. An and C.-A. Fan, *J. Am. Chem. Soc.*, 2015, **137**, 4267–4273.
- 16 C. R. O'Donnell and C. B. W. Stark, *Org. Lett.*, 2024, **26**, 9689–9692.
- 17 K. Du, H. Yang, P. Guo, L. Feng, G. Xu, Q. Zhou, L. W. Chung and W. Tang, *Chem. Sci.*, 2017, **8**, 6247–6256.
- 18 D. Jiang, P. Tang, H. Xiong, S. Lei, Y. Zhang, C. Zhang, L. He, H. Qiu and M. Zhang, *Angew. Chem., Int. Ed.*, 2023, **62**, e202307286.
- 19 S. B. Jones, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature*, 2011, **475**, 183–188.
- 20 B. N. Laforteza, M. Pickworth and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2013, **52**, 11269–11272.
- 21 Y. Minko, M. Pasco, L. Lercher, M. Botoshansky and I. Marek, *Nature*, 2012, **490**, 522–526.
- 22 K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191.
- 23 Y. Liu, S.-J. Han, W.-B. Liu and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740–751.
- 24 X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou and J. Zhou, *Chem. Rev.*, 2016, **116**, 7330–7396.
- 25 C. Li, S. S. Ragab, G. Liu and W. Tang, *Nat. Prod. Rep.*, 2020, **37**, 276–292.
- 26 R.-X. Liang and Y.-X. Jia, *Acc. Chem. Res.*, 2022, **55**, 734–745.
- 27 J.-C. Gramain, H.-P. Husson and Y. Troin, *Tetrahedron Lett.*, 1985, **26**, 2323–2326.
- 28 J.-C. Gramain, H. P. Husson and Y. Troin, *J. Org. Chem.*, 1985, **50**, 5517–5520.
- 29 J. C. Gramain, Y. Troin and H. P. Husson, *J. Heterocycl. Chem.*, 1988, **25**, 201–203.
- 30 A. B. Dounay, L. E. Overman and A. D. Wroblewski, *J. Am. Chem. Soc.*, 2005, **127**, 10186–10187.
- 31 A. B. Dounay, P. G. Humphreys, L. E. Overman and A. D. Wroblewski, *J. Am. Chem. Soc.*, 2008, **130**, 5368–5377.
- 32 A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945–2964.
- 33 M. Shibasaki and T. Ohshima, in *The Mizoroki–Heck Reaction*, 2009, pp. 463–483.
- 34 J.-Q. Xie, R.-X. Liang and Y.-X. Jia, *Chin. J. Chem.*, 2021, **39**, 710–728.
- 35 Z. Dong, X.-W. Zhang, W. Li, Z.-M. Li, W.-Y. Wang, Y. Zhang, W. Liu and W.-B. Liu, *Org. Lett.*, 2019, **21**, 1082–1086.
- 36 W. Li, Z. Dong, Y. Zhang, Z. Zeng, M. Usman and W.-B. Liu, *J. Org. Chem.*, 2019, **84**, 7995–8005.
- 37 S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402–3415.
- 38 R.-X. Liang, C. Zhong, Z.-H. Liu, M. Yang, H.-W. Tang, J.-F. Chen, Y.-F. Yang and Y.-X. Jia, *ACS Catal.*, 2021, **11**, 1827–1832.
- 39 A. Walser and C. Djerassi, *Helv. Chim. Acta*, 1965, **48**, 391–404.
- 40 R. H. Burnell, J. D. Medina and W. A. Ayer, *Can. J. Chem.*, 1966, **44**, 28–31.
- 41 J. D. Medina and L. D. Genova, *Planta Med.*, 1979, **37**, 165–167.
- 42 L. Wei, X. Chang and C.-J. Wang, *Acc. Chem. Res.*, 2020, **53**, 1084–1100.
- 43 D. Pierrot and I. Marek, *Angew. Chem., Int. Ed.*, 2020, **59**, 36–49.
- 44 M. Wang, Z. Zhang and W. Zhang, *Acc. Chem. Res.*, 2022, **55**, 2708–2727.
- 45 H. Zheng, Y. Wang, C. Xu, X. Xu, L. Lin, X. Liu and X. Feng, *Nat. Commun.*, 2018, **9**, 1968–1974.
- 46 G. Zhang, M. D. Wodrich and N. Cramer, *Science*, 2024, **383**, 395–401.
- 47 A. M. Martín Castro, *Chem. Rev.*, 2004, **104**, 2939–3002.
- 48 T. Imamoto, *Chem. Rev.*, 2024, **124**, 8657–8739.
- 49 W.-B. Liu, C. Zheng, C.-X. Zhuo, L.-X. Dai and S.-L. You, *J. Am. Chem. Soc.*, 2012, **134**, 4812–4821.
- 50 M. R. Krout, J. T. Mohr and B. M. Stoltz, *Org. Synth.*, 2009, **86**, 181–193.
- 51 T. Imamoto, K. Sugita and K. Yoshida, *J. Am. Chem. Soc.*, 2005, **127**, 11934–11935.
- 52 M. S. Viciu, G. A. Grasa and S. P. Nolan, *Organometallics*, 2001, **20**, 3607–3612.
- 53 H. Li, K. M. Belyk, J. Yin, Q. Chen, A. Hyde, Y. Ji, S. Oliver, M. T. Tudge, L.-C. Campeau and K. R. Campos, *J. Am. Chem. Soc.*, 2015, **137**, 13728–13731.
- 54 E. Fereyduni, J. N. Sanders, G. Gonzalez, K. N. Houk and A. J. Grenning, *Chem. Sci.*, 2018, **9**, 8760–8764.
- 55 T. J. Fulton, A. Q. Cusumano, E. J. Alexy, Y. E. Du, H. Zhang, K. N. Houk and B. M. Stoltz, *J. Am. Chem. Soc.*, 2020, **142**, 21938–21947.
- 56 A. Nilova, M. D. Mannchen, A. N. Noel, E. Semenova and A. J. Grenning, *Chem. Sci.*, 2023, **14**, 2755–2762.
- 57 E. N. Marvell and C. Lin, *J. Am. Chem. Soc.*, 1978, **100**, 877–883.
- 58 X. Yu, F. Su, C. Liu, H. Yuan, S. Zhao, Z. Zhou, T. Quan and T. Luo, *J. Am. Chem. Soc.*, 2016, **138**, 6261–6270.
- 59 B. M. Tomiczek and A. J. Grenning, *Org. Biomol. Chem.*, 2021, **19**, 2385–2398.
- 60 W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 1952, 4735–4740.
- 61 A. W. Rand, K. J. Gonzalez, C. E. Reimann, S. C. Virgil and B. M. Stoltz, *J. Am. Chem. Soc.*, 2023, **145**, 7278–7287.
- 62 H. Wang and K. N. Houk, *Chem. Sci.*, 2014, **5**, 462–470.
- 63 N. Benchekroun-Mounir, D. Dugat, J. C. Gramain and H. P. Husson, *J. Org. Chem.*, 1993, **58**, 6457–6465.
- 64 H. Ishikawa, G. I. Elliott, J. Velcicky, Y. Choi and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 10596–10612.
- 65 N. Wang, S. Du, D. Li and X. Jiang, *Org. Lett.*, 2017, **19**, 3167–3170.
- 66 T. A. Grigolo and J. M. Smith, *Chem. Eur. J.*, 2022, **28**, e202202813.
- 67 E. L. Campbell, A. M. Zuhl, C. M. Liu and D. L. Boger, *J. Am. Chem. Soc.*, 2010, **132**, 3009–3012.
- 68 K. L. White and M. Movassaghi, *J. Am. Chem. Soc.*, 2016, **138**, 11383–11389.
- 69 A. K. Ghosh, J. R. Born and L. A. Kassekert, *J. Org. Chem.*, 2019, **84**, 5167–5175.



- 70 S.-X. Zhang, X.-L. Shen, Z.-Q. Li, L.-W. Zou, F.-Q. Wang, H.-B. Zhang and Z.-H. Shao, *J. Org. Chem.*, 2013, **78**, 11444–11449.
- 71 B. P. Pritchett, E. J. Donckele and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2017, **56**, 12624–12627.
- 72 Y. Han-ya, T. Inui, S. Yokoshima, H. Tokuyama and T. Fukuyama, *Chem. Pharm. Bull.*, 2016, **64**, 800–804.
- 73 D.-X. Tan, J. Zhou, C.-Y. Gu, Z.-Y. Li, Y.-J. Shen and F.-S. Han, *Chem*, 2025, **11**, DOI: [10.1016/j.chempr.2025.102440](https://doi.org/10.1016/j.chempr.2025.102440).

