

Cite this: *Chem. Sci.*, 2022, 13, 2317

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# Highly regioselective and diastereodivergent aminomethylative annulation of dienyl alcohols enabled by a hydrogen-bonding assisting effect†

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A ligand-controlled palladium-catalyzed highly regioselective and diastereodivergent aminomethylative annulation of dienyl alcohols with aminals has been established, which allows for producing either *cis*- or *trans*-disubstituted isochromans in good yields with complete regioselectivity and good to excellent diastereoselectivity. Moreover, the chiral *cis*-products were also obtained in good yields with up to 94% ee by using a chiral phosphinamide as the ligand. Mechanistic studies revealed that the hydroxyl group plays a key role in facilitating the Pd-catalyzed Heck insertion regioselectively taking place across the internal C=C bond of conjugated dienes.

Received 20th November 2021

Accepted 18th January 2022

DOI: 10.1039/d1sc06479g

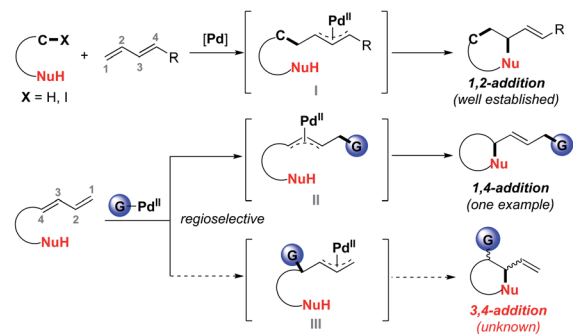
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## Introduction

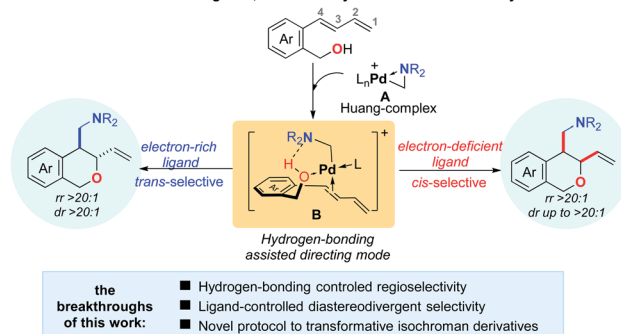
The ready availability and versatile reactivity as well as broad functionalization potential of conjugated dienes make them extremely promising and privileged starting materials for organic synthesis.<sup>1</sup> In particular, the two-component Pd-catalyzed annulation of dienes involving the formation of  $\pi$ -allylpalladium species and intramolecularly intercepting them with a nucleophile allows for the rapid construction of cyclic molecules, and significant progress has been achieved.<sup>2,3</sup> However, a serious limitation is that most of these reactions are performed *via* formation of a  $\pi$ -allylpalladium intermediate like **I** or **II**,<sup>2</sup> which leads to the generation of 1,2- or 1,4-difunctionalization products (Scheme 1A). A different type of  $\pi$ -allylpalladium intermediate **III** would be expected that can deliver the 3,4-difunctionalized cyclic products *via* its subsequent intramolecular interception with a nucleophile. Such compounds are more synthetically useful as the terminal olefin functionality could act as a versatile handle group for further elaboration (Scheme 1A).<sup>4</sup> However, in stark contrast to 1,2- and 1,4-annulations, the 3,4-annulation of 1,3-dienes has remained elusive.<sup>3</sup>

The underlying reason might be attributed to the lack of efficient strategy and appropriate alkylpalladium species to enable the Heck insertion to occur across the internal C=C bond for regioselective formation of intermediate **III**. Moreover, intramolecular interception of intermediate **III** may generate an

### A. Pd-catalyzed alkylative annulation of dienes



### B. This work: diastereodivergent 3,4-aminomethylative annulation of dienyl alcohols



the breakthroughs of this work: ■ Hydrogen-bonding controlled regioselectivity ■ Ligand-controlled diastereodivergent selectivity ■ Novel protocol to transformative isochroman derivatives

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† Electronic supplementary information (ESI) available. CCDC 2111895, 2111898 and 2111899. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc06479g

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Scheme 1 Regioselective and diastereodivergent aminomethylative annulation of dienyl alcohols.



inseparable mixture of *trans*- and *cis*-isomers, which makes such reactions more challenging.

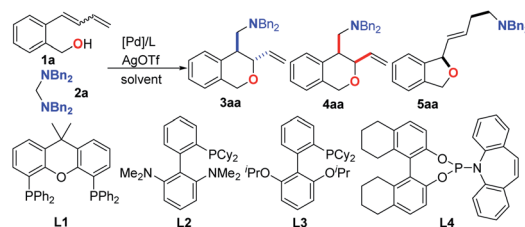
To address these limitations, we envisioned that once the nucleophile suspended in the diene backbone can complex with an appropriate alkylpalladium species, the chelation between the palladium species and the nucleophile will bring the palladium center close to the internal C=C bond of the diene, thus facilitating the formation of the internal alkylated  $\pi$ -allylpalladium intermediate **III**. It is well known that the hydroxyl group can not only act as a nucleophile for palladium-catalyzed allylic C–O bond formation reactions,<sup>5</sup> but also be frequently utilized as a directing group for various metal catalyzed reactions.<sup>6,7</sup> However, due to the weak coordination ability of the oxygen atom to the palladium, the hydroxyl group may not act as an effective directing group to make the palladium interact with the internal C=C bond of the diene. In this context, we surmised that the directing ability would be enhanced to facilitate the regioselective annulation once the alkylpalladium species interacts with the hydroxyl group like intermediate **B** *via* hydrogen-bonding. In line with our continuous interest in developing new transformations by using aminomethyl cyclo-palladated complex **A** (Huang-complex) as a leading complex<sup>8</sup> and inspired by our recent results on the hydrogen-bonding-assisted alcohol allylation reactions,<sup>5h</sup> we envisioned that complex **A** might be a suitable alkylpalladium species to

coordinate with the hydroxyl group under the assistance of hydrogen-bonding. Once the diene-tethered benzyl alcohol reacted with complex **A**, intermediate **B** might be formed, in which the hydrogen-bonding between the hydroxyl group and the amine moiety would promote the palladium to coordinate with the O-atom of the hydroxyl and facilitate the internal C=C bond binding to the palladium. Such interactions would guide the Heck insertion to take place selectively across the internal C=C bond of the diene. Herein, we report for the first time a regioselective and diastereodivergent aminomethylative annulation of diene-tethered benzyl alcohols with amins (Scheme 1B). This transformation offers an unprecedented efficient route for the selective synthesis of both *trans*- and *cis*-diastereoisomers of 1,2-disubstituted isochroman derivatives that are pervasive structural motifs omnipresent in myriad natural products and synthetic pharmaceuticals exhibiting an array of biological properties.<sup>9</sup>

## Results and discussion

At first, we examined the reaction of (2-(buta-1,3-dien-1-yl)phenyl)methanol **1a** with *N,N,N',N'*-tetrabenzylmethanedi-amine **2a** by using a series of palladium-catalysts bearing different phosphine ligands. On the basis of our previous work, the reaction was carried out in toluene at 80 °C with [Pd(allyl)]

Table 1 Optimization of reaction conditions<sup>a</sup>



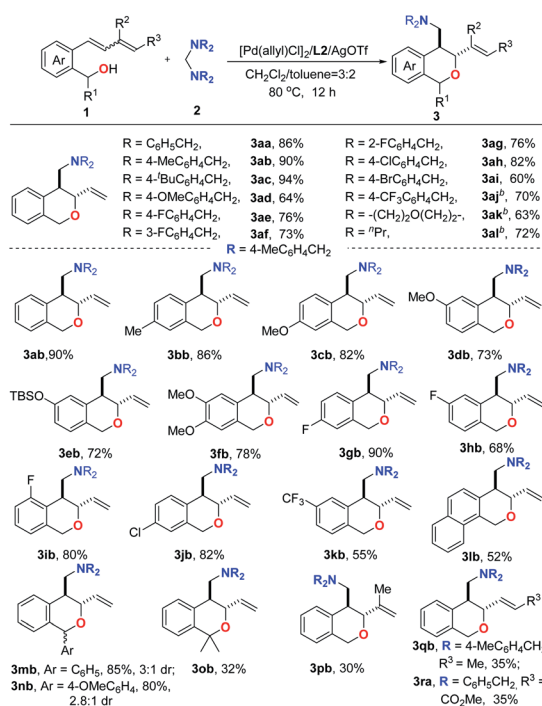
Entry	[Pd]	Ligand	T (°C)	Solvent	Yield (%)		5aa Yield (%)
					3aa + 4aa	3aa/4aa	
1	[Pd(allyl)Cl] <sub>2</sub>	L1	80	Toluene	40	5 : 1	45
2 <sup>b</sup>	[Pd(allyl)Cl] <sub>2</sub>	PPh <sub>3</sub>	80	Toluene	63	18 : 1	5
3 <sup>b</sup>	[Pd(allyl)Cl] <sub>2</sub>	L2	80	Toluene	59	>20 : 1	Trace
4 <sup>b</sup>	[Pd(allyl)Cl] <sub>2</sub>	L3	80	Toluene	43	>20 : 1	Trace
5 <sup>b,c</sup>	PdCl <sub>2</sub>	L2	80	Toluene	48	>20 : 1	Trace
6 <sup>b,c</sup>	PdBr <sub>2</sub>	L2	80	Toluene	50	>20 : 1	Trace
7 <sup>b</sup>	[Pd(allyl)Cl] <sub>2</sub>	L2	80	CH <sub>2</sub> Cl <sub>2</sub>	65	18 : 1	Trace
8 <sup>b</sup>	[Pd(allyl)Cl] <sub>2</sub>	L2	80	CH <sub>2</sub> Cl <sub>2</sub> /toluene = 3 : 2	67	>20 : 1	Trace
9 <sup>b,c</sup>	[Pd(allyl)Cl] <sub>2</sub>	L2	80	CH <sub>2</sub> Cl <sub>2</sub> /toluene = 3 : 2	86	>20 : 1	Trace
10 <sup>b,c</sup>	[Pd(allyl)Cl] <sub>2</sub>	L4	80	CH <sub>2</sub> Cl <sub>2</sub>	79	1 : 5	Trace
11 <sup>b,c,d</sup>	PdBr <sub>2</sub>	L4	80	CH <sub>2</sub> Cl <sub>2</sub>	90	1 : 7	Trace
12 <sup>b,c,d</sup>	PdBr <sub>2</sub>	L4	60	CH <sub>2</sub> Cl <sub>2</sub>	84	1 : 9	Trace
13 <sup>b,c,d</sup>	PdBr <sub>2</sub>	L4	40	CH <sub>2</sub> Cl <sub>2</sub>	81	1 : 10	Trace
14 <sup>b,c,d</sup>	PdBr <sub>2</sub>	L4	rt	CH <sub>2</sub> Cl <sub>2</sub>	62	1 : 14	Trace
15 <sup>b,c,d,e</sup>	PdBr <sub>2</sub>	L4	rt	CH <sub>2</sub> Cl <sub>2</sub>	89	1 : 14	Trace

<sup>a</sup> Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), [Pd] (5 mol%), AgOTf (6 mol%), ligand (5 mol%), solvent (1.0 mL), 12 h, isolated yield, the dr value was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>b</sup> Ligand (10 mol%). <sup>c</sup> AgOTf (12 mol%). <sup>d</sup> **1a** (0.36 mmol), **2a** (0.30 mmol). <sup>e</sup> 24 h.



$\text{Cl}]_2$  as the palladium source. In the presence of  $\text{AgOTf}$  as the counter anion source, a Xantphos-ligated Pd-catalyst showed high activity, and an almost quantitative conversion was observed, which resulted from either internal (*trans*-**3aa** and *cis*-**4aa**) or terminal Heck-insertion (**5aa**) (Table 1, entry 1). To our delight, when  $\text{PPh}_3$  was used as the ligand, the selectivity dramatically improved to give *trans*-**3aa** as the major product, although concomitantly with a trace amount of 1,4-difunctionalized cyclization product **5aa**. The high regioselectivity observed by using the monodentate ligands might be attributed to the fact that the ligated-palladium complex can provide a vacant coordination site to complex with the hydroxyl group to furnish the directing effect. Encouraged by this promising result, a series of mono-phosphine ligands were examined. Biaryl monophosphines were identified as privileged ligands for the present reaction, offering satisfactory conversions and selectivities of *trans*-products while effectively suppressing the formation of **5aa**. When Cphos (**L2**) was used, **3aa** could be generated exclusively in 59% yield. Further optimization of the reaction parameters by changing the solvent and the ratio of **1a** to **2a** improved the yield to 86% while maintaining high regio- and diastereoselectivities (Table 1, entry 9). Intriguingly however, the use of more electron-deficient phosphinamide **L4** reversed the diastereoselectivity, giving an uncommon *cis*-enriched diastereoisomer mixture, albeit with poor selectivity (*trans*-**3aa**/*cis*-**4aa** = 1 : 5) (Table 1, entry 10). Switching the pre-catalyst to  $\text{PdBr}_2$  increased the *cis*-selectivity to *trans*-**3aa**/*cis*-**4aa** = 1 : 7 with a yield as high as 90%. Remarkably, the *cis*-selectivity could be further improved to *trans*-**3aa**/*cis*-**4aa** = 1 : 14 at room temperature without losses in yields (Table 1, entry 15).

Having established the highly regioselective and diastereodivergent conditions for the annulation of **1a** with **2a** as shown above, we then examined the substrate scope with an **L2**/ or **L4**/ $\text{PdBr}_2$ /AgOTf catalysis system. Table 2 summarizes the substrates compatible for *trans*-selective annulation. Aminals derived from benzylamines bearing electron-rich and -deficient substituents worked smoothly with **1a** to exclusively give the corresponding *trans*-products (**3aa**–**3aj**) in 60–94% yields with complete regioselectivity. Functional groups such as halides (F, Cl, Br),  $\text{CF}_3$ , and OMe were compatible. Gratifyingly, aminals derived from aliphatic amines, such as dipropylamine and morpholine, could react with **1a** to give the corresponding products as well (**3ak** and **3al**) in good yields in the presence of 10 mol% of catalyst. Next, the scope of the diene-tethered benzyl alcohols was also explored under optimized conditions. As shown in Table 2, a variety of substrates bearing electron-donating and -withdrawing functional groups on the phenyl rings underwent regioselective and diastereoselective annulations to provide the *trans*-products (**3ab**–**3kb**) in good to excellent yields (55–90%). The naphthyl-containing **1l** was also compatible, generating the corresponding annulation product **3lb** in 52% yield. Meanwhile, the dienes containing a substituent at the benzyl site could also be converted into the desired products with three chiral centers (**3mb** and **3nb**) in good yields. Importantly, substrates containing substituents at  $\text{C}_2$  or  $\text{C}_1$  positions also proved to be competent reaction partners to afford the corresponding products (**3pb**, **3qb** and **3ra**) in

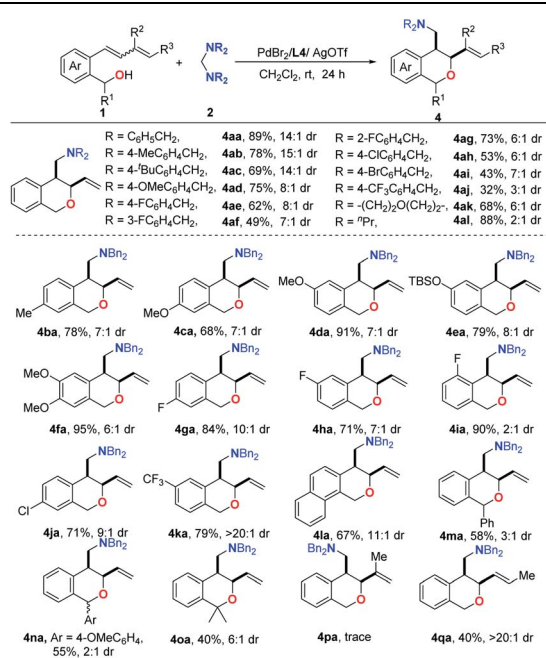
Table 2 *Trans*-diastereoselective annulation<sup>a</sup>

<sup>a</sup> Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol),  $[\text{Pd}(\text{allyl})\text{Cl}]_2$  (2.5 mol%), AgOTf (6 mol%), **L2** (10 mol%), solvent ( $\text{CH}_2\text{Cl}_2$  : toluene = 3 : 2, 1.0 mL),  $80^\circ\text{C}$ , 12 h, isolated yields, >20 : 1 rr, and >20 : 1 dr in all cases as shown by  $^1\text{H}$  NMR analysis of the crude reaction mixture, unless otherwise noted. <sup>b</sup>  $[\text{Pd}(\text{allyl})\text{Cl}]_2$  (5 mol%), AgOTf (12 mol%), **L2** (20 mol%).

moderate yields with excellent diastereoselectivities and regioselectivities. It is noteworthy that the regio- and diastereoselectivities of this reaction were not affected by the *E/Z* ratio of the corresponding diene-tethered benzyl alcohols (see the ESI<sup>†</sup>).

We next focused on exploring the scope of the *cis*-diastereoselective annulation reaction by using  $\text{PdBr}_2/\text{L4}/\text{AgOTf}$  as the catalyst. As shown in Table 3, the diastereoselectivity was significantly influenced by the substrates, though the exclusive internal carbo-oxygenation products were observed in all cases. Evaluation of the scope was initiated with the investigation of various aminals. The *para*-methyl-, *t*-Bu-substituted benzylamine-derived aminals exhibited high *cis*-selectivity (15 : 1 and 14 : 1, respectively) to give the corresponding *cis*-annulation products **4ab** and **4ac** in 69–78% yields. Other benzyl aminals bearing electron-withdrawing substituents showed decreased selectivities (**4ae**–**4aj**), among which the lowest was given by aminal **2j** containing  $\text{CF}_3$  (**4aj**). The substrates **2k** and **2l** derived from alkyl amines were also compatible, albeit with low to moderate selectivities (**4ak** and **4al**). Next, with **2a** as the standard coupling partner, a series of diene-tethered benzyl alcohols were tested. Obviously, the introduction of a substituent on the phenyl ring of the substrate resulted in lower diastereoselectivities, and the lowest *cis*-selectivity (2 : 1) was observed when the substrate bore an *ortho*-

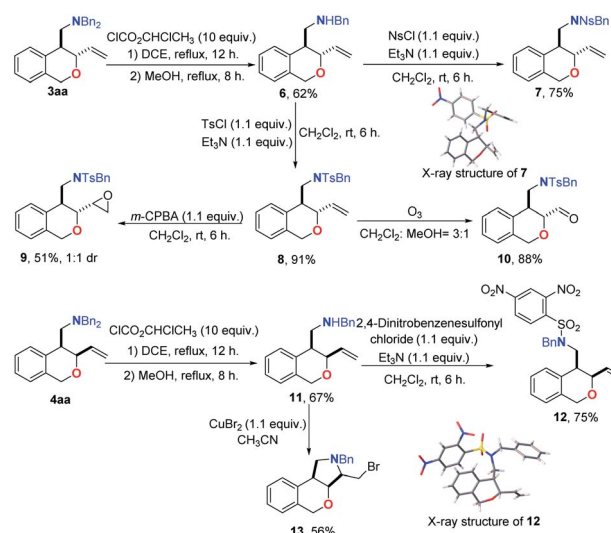


Table 3 *Cis*-diastereoselective annulation<sup>a</sup>

<sup>a</sup> Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), PdBr<sub>2</sub> (5 mol%), AgOTf (12 mol%), **L4** (10 mol%), CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL), rt, 24 h, isolated yield, the dr value was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture, >20 : 1 rr in all cases.

fluoro substituent on the phenyl ring (**4ia**). However, when there was a CF<sub>3</sub> at the 5-position, up to >20 : 1 diastereoselectivity was observed (**4ka**). In addition, substrate **11** containing naphthalene gave a moderate yield with 11 : 1 diastereoselectivity (**4la**). Substrates with substituents at the benzyl carbon bearing the hydroxyl group could also give moderate yields with lower selectivity (**4ma–4oa**). Nevertheless, the introduction of a methyl group at the C<sub>2</sub>-position of the diene resulted in no reaction, which might be due to steric hindrance. However, when the methyl group was instead introduced at the C<sub>1</sub> position, the desired product could be obtained in 40% yield with excellent selectivity (>20 : 1 dr) (**4qa**).

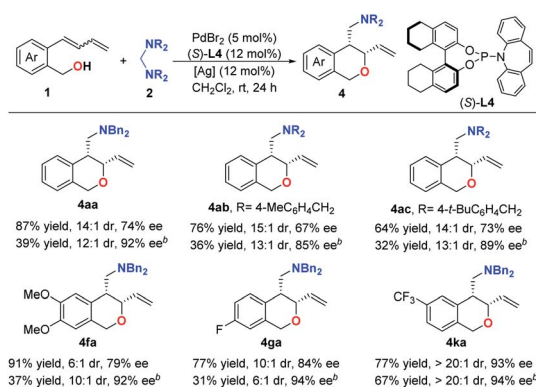
To explore the synthetic potential of the present reaction, several transformations of the obtained *trans*-**3aa** and *cis*-**4aa** were conducted (Scheme 2). One of the benzyl groups in **3aa** could be selectively removed to give **6** by treatment with ClCO<sub>2</sub>CHClCH<sub>3</sub>.<sup>10a</sup> To further confirm the structure of the product, the easily crystallizable Ns-protected amide **7** was obtained, whose structure was unambiguously confirmed by an X-ray diffraction analysis. The nucleophilic substitution reaction of **6** with TsCl in the presence of Et<sub>3</sub>N afforded the sulfamide **8**. Oxidation of the sulfamide **8** by using *m*-CPBA afforded the epoxide **9**.<sup>10b</sup> Highly valuable amino aldehyde **10** was cleanly formed by exposure of **8** to O<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>/MeOH at –78 °C.<sup>10c</sup> Similarly, the *cis*-**4aa** could also be transformed into sulfonamide **12** in excellent yield *via* de-benzylation and sulfonation. The structure of **12** was also verified by single-crystal X-ray diffraction.<sup>11</sup> The obtained *cis*-product **11** could be further



Scheme 2 Synthetic transformations.

converted into the ring-fused [6, 6, 5] tricyclic isochroman **13** by a CuBr<sub>2</sub>-mediated cyclization reaction.<sup>10d</sup>

To achieve an enantioselective aminomethylative annulation reaction, (*S*)-**L4** was utilized as the chiral ligand. As evident from the results compiled in Table 4, a series of chiral *cis*-diastereoselective products (**4aa–4ac** and **4fa–4ka**) could be obtained in good yields with moderate to good enantioselectivities under the standard reaction conditions by using PdBr<sub>2</sub>/*(S)*-**L4**/AgOTf as the asymmetric catalysis system. Further optimization of the reaction revealed that the enantioselectivities could be increased when executing the reaction with TsO<sup>–</sup> as the counter anion of the palladium catalyst. However, although good to excellent enantioselectivities (85–94% ees) could be obtained, the yields of the desired products decreased. Following a two-step derivatization of chiral compound **4aa**, the absolute

Table 4 Enantioselective annulation of dienes with amins<sup>a</sup>

<sup>a</sup> Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), PdBr<sub>2</sub> (5 mol%), AgOTf (12 mol%), (*S*)-**L4** (12 mol%), CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL), rt, 24 h, isolated yield, the dr value was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture, >20 : 1 rr in all cases, ee values were determined by chiral HPLC analysis. <sup>b</sup> [Pd(allyl)Cl]<sub>2</sub> (2.5 mol%), AgOTf (6 mol%).

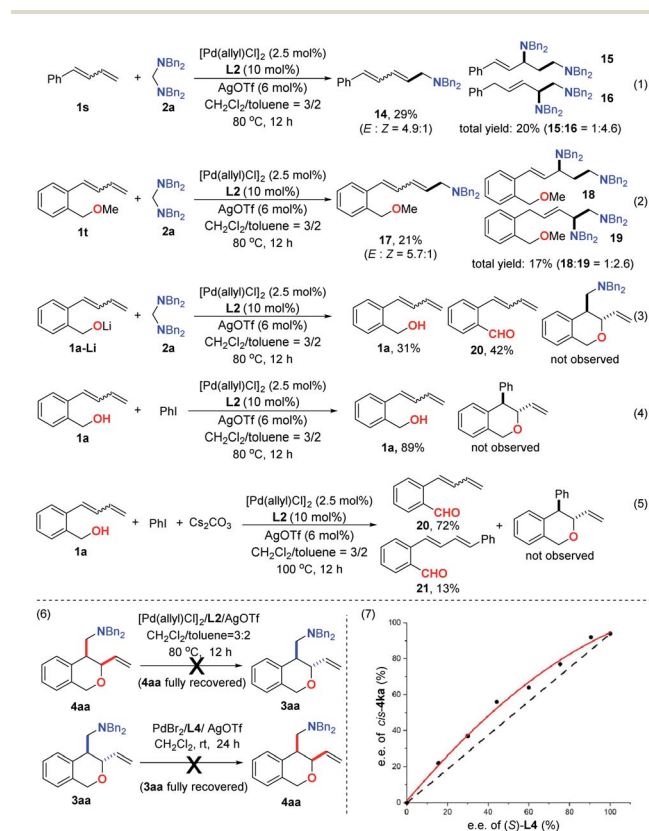


configuration of **4aa** was determined to be (3*S*, 4*R*) by X-ray diffraction analysis of chiral compound **12** (see the ESI†).

A series of experiments were conducted to shed light on the mechanism of this transformation. First, the simple diene **1s** was subjected to the standard reaction conditions for the generation of *trans*-products. However, only three major products (**14**, **15** and **16**)<sup>8a,b</sup> derived from terminal C=C bond insertion were observed and none from internal C=C bond insertion was detected (Scheme 3-1), showing the importance of the directing-effect of the hydroxyl group. The diene-tethered benzyl methyl ether **1t** was prepared and treated with **2a** under identical conditions. Although the OMe should be able to coordinate with the palladium, there was no product originating from internal C=C bond insertion detected again (Scheme 3-2). This result indicated that the coordination of O to Pd alone could not direct the desired Heck insertion. On the other hand, no desired product but the aldehyde **20** was detected in the reaction with the Li-salt of **1a**, which excluded the possibility that the directing effect was furnished *via* the formation of the Pd–O sigma-bond (Scheme 3-3). In addition, replacing the aminal with PhI led to the recovery of the starting material **1a** when the reaction was conducted in the absence of a base. In the presence of a base and at higher temperature, the aldehydes **20** and **21** were generated as major products, and yet gave no desired cyclization product. Besides, we observed an intriguing relationship between the regioselectivity of the reaction and the electronic nature of the substituted aminal. Higher regioselectivity was observed when the aminal contained an electron-rich *para*-substituent, and the selectivity

diminished gradually as the substituent became more electron deficient. The aromatic electronic effect can be represented by a Hammett relationship. The Hammett plot of lg (ratio of regioisomers) against  $\sigma_p$  shows a linear free-energy relationship ( $\rho = -1.27$ ,  $r = 0.969$ ) between regioselectivity and the electronic character of the substituent (see the ESI†).<sup>12</sup> These results further confirmed that the formation of hydrogen-bonding was key to furnish the 3,4-difunctionalized annulation. Subjecting the purified *cis*-**4aa** to the reaction conditions for producing *trans*-products resulted in fully recovered *cis*-**4aa** (Scheme 3-6). This result ruled out the possibility that C–O bond formation is reversible and the thermodynamically preferred *trans*-product is generated from the kinetically preferred *cis*-product in the case of Cphos. Furthermore, no *cis*-product was detected when a purified *trans*-product, **3aa**, was subject to the reaction conditions for generation of *cis*-products. On the other hand, the non-linear relationship between the ee value of optically active ligand **L4** and the ee value of the *cis*-**4ka** (Scheme 3-7) provided evidence that two phosphoramidite ligands and one palladium were involved in the enantioselectivity-determining step.

A tentative mechanism is thus proposed based on the above results and previous reports.<sup>8</sup> As depicted in Fig. 1, the cyclopalladated complex **A** is generated *via* either oxidative addition of the Pd(0) to the protonated aminal or an S<sub>N</sub>2-type reductive elimination and oxidative addition process between the aminal and the  $\pi$ -allylpalladium catalyst. The hydroxyl group acts as a directing group to bring the palladium center close to the internal C=C double bond, in which the hydrogen-bonding between the aminal moiety of complex **A** and the hydroxyl group plays a key role in facilitating the formation of intermediate **B**. The relative free energy of intermediate **B** is only 2.6 kcal mol<sup>-1</sup>, when electron-deficient **L4** is utilized as the ligand. Subsequently, the migratory insertion of the internal C=C bond into the C–Pd bond of complex **A** takes place to form the  $\pi$ -allylpalladium intermediate **C** which is exergonic by 11.1 kcal mol<sup>-1</sup>. The strong  $\pi$ -acceptor ability of the **L4** would



Scheme 3 Mechanistic studies.

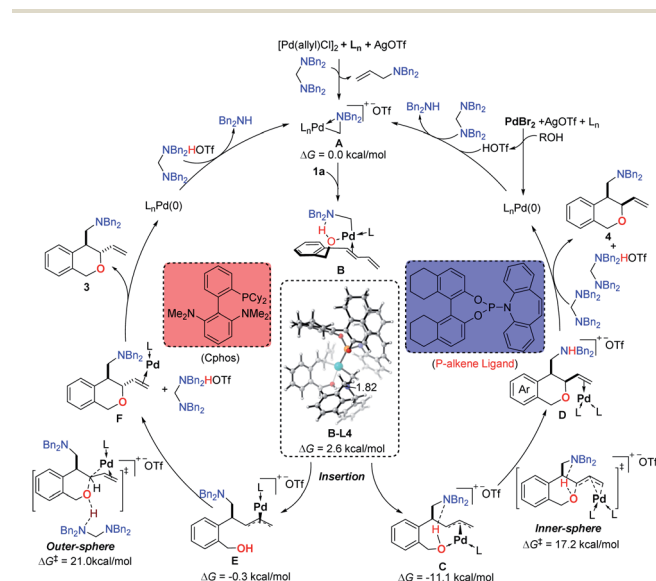


Fig. 1 Proposed reaction mechanism.



induce the palladium center to coordinate with the alcohol in intermediate **C**,<sup>13</sup> which undergoes inner-sphere reductive elimination with a free energy barrier of 17.2 kcal mol<sup>-1</sup> to afford the *cis*-diastereoselective product **4** and regenerates the Pd(0) to enter the next catalytic cycle. Notably, there are two phosphoramidite ligands that coordinate with the Pd(II) center in this inner-sphere reductive elimination transition state. The calculated results are consistent with the non-linear relationship. When the electron-rich **L2** (Cphos) acts as the ligand,<sup>14</sup> the alcohol does not coordinate with the Pd(II) center in  $\pi$ -allylpalladium intermediate **E**. Then the  $\pi$ -allylpalladium is intramolecularly trapped by the alcohol *via* the outer-sphere mode with an energy barrier of 21.0 kcal mol<sup>-1</sup> to produce the *trans*-diastereoselective cyclization product **3**, and the Pd(0) is regenerated with the assistance of a mineral.

## Conclusions

In summary, we have developed a new and efficient hydrogen-bonding assisted directing strategy to enable the Heck insertion to regioselectively take place across the internal C=C bond of dienes. By using this strategy, a palladium-catalyzed regioselective and ligand-controlled diastereodivergent aminomethylative annulation of diene-tethered benzyl alcohols with a mineral was established for the first time. The combination of the palladium catalyst with electron-rich ligands such as Cphos preferably affords the annulation products in a *trans*-selective fashion. In contrast, the homologous catalyst with electron-deficient phosphoramidite enables the selective formation of the *cis*-diastereoisomers. Moreover, the chiral *cis*-products were also obtained in good to excellent enantioselectivities when chiral phosphoramidite was utilized as the ligand. We envision that this work on the hydrogen-bonding-assisting effect will spur further investigations on exploring new and efficient directing strategies for metal-catalyzed reactions.

## Data availability

The data that support the findings of this study are available in the ESI† or on request from the corresponding author.

## Author contributions

H. H. designed the project and wrote the manuscript. Y. H., S. Z., B. Y., and X. Y. conducted experimental studies. S. L. conducted the DFT calculations.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank the National Natural Science Foundation of China (21925111 and 21790333) and the Strategic Priority Research Program of the CAS (XDPB14) for financial support.

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