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Highly Diastereo- and Enantioselective Pd-Catalyzed Spiroaminoalkylation: One-Step Construction of Multifunctional Angular Polycyclic Amines

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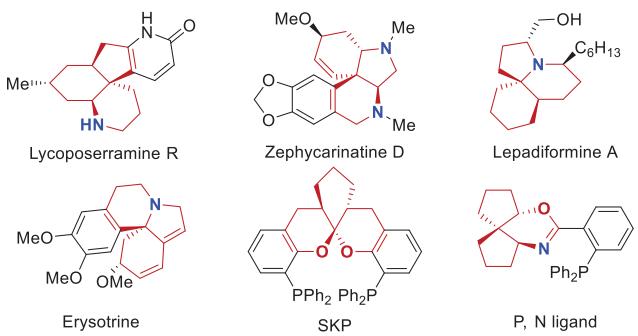
Abstract: Angular polycycles are ubiquitous in natural products with significant biological properties. However, the straightforward catalytic asymmetric synthesis of spirocyclic scaffolds with multiple stereogenic centers from readily available starting materials remains largely underdeveloped and a formidable challenge. Using the aminoalkyl cyclopalladated complex as the key intermediate, we report herein the first example of diastereo- and enantioselective multifunctional angular tetracyclic- and pentacyclic amines synthesis through palladium-catalyzed spiroaminoalkylation/allylic substitution reaction (up to 92% yield, up to 99% ee). The synthetic versatility of this methodology is underscored by the efficient synthesis of chiral phosphine ligands, which further demonstrates its robust utility in concisely constructing versatile chiral ligands.

Spiro rings such as piperidine and pyrrolidine-containing angular tetracyclic and pentacyclic are privileged structural motifs found in numerous natural products and pharmaceutically active molecules (Scheme 1).[1,2] Furthermore, such motifs significantly impact the physicochemical and biological properties of organic molecules. As such, the incorporation of a spiro ring system into clinical drug candidates has emerged as a widely used strategy in drug design and development.[3–5] On the other hand, chiral angular molecules have been demonstrated to be as effective skeletons of chiral ligands in asymmetric catalysis chemistry.[6,7] For example, the chiral diphosphines (SKP) invented by Ding have proved to be excellent and versatile chiral ligands for many transition-metal catalyzed enantioselective reactions.[8–10] This distinctive molecular structure along with biologically interesting activities of these molecules has inspired enormous synthetic investigations. In this context, various approaches to access these angular polycycles are based on the intramolecular condensation of functionalized linear precursors.[11–17] However, construction of the functional chain precursors could be challenging, although successful examples have been reported recently.[18–27] Furthermore, the synthesis of these spiroamine frameworks in an enantioselective manner is much more challenging. Thus, the development of novel strategies for efficient catalytic asymmetric construction of these angular skeletons from readily available starting materials is still in great demand.

The development of new and efficient reactions is a fundamental goal and challenge in synthetic organic chemistry. Key to this is the discovery and identification of novel and versatile reactive intermediates and insights into the fundamental transformation of these intermediates.[28–32] In the past decade, our group has discovered that the unique aminoalkyl cyclopalladated complex (Huang complex) generated via oxidative addition of aminal or its surrogate with Pd(0) could be utilized as a leading complex to guide the development of diverse catalytic transformations for constructing C–C and C–X bonds.[33–36] Salicylaldehydes and aminodienes are readily available and serve as very important starting materials in organic synthesis. Oxidative addition of the *N,O*-acetal of salicylaldehyde and aminodiene could produce highly reactive cyclopalladated intermediates, leading to establishing efficient aminoalkylative cyclization reactions for construction of chiral heterocycles bearing multiple contiguous stereocenters, in which the C–N bond metathesis and dynamic kinetic resolution (DKR) were involved to



Scheme 1. Examples of nature products and chiral ligands bearing angular polycycle.

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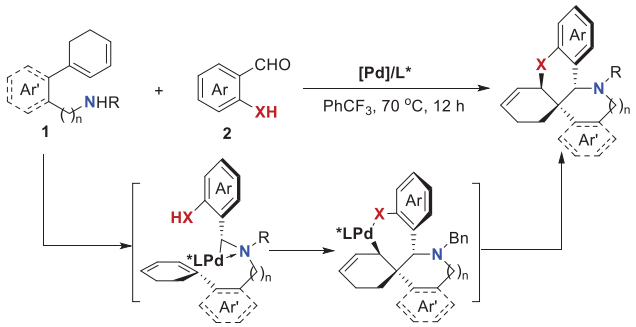
Additional supporting information can be found online in the Supporting Information section

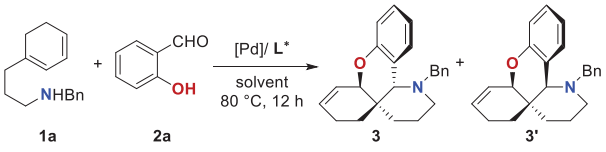


Scheme 2. Pd-catalyzed enantio- and diastereoselective spiroaminoalkylation.

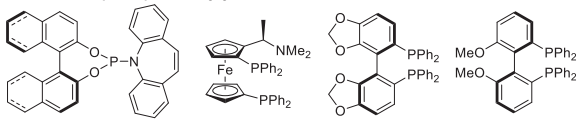
guarantee high stereoselectivity.[37,38] Based on these findings, we envisaged that a tandem spiroaminoalkylation/allylic substitution reaction might be also established once amine-tethered cyclic diene was utilized as coupling partner, which will provide direct access to the desired angular skeleton (Scheme 2). Despite the bulkiness of the cyclopalladated intermediate and energetic barrier encountered during the spirocyclization process, the spiroaminoalkylation and allylic substitution processes proceeded very well. Herein, we report such an efficient asymmetric synthesis of these unique tetracyclic and pentacyclic spiroamines via Pd(0)-catalyzed intermolecular spiroaminoalkylation/allylic substitution. The new protocol was found to be general for a wide range of substrates and successfully applied in the synthesis of chiral phosphine ligands.

To test the above hypothesis, a model reaction of amine-tethered cyclohexa-1,3-diene **1a** and salicylaldehyde **2a** was conducted at 80 °C under the palladium catalysis. A variety of commercially available chiral ligands were first examined with $Pd(acac)_2$ as the catalyst precursor (Table 1, entries 1–5). It was found that electron-deficient ligand **(*S*)-L2** gave the best results, furnishing the desired piperidine product **3** in 78% yield with 94:6 dr and 94% ee. The absolute configurations of the major product (*S*,*R*,*R*)-**3** and minor product (*S*,*R*,*S*)-**3′** were determined by X-ray diffraction analysis, respectively.[39] By contrast, electron-rich bisphosphine ligands **L3**, **L4** and **L5** led to diminished reactivities and selectivities (Table 1, entries 3–5). Based on these results, we then shifted to optimize the palladium precursor with phosphoramidite **(*S*)-L2** as the chiral ligand (Table 1, entries 6–9). The results demonstrated that $Pd(acac)_2$ was still the optimal catalyst precursor for this cycloaddition reaction, while other catalyst precursors, such as $[Pd(allyl)Cl]_2$, $Pd(TFA)_2$, $Pd(OAc)_2$, and $Pd_2(dba)_3$ showed lower catalytic efficiency. Further screening of different counterions did not improve the reaction efficiency (see Supporting Information for details). For example, the desired product **3** was obtained in decreased yields, albeit with comparable enantioselectivities when the catalytic reaction was performed in the presence of AgOTf. Subsequently, some common solvents were examined, and found that the best result was obtained when the $PhCF_3$ was utilized as the solvent (Table 1, entries 10–13). Notably, the ee value of the desired product **3** could

Table 1: Optimization of the reaction conditions.[a]



Entry	Pd	L*	solvent	Yield 3 (%)	dr (3:3′)	ee (%)
1	$Pd(acac)_2$	**(*S*)-L1**	DCM	23	86:14	93
2	$Pd(acac)_2$	**(*S*)-L2**	DCM	78	94:6	94
3	$Pd(acac)_2$	**(*R*, S_p)-L3**	DCM	37	93:7	27
4	$Pd(acac)_2$	**(*S*)-L4**	DCM	14	91:9	−55
5	$Pd(acac)_2$	**(*S*)-L5**	DCM	9	85:15	−51
6	$[Pd(allyl)Cl]_2$	**(*S*)-L2**	DCM	44	91:9	99
7	$Pd(TFA)_2$	**(*S*)-L2**	DCM	73	88:12	98
8	$Pd(OAc)_2$	**(*S*)-L2**	DCM	75	89:11	98
9	$Pd_2(dba)_3$	**(*S*)-L2**	DCM	48	85:15	97
10	$Pd(acac)_2$	**(*S*)-L2**	MeCN	40	96:4	96
11	$Pd(acac)_2$	**(*S*)-L2**	THF	22	89:11	99
12	$Pd(acac)_2$	**(*S*)-L2**	DCE	94	93:7	93
13	$Pd(acac)_2$	**(*S*)-L2**	$PhCF_3$	90	91:9	94
14[b]	$Pd(acac)_2$	**(*S*)-L2**	$PhCF_3$	92	92:8	>99

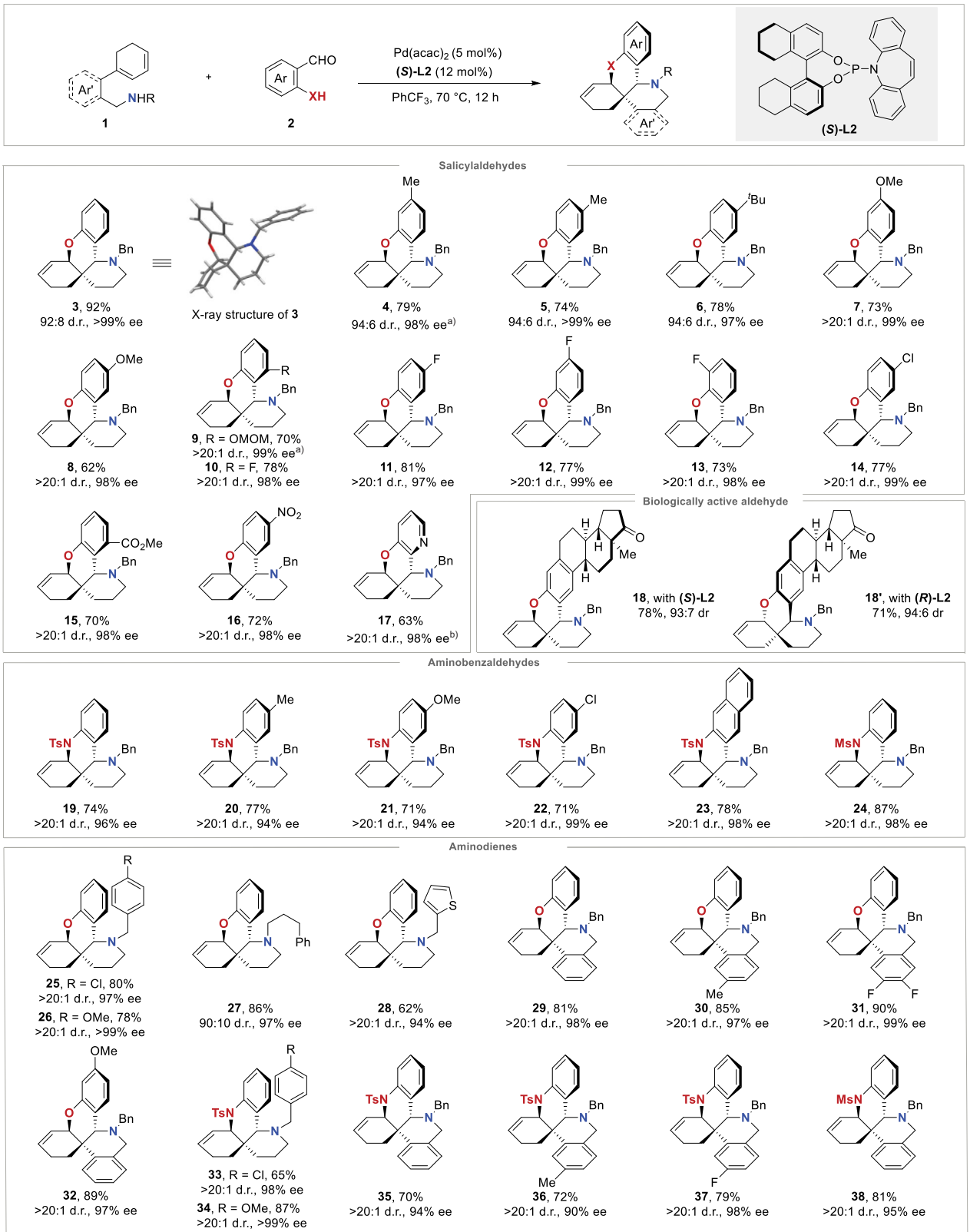


[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), [Pd] (5 or 2.5 mol%), ligand (6 or 12 mol%), solvent (1.0 mL) at 80 °C for 12 h, isolated yield. The d.r. value was determined by GC analysis. The ee value was determined by HPLC analysis with a chiral column. [b] 70 °C.

be further improved to >99% by lowering the reaction temperature to 70 °C (Table 1, entry 14).

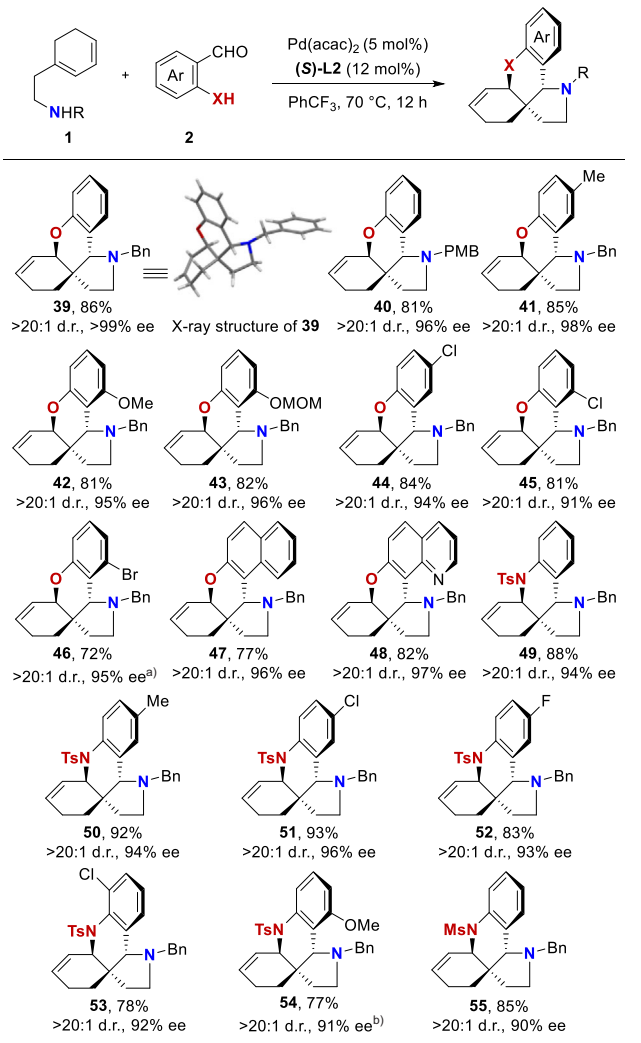
To explore the scope of this palladium-catalyzed cycloaddition process, various substituted salicylaldehydes were coupled with amine-tethered cyclohexa-1,3-diene **1a** under the optimized reaction conditions (Table 2). As shown in Table 2, both electron-rich and electron-deficient salicylaldehydes were compatible with the reaction system, affording the corresponding products in good to excellent yields (62–92% yields) with excellent diastereo- (>20:1 dr) and enantioselectivities (97–99% ee). The electronic factor had negligible effect on this reaction, as strongly electron-withdrawing substituents or donating groups like $–NO_2$ and –OMe afforded their corresponding spiro tetracyclic piperidines (**16**, **7** and **8**) in good yields with perfect stereoselectivities. Significantly, both *ortho*-, *meta*- and *para*-substituted salicylaldehydes were converted into the desired products in good yields with excellent selectivities. To our delight, 3-hydroxypicolinaldehyde, bearing a hydroxy-group with lower nucleophilicity, was also compatible with this reaction to afford the pyridine-containing product **17** in 63% yield with 98% ee and >20:1 diastereoselectivity under slightly modified reaction conditions. These observations suggested a distinct mechanism for the allylic substitution-mediated cyclization compared to our prior studies.[37] Unfortunately, 2-bromo-6-hydroxybenzaldehyde failed to yield the desired

Table 2: Substrate scope of the asymmetric spiroaminoalkylation for construction of [6–6–6] polycycles.



Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), $Pd(acac)_2$ (5 mol%), ***(S)*-L2** (12 mol%), $PhCF_3$ (1.0 mL), 70 °C, 12 h, isolated yield. The d.r. value was determined by ^1H NMR analysis. The ee value was determined by chiral HPLC analysis. [a)] 24 h. [b)] $[Pd(allyl)Cl]_2$ (2.5 mol%) and dioxane (1.0 mL) were used.

Table 3: Substrate scope of the asymmetric spiroaminoalkylation for construction of [6–6–5] polycycles.



Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), $Pd(acac)_2$ (5 mol%), ***(S)*-L2** (12 mol%), $PhCF_3$ (1.0 mL), 70 °C, 12 h, isolated yield. The d.r. value was determined by ^1H NMR analysis. The ee value was determined by chiral HPLC analysis. [a] $Pd(TFA)_2$ (5 mol%) was used. [b] 60 °C, 24 h.

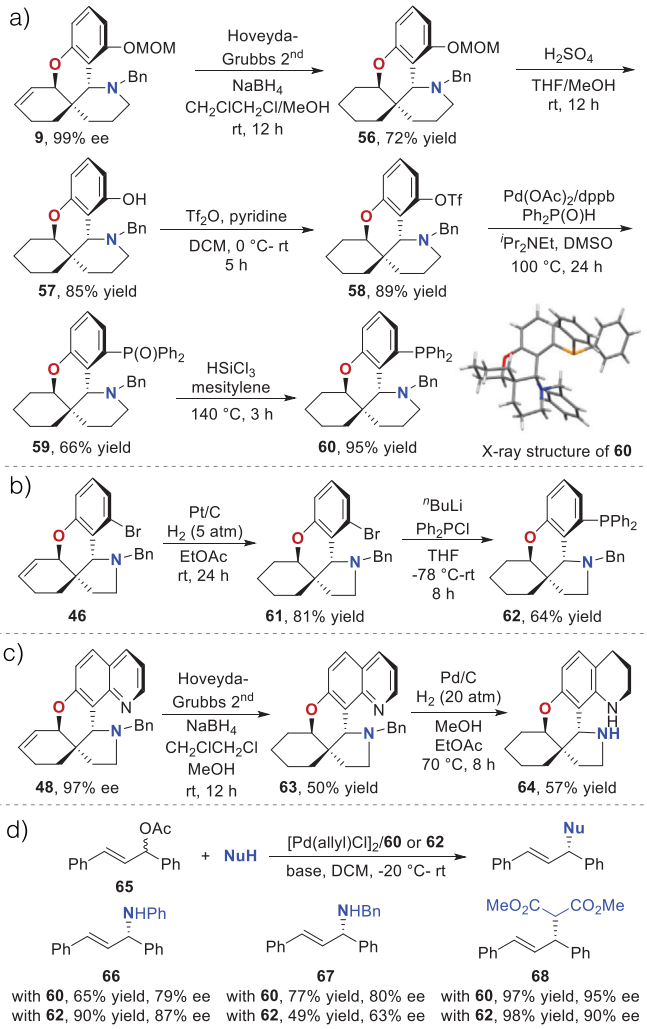
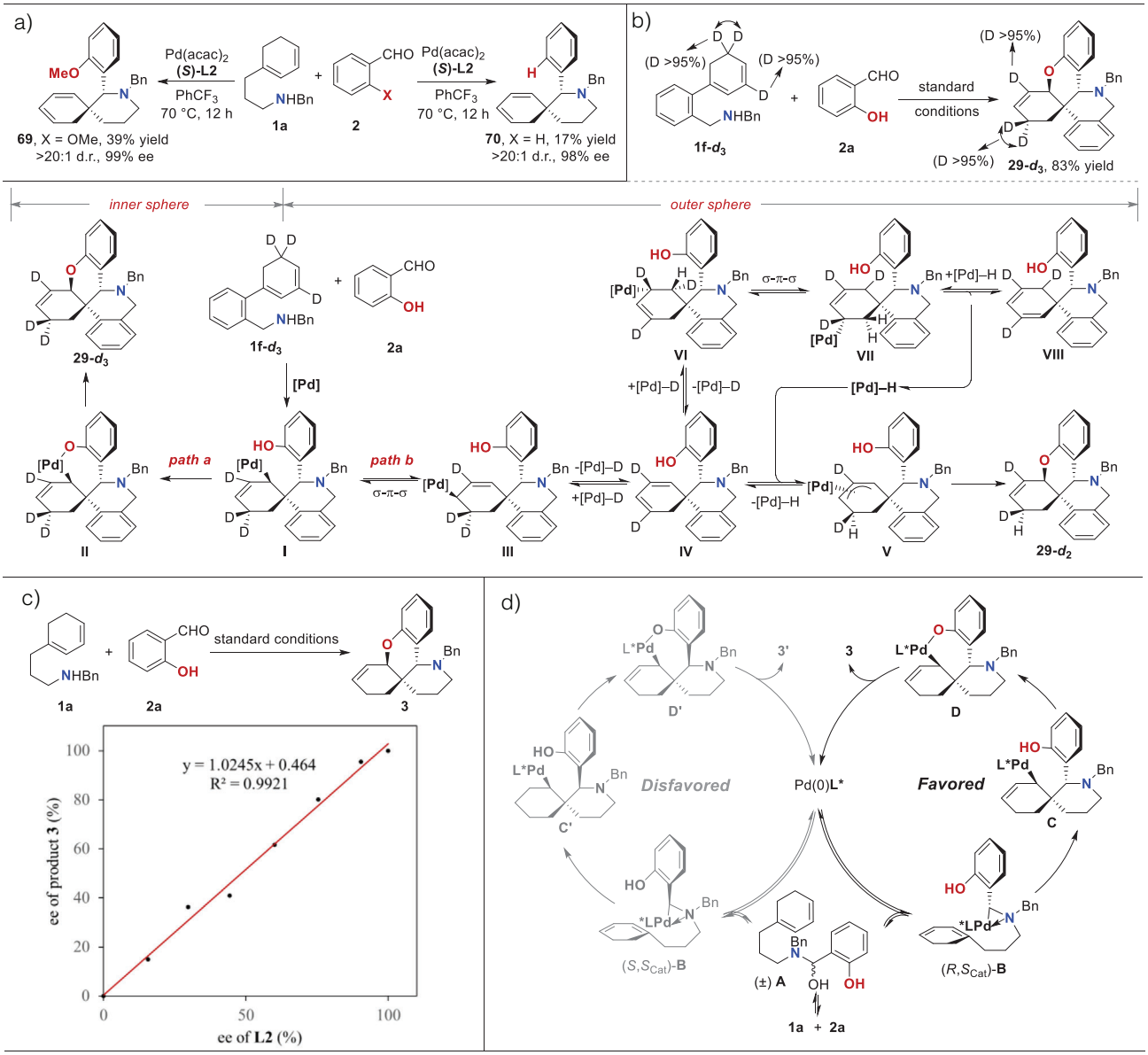


Figure 1. Synthetic applications. a, b) The synthesis of chiral spiro P, N-ligands. c) The synthesis of chiral spiro N, N-ligand. d) The applications of P, N-ligands.

product. In addition, the protocol also enabled the late-stage modification of bioactive estrone derivative, providing the corresponding products (**18** and **18′**) in good yields with high diastereoselectivity. Apart from salicylaldehyde derivatives, the sulfamide-containing aromatic aldehydes are also applicable coupling partners for this transformation to afford a variety of tetracyclic acridines bearing three consecutive chiral centers. As expected, good reaction efficiencies (71–87% yields) as well as excellent stereoselectivities (>20:1 diastereoselectivities and 94–99% ee) were obtained for substrates comprising substituted aromatic rings or naphthalene (**19**–**24**).

Next, the scope of amine-tethered cyclohexa-1,3-diene was also examined (Table 3). A series of amine-tethered cyclohexa-1,3-dienes derived from benzylamines and simple aliphatic amines were examined. Substituted benzylamines and simple aliphatic amines as well as thiophene-containing amine could undergo the desired reaction smoothly, furnishing the desired spiro products (**25**–**28**, **33**–**34**) in good yields with excellent enantioselectivities (94->99% ee). Motivated by these results, we sought to extend this cycloaddition reaction to construct more rigid polycyclic scaffolds. As expected, aryl-tethered aminodienes were also compatible with this catalytic system, affording the corresponding pentacyclic acridines (**29**–**32**, **35**–**38**) in good to excellent yields with excellent diastereo- and enantioselectivities (>20:1 dr and 90–99% ee).

Following the successful accomplishment of the diastereo- and enantioselective construction of [6–6–6] spiro heterocycles, our focus subsequently shifted to expanding this strategy to forge [6–6–5] chiral polycycles (Table 3). Similarly, a range of substituted salicylaldehydes reacted smoothly with *N*-alkyl-2-(cyclohexa-1,3-dien-1-yl)ethan-1-amine, delivering the desired rigid spiro compounds (**39**–**47**) in good yields with 91->99% ee and >20:1 d.r. In particular, 7-hydroxyquinoline-8-carbaldehyde could also be successfully converted to the



Scheme 3. Mechanism investigations. a) Control experiments. b) Isotopic-labelling experiment. c) Nonlinear effect study. d) Proposed mechanism.

desired product **48** in 82% yield with 97% ee. Moreover, the present reaction demonstrated broad compatibility with various sulfamide-containing aromatic aldehydes, as indicated by the successful construction of diaza [6–6–5] spiro products (**49**–**55**). Notably, the absolute configuration of product **39**, confirmed by X-ray diffraction analysis, aligned with that of the spiro [6–6–6] polycycles.[39]

Spirocyclic backbone-based ligands are well-known for their broad applicability in metal-catalyzed asymmetric transformations.[40] Consequently, the following efforts were focused on verifying the potential of spirocyclic products as versatile scaffolds to prepare new chiral spirocyclic ligands (Figure 1). First, the gram-scale reaction of **1a** and **2g** was performed under standard conditions, and the desired product **9** was obtained in 69% yield without loss of enantioselectivity (see Supporting Information). Subsequent hydrogenation and deprotection of **9** delivered the chiral phenol **57**.[41] Triflation of **57** afforded triflated product **58**, which was then coupled with phosphine oxide in the presence of $Pd(OAc)_2$/dppb to give the chiral spiro phosphine oxide **59** in 66% yield.[42] Finally, reduction of phosphine oxide **59** afforded the desired chiral phosphine **60** in 95% yield.[43] The structure of **60** was further confirmed by single crystal X-ray diffraction analysis (Figure 1a).[39] Alternatively, P, N-ligand **62** could be readily prepared by a two-step transformation from brominated product **46** (Figure 1b). Besides, the downstream transformation of quinoline-containing **48** also provided concise access to spirocyclic diamine ligand **64**[44] via hydrogenation and debenzylation processes[45,46] (Figure 1c). To demonstrate the effectiveness of the newly developed chiral P, N-ligands in asymmetric catalysis, palladium catalyzed Tsuji–Trost reactions were conducted.[47,48] By using (*E*)-1,3-

diphenylallyl acetate **65** as model substrate, the asymmetric allylic amination was tested and the corresponding allylic amines **66** and **67** were obtained in 49–90% yields and 63–87% ee. To our delight, the asymmetric allylic alkylation could also proceed smoothly, delivering the desired product **68** in 97–98% yields with 90–95% ee when dimethyl malonate was used as a coupling partner (Figure 1d).

A series of experiments were performed to shed light on the mechanism of this transformation. Several control experiments were conducted to explore the necessity of the hydrogen-bonding effect exerted by salicylaldehyde substrates (Scheme 3a). When the hydroxyl group of salicylaldehyde **2a** was replaced by a methoxyl or hydrogen atom, spiro diene products (**69** and **70**) were formed with excellent enantioselectivities, in which β-H elimination of allylpalladium intermediate took place instead of allylic substitution, implying that hydrogen-bonding was not crucial to the migratory insertion step. To further investigate the specific process of intramolecular cyclization of the allyl palladium intermediate (outer-sphere versus inner-sphere),[49,50] an isotope labeling experiment was conducted. As outlined in Scheme 3b, the distinction between the two processes lies in whether palladium-hydrogen species are involved in the formation of product.[51,52] The outer-sphere cyclization most likely undergoes sequential β-H elimination and re-insertion to realize the interconversion of allylpalladium complexes (**I** to **V**), which may produce Pd-H species leading to H/D scrambling. In contrast, the inner-sphere cyclization directly produces a single isotope-labeled product via the reductive elimination process. As expected, the corresponding deuterated product (**29-d_3**) was obtained in 83% yield with no loss of deuterium content when a deuterium-labeled cyclic aminodiene (**1f-d_3**) was subjected to our standard conditions, which supported the inner-sphere allylation pathway. Furthermore, a good linear relationship between the enantiopurities of the product **3** and the chiral ligand **(*S*)-L2** was observed, which revealed a palladium complex bearing one equivalent of **L2** might work as a reactive species (Scheme 3c).[53] In addition, the HRMS analysis of the reaction mixture suggested that allylic palladium **C** and Pd(0) intermediate were generated in the reaction system (see Supporting Information). On the basis of these experimental results and our previous reports,[37,54] a plausible catalytic cycle was proposed (Scheme 3d). First, the condensation of amine-tethered cyclohexa-1,3-diene **1a** with salicylaldehyde **2a** produces racemic *N,O*-hemiacetal **A**, where the two enantiomers can interconvert to each other via rapid condensation-hydrolysis. Then, **A** undergoes oxidative addition with Pd(0), generating cyclopalladated complex **B** featuring different configurations ((S,S_{Cat}) versus (R,S_{Cat})). Among them, (R,S_{Cat})-**B** is dominantly generated via dynamic kinetic resolution to undergo the intramolecular diene insertion delivering allylpalladium **C**. Subsequently the oxygen-bound allylpalladium intermediate **D** is formed, which undergoes reductive elimination to produce the desired product **3**.

In summary, we have developed a novel modular and effective Pd-catalyzed domino process, initiated via aminoalkylpalladium species directed spiroaminoalkylation and followed by allylic substitution process. Remarkably, the protocol provides the most expedient and effective construction of chiral tetracyclic and pentacyclic spiroamines in one-step under mild and operationally convenient conditions. High stereoselectivity was observed for a broad range of products of various ring sizes, incorporating heteroatoms and additional substituents. These chiral scaffolds presented significant potential as a versatile platform for the design of chiral ligands. Further studies regarding the development of related transformations and developing novel chiral ligands based on these rigid angular skeletons as well as their applications are currently underway in our laboratory.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Angular polycycles · Asymmetric catalysis · Ligand design · Palladium catalysis · Spiroaminoalkylation

[1] Z. G. Brill, M. L. Condakes, C.-P. Ting, T. J. Maimone, *Chem. Rev.* **2017**, *117*, 11753–11795, https://doi.org/10.1021/acs.chemrev.6b00834.
[2] V. A. D'yakonov, O. g. A. Trapeznikova, A. de Meijere, U. M. Dzhemilev, *Chem. Rev.* **2014**, *114*, 5775–5814.
[3] K. Hiesinger, D. Dar'In, E. Proschak, M. Krasavin, *J. Med. Chem.* **2021**, *64*, 150–183, https://doi.org/10.1021/acs.jmedchem.0c01473.
[4] Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673–3682, https://doi.org/10.1016/j.bmcl.2014.06.081.
[5] Y.-J. Zheng, C. M. Tice, *Expert Opin. Drug Discov.* **2016**, *11*, 831–834.
[6] X. Wang, Z. Han, Z. Wang, K. Ding, *Acc. Chem. Res.* **2021**, *54*, 668–684, https://doi.org/10.1021/acs.accounts.0c00697.
[7] S. M. Lait, M. Parvez, B. A. Keay, *Tetrahedron: Asym.* **2004**, *15*, 155–158, https://doi.org/10.1016/j.tetasy.2003.10.031.
[8] X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2012**, *51*, 936–940, https://doi.org/10.1002/anie.201106488.
[9] C. Wang, X. Wang, Z. Wang, X. Wang, K. Ding, *J. Am. Chem. Soc.* **2024**, *146*, 18440–18450, https://doi.org/10.1021/jacs.4c03854.
[10] C. Luo, C. Wu, X. Wang, Z. Han, Z. Wang, K. Ding, *J. Am. Chem. Soc.* **2024**, *146*, 35043–35056, https://doi.org/10.1021/jacs.4c05365.

[11] F. W. W. Hartrampf, T. Furukawa, D. Trauner, *Angew. Chem. Int. Ed.* **2017**, *56*, 893–896, https://doi.org/10.1002/anie.201610021.
[12] F. He, S. Feng, Y. Zhao, H. Shi, X. Duan, H. Li, X. Xie, X. She, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205439, https://doi.org/10.1002/anie.202205439.
[13] H. Takeuchi, S. Inuki, K. Nakagawa, T. Kawabe, A. Ichimura, S. Oishi, H. Ohno, *Angew. Chem. Int. Ed.* **2020**, *59*, 21210–21215, https://doi.org/10.1002/anie.202009399.
[14] M. Lee, T. Lee, E.-Y. Kim, H. Ko, D. Kim, S. Kim, *Org. Lett.* **2006**, *8*, 745–748, https://doi.org/10.1021/ol053010j.
[15] S. Lee, M. Bae, J. In, J. H. Kim, S. Kim, *Org. Lett.* **2017**, *19*, 254–257, https://doi.org/10.1021/acs.orglett.6b03550.
[16] C. L'Homme, M.-A. Ménard, S. Canesi, *J. Org. Chem.* **2014**, *79*, 8481–8485, https://doi.org/10.1021/jo501583c.
[17] H. Ishida, S. Kimura, N. Kogure, M. Kitajima, H. Takayama, *Org. Biomol. Chem.* **2015**, *13*, 7762–7771, https://doi.org/10.1039/C5OB00827A.
[18] C. Muller, A. Bauer, T. Bach, *Angew. Chem. Int. Ed.* **2009**, *48*, 6640–6642, https://doi.org/10.1002/anie.200901603.
[19] Q. Cai, C. Zheng, J. Zhang, S. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 8665–8669, https://doi.org/10.1002/anie.201103937.
[20] Z. L. Niemeyer, S. Pindi, D. A. Khrakovsky, C. N. Kuzniewski, C. M. Hong, L. A. Joyce, M. S. Sigman, F. D. Toste, *J. Am. Chem. Soc.* **2017**, *139*, 12943–12946, https://doi.org/10.1021/jacs.7b08791.
[21] Q.-B. Zhuang, J.-R. Tian, K. Lu, X.-M. Zhang, F.-M. Zhang, Y.-Q. Tu, R. Fan, Z.-H. Li, Y.-D. Zhang, *J. Am. Chem. Soc.* **2023**, *145*, 26550–26556, https://doi.org/10.1021/jacs.3c11178.
[22] S. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183–188, https://doi.org/10.1038/nature10232.
[23] X. Liu, Z.-S. Wang, T.-Y. Zhai, C. Luo, Y.-P. Zhang, Y.-B. Chen, C. Deng, R.-S. Liu, L.-W. Ye, *Angew. Chem. Int. Ed.* **2020**, *59*, 17984–17990, https://doi.org/10.1002/anie.202007206.
[24] J. S. Trimble, R. Crawshaw, F. J. Hardy, C. W. Levy, M. J. B. Brown, D. E. Fuerst, D. J. Heyes, R. Obexer, A. P. Green, *Nature* **2022**, *611*, 709–714, https://doi.org/10.1038/s41586-022-05335-3.
[25] N. Sun, J. Huang, J. Qian, T.-P. Zhou, J. Guo, L. Tang, W. Zhang, Y. Deng, W. Zhao, G. Wu, R.-Z. Liao, X. Chen, F. Zhong, Z. Wu, *Nature* **2022**, *611*, 715–720, https://doi.org/10.1038/s41586-022-05342-4.
[26] H.-K. Liu, S. R. Wang, X.-Y. Song, L.-P. Zhao, L. Wang, Y. Tang, *Angew. Chem. Int. Ed.* **2019**, *58*, 4345–4349, https://doi.org/10.1002/anie.201812294.
[27] Y. Sun, X. Huang, J. Ren, Z. Wang, *Nat. Commun.* **2024**, *15*, 9206, https://doi.org/10.1038/s41467-024-53562-1.
[28] Y. Zhu, R. G. Cornwall, H. Du, B. Zhao, Y. Shi, *Acc. Chem. Res.* **2014**, *47*, 3665–3678, https://doi.org/10.1021/ar500344t.
[29] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944, https://doi.org/10.1021/cr020027w.
[30] D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307–9387, https://doi.org/10.1021/acs.chemrev.5b00060.
[31] J. Wang, G. Dong, *Chem. Rev.* **2019**, *119*, 7478–7528, https://doi.org/10.1021/acs.chemrev.9b00079.
[32] Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, *117*, 13810–13889, https://doi.org/10.1021/acs.chemrev.7b00382.
[33] Y. Xie, J. Hu, Y. Wang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 20613–20616, https://doi.org/10.1021/ja310848x.
[34] H. Zhang, T. Jiang, J. Zhang, H. Huang, *Acc. Chem. Res.* **2021**, *54*, 4305–4318, https://doi.org/10.1021/acs.accounts.1c00365.
[35] S. Cai, Z. Zhao, G. Yang, H. Huang, *Nat. Chem.* **2024**, *16*, 1972–1981, https://doi.org/10.1038/s41557-024-01673-z.
[36] S. Cai, Z. Zhao, G. Yang, H. Huang, *J. Am. Chem. Soc.* **2025**, *147*, 28624–28631, https://doi.org/10.1021/jacs.5c09837.
[37] B. Yu, Y. Huang, H. Zhang, H. Huang, *Nat. Chem.* **2025**, *17*, 1256–1264, https://doi.org/10.1038/s41557-025-01850-8.
[38] H. Zhang, Y. Huang, X. Yang, B. Yu, H. Huang, *CCS Chem.* **2025**, https://doi.org/10.31635/ccschem.025.202506366.
[39] Deposition numbers 2491089 (for **3**), 2491091 (for **3′**), 2491092 (for **19**), 2491094 (for **29**), 2491096 (for **39**), and 2491100 (for **60**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.
[40] K. Ding, Z. Han, Z. Wang, *Chem. Asian J.* **2009**, *4*, 32–41, https://doi.org/10.1002/asia.200800192.
[41] T. Connolly, Z. Wang, M. A. Walker, I. M. McDonald, K. M. Peese, *Org. Lett.* **2014**, *16*, 4444–4447, https://doi.org/10.1021/ol5019739.
[42] G.-Q. Chen, B.-J. Lin, J.-M. Huang, L.-Y. Zhao, Q.-S. Chen, S.-P. Jia, Q. Yin, X. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 8064–8068, https://doi.org/10.1021/jacs.8b03642.
[43] M. P. Carroll, P. J. Guiry, *Chem. Soc. Rev.* **2014**, *43*, 819–833, https://doi.org/10.1039/C3CS60302D.
[44] J.-C. Kizirian, *Chem. Rev.* **2008**, *108*, 140–205, https://doi.org/10.1021/cr040107v.
[45] V. Arora, E. Yasmin, N. Tanwar, V. R. Hathwar, T. Wagh, S. Dhole, A. Kumar, *ACS Catal.* **2023**, *13*, 3605–3617, https://doi.org/10.1021/acscatal.2c05587.
[46] Y. Peng, G. Wang, H. F. T. Klare, M. Oestreich, *Angew. Chem. Int. Ed.* **2024**, *63*, e202410483, https://doi.org/10.1002/anie.202410483.
[47] J. Margalef, M. Biosca, P. de la Cruz Sánchez, J. Faiges, O. Pàmies, M. Diéguez, *Coord. Chem. Rev.* **2021**, *446*, 214120, https://doi.org/10.1016/j.ccr.2021.214120.
[48] Z. Lu, S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297, https://doi.org/10.1002/anie.200605113.
[49] O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J.-E. Bäckvall, A. Pfaltz, M. A. Pericàs, M. Diéguez, *Chem. Rev.* **2021**, *121*, 4373–4505, https://doi.org/10.1021/acs.chemrev.0c00736.
[50] L.-Z. Zhang, P.-C. Zhang, Q. Wang, M. Zhou, J. Zhang, *Nat. Commun.* **2025**, *16*, 930, https://doi.org/10.1038/s41467-025-56142-z.
[51] K. Itami, A. Palmgren, A. Thorarensen, J.-E. Bäckvall, *J. Org. Chem.* **1998**, *63*, 6466–6471, https://doi.org/10.1021/jo980561x.
[52] P. M. Khan, K. S. Bisht, *Tetrahedron Lett.* **2010**, *51*,1407–1410, https://doi.org/10.1016/j.tetlet.2010.01.025.
[53] T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem. Int. Ed.* **2009**, *48*, 456–494, https://doi.org/10.1002/anie.200705241.
[54] B. Yu, S. Zou, H. Liu, H. Huang, *J. Am. Chem. Soc.* **2020**, *142*, 18341–18345, https://doi.org/10.1021/jacs.0c10615.

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