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Enantioselective Aminomethylamination of Conjugated Dienes with Aminals Enabled by Chiral Palladium Complex-Catalyzed C−N Bond Activation

Yang Liu,[†,‡,§] Yinjun Xie,[†,§] Hongli Wang,[†] and Hanmin Huang*[,†]

[†]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

[‡]University of Chinese Academy of Sciences, Beijing 100049, P. R. China

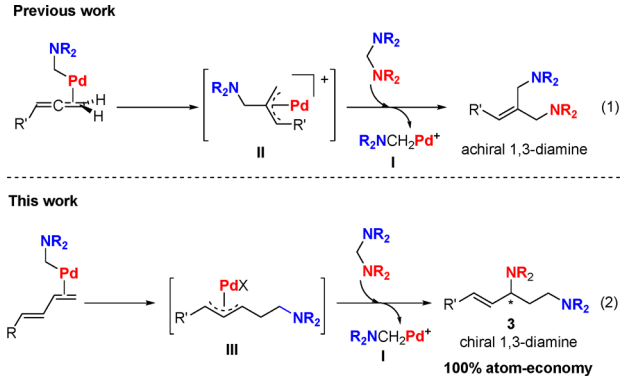
Supporting Information

ABSTRACT: A novel highly enantioselective aminomethylamination of conjugated dienes with aminals catalyzed by a chiral palladium complex ligated with BINOL-derived chiral diphosphinite has been successfully developed. This reaction proceeds via a Pd-catalyzed cascade C−N bond activation, aminomethylation, and asymmetric allylic amination reaction under mild reaction conditions, providing a unique and efficient strategy for the synthesis of enantiomerically pure allylic 1,3-diamines.

The chiral 1,3-diamine is an important structural element in various bioactive natural products and pharmaceuticals. It is also a key core of chiral ligands and auxiliaries used for asymmetric transformations.[1] Among these, the alkenyl-substituted ones are especially versatile because the vinylic and allylic moieties in the product exhibit orthogonal reactivity and can be transformed into a wide range of functionalities, thereby facilitating further elaboration. Although several approaches based on Mannich reaction, intramolecular diastereoselective C−H amination, and the diastereoselective reduction of ketimines are available for synthesis of normal chiral 1,3-diamines,[2] the catalytic approach to chiral allylic 1,3-diamines from simple alkenes remains a largely unsolved problem. Thus, development of an efficient enantioselective protocol to chiral alkenyl-substituted 1,3-diamines is highly desired.

The selective insertion of a double bond of 1,3-dienes to element−element bond is a powerful tool for the synthesis of 1,2- or 1,4-difunctionalization products.[3] In this context, the insertion of such kind of double bond to C−N bond for the formation of one C−C and C−N bonds is a promising protocol for synthesis of nitrogenated molecules.[4] However, highly enantioselective difunctionalization reactions of 1,3-dienes, in particular, the protocols access to chiral 1,3-diamines, have never been realized. We recently developed a new type of C−N bond activation reaction, which provided a unique cyclopalladated complex benefited from the facile C−N bond cleavage of aminals.[4] The aminomethyl moiety ($R_2NCH_2^-$) contained in the cyclopalladated complex **I** and the amino nucleophile (R_2N^-) released from the C−N bond activation process have been successfully incorporated into the unsaturated double bond of allenes under the palladium catalysis.[5] Detailed mechanistic studies suggested this reaction proceeds by migratory insertion of terminal alkene into the Pd−C bond of the cyclopalladated complex **I**, and a π-allylic-Pd complex was formed, which was then nucleophilically attacked by the aminal to furnish the corresponding allylic 1,3-diamine and regenerated the active palladium complex (Scheme 1-1). This reaction is operative for a wide range of substituted

Scheme 1. A New Strategy for Synthesis of 1,3-Diamines



allenes, affording the achiral allylic 1,3-diamines in good to excellent yields. Considering the olefin insertion involving 1,3-diene likely benefits from a similar incipient π bond, it was of interest to determine whether the cyclopalladated complex **I** efficient for insertion of allene would be effective in catalytic synthesis of 1,3-diamine with conjugated dienes. We anticipated that once an effective chiral ligand was identified, the chiral allylic 1,3-diamines would be obtained from the proposed catalytic system. Herein, we report the first highly enantioselective 1,2-aminomethylamination of conjugated 1,3-dienes with aminals via transition-metal-catalyzed C−N bond activation (Scheme1-2), which provided an efficient approach to chiral allylic 1,3-diamines from simple alkenes and aminals.

To validate our hypothesis, we commenced our studies by attempting the proposed difunctionalization of 1,3-diene **1a** with stoichiometric amounts of xantphos-ligated cyclopalladated complex **I** (confirmed by X-ray analysis)[4a] and Bn_2NLi (Scheme 2-1) at room temperature. To our delight, the reaction took place smoothly, and the aminomethyl moiety ($R_2NCH_2^-$) contained

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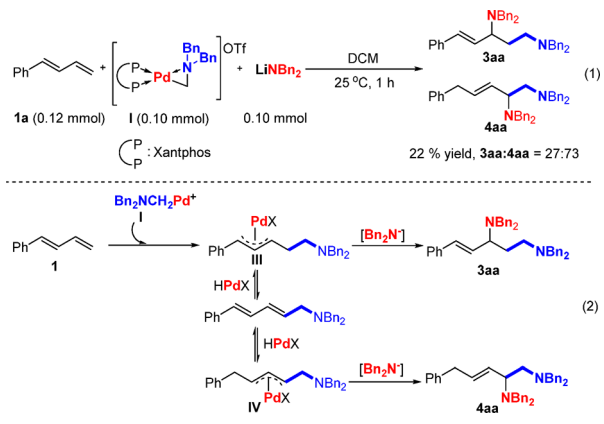
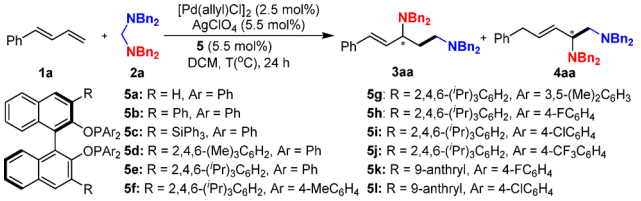
Scheme 2. Stoichiometric Reaction of Cyclopalladated-Complex I and 1,3-Diene



in the cyclopalladated complex **I** and the amino nucleophile (R_2N^-) were indeed successfully incorporated into the 1,3-diene **1a**. The desired 1,2-difunctional product **3aa** and an unexpected 1,1-difunctional product **4aa** were obtained in 22% yield with 27:73 ratio. The structures of **3aa** and **4aa** were fully characterized and confirmed by their X-ray crystallographic analysis.[6] This result indicated that the π-allylic-Pd intermediate **III** indeed formed via the insertion of the double bond to the C−Pd bond and was nucleophilic attacked by Bn_2N^- to form the racemic **3aa**. Moreover, the product **4aa** was most likely produced from the intermediate **IV** which derived from intermediate **III** via β-hydride elimination and reinsertion (Scheme 2-2).[7]

The above results intrigued us to investigate the enantioselective catalytic aminomethylamination of conjugated 1,3-dienes with aminals according to the proposed reaction pathway. (*E*)-buta-1,3-dien-1-ylbenzene **1a** was chosen as a model substrate to react with *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine **2a** for identifying a suitable chiral catalyst and reaction conditions (Table 1). The reaction carried out with 5 mol % catalyst loading in CH_2Cl_2 at 25 °C for 24 h. The catalyst was prepared in situ by mixing 2.5 mol % of $[Pd(allyl)Cl]_2$ and 5.5 mol % of $AgClO_4$ with the ligand in CH_2Cl_2. Under these reaction conditions, a variety of commercially available chiral ligands, such as diphosphine, monophosphine, chiral phosphine-oxazoline-type P,N ligands, which were highly efficient in the Pd-catalyzed asymmetric allylic alkylations,[8] were initially evaluated. However, none of these ligands gave good results. Further screening disclosed that BINAPO (**5a**)[9] derived from BINOL could deliver the difunctional products **3aa** and **4aa** in 81% isolated yield and the desired 1,3-diamine **3aa** was obtained in 25% ee with lower regioselectivity (Table 1, entry 1). Inspired by this promising result, a series of modified BINAPO ligands (**5b**−**5l**), bearing substituents at 3,3′-positions of the binaphthyl scaffold and the phenyl ring of the phosphine, were prepared and assessed (the structure of **5i** was confirmed by X-ray analysis).[6] The screening experiments demonstrated that the sterically congested ligands were found to be crucial for obtaining high enantioselectivity and regioselectivity (Table 1, entries 2−12). Among these, **5h** was the most effective ligand which could deliver the desired 1,3-diamine **3aa** in 84% yield with 84% ee and good regioselectivity (Table 1, entry 8). The impact of the counterions over the reactivity and selectivity of this process was investigated, and it was discovered that ClO_4^- remained the optimal choice (see Supporting Information (SI)). Finally, the ee value was increased

Table 1. Optimization of Reaction Conditions[a]



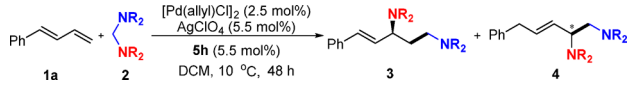
entry	ligand	*T* (°C)	yield (%)	ee (%)[b]	ratio (**3**/**4**)[c]
1	**5a**	25	81	−25	52:48
2	**5b**	25	85	30	61:39
3	**5c**	25	78	72	>20:1
4	**5d**	25	86	50	70:30
5	**5e**	25	88	83	89:11
6	**5f**	25	46	86	79:21
7	**5g**	25	64	83	>20:1
8	**5h**	25	84	84	94:6
9	**5i**	25	81	83	93:7
10	**5j**	25	56	76	82:18
11	**5k**	25	43	58	82:18
12	**5l**	25	54	75	>20:1
13	**5h**	10	77	87	92:8
14	**5h**	0	69	90	85:15
15[d]	**5h**	10	91	87	>20:1

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %), ligand (5.5 mol %), $AgClO_4$ (5.5 mol %), CH_2Cl_2 (0.5 mL), 24 h, isolated yield for **3** and **4**. [b]Determined by HPLC analysis, and the ee value is for **3**. [c]Determined by ^{1}H NMR analysis. [d]48 h.

to 90%, but with lower regioselectivity and reactivity when the reaction temperature decreased to 0 °C (Table 1, entry 14). Prolonging the reaction time to 48 h and conducting the reaction at 10 °C, a high yield with good enantioselectivity and regioselectivity was obtained (Table 1, entry 13 vs 15).

With the optimized reaction conditions identified, we then investigated the reaction of aminals with (*E*)-buta-1,3-dien-1-ylbenzene **1a**. As shown in Table 2, the benzyl aminals with both electron-withdrawing and -donating groups on the phenyl ring were well tolerated with good to excellent yields and selectivities under this protocol. It was noted that the electronic nature on the

Table 2. Substrate Scope of Aminals[a]



entry	R	yield (%)	ee (%)[b]	ratio (**3**/**4**)[c]
1	$C_6H_5CH_2$	**3aa** (91)	87	>20:1
2	4-$FC_6H_4CH_2$	**3ab** (92)	88	93:7
3	2-$ClC_6H_4CH_2$	**3ac** (93)	84	>20:1
4	4-$ClC_6H_4CH_2$	**3ad** (91)	93	>20:1
5	2-$BrC_6H_4CH_2$	**3ae** (85)	91	>20:1
6	4-$BrC_6H_4CH_2$	**3af** (82)	94	>20:1
7	4-$CF_3C_6H_4CH_2$	**3ag** (68)	96	76:24
8	4-$CH_3OC_6H_4CH_2$	**3ah** (46)	78	>20:1
9	CH_3CH_2	**3ai** (40)	55	>20:1
10	$CH_3CH_2CH_2$	**3aj** (56)	56	>20:1
11	$CH_3CH_2CH_2CH_2$	**3ak** (62)	59	>20:1

[a]Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %), **5h** (5.5 mol %), $AgClO_4$ (5.5 mol %), CH_2Cl_2 (0.5 mL), 10 °C, 48 h, isolated yield for **3** and **4**. [b]Determined by HPLC analysis, and the ee value is for **3**. [c]Determined by ^{1}H NMR analysis.

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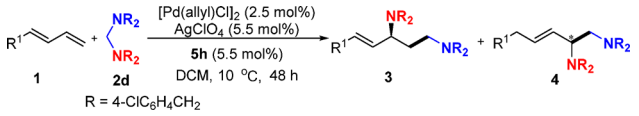
phenyl ring of the aminals had a strong influence on the reactivities, enantio- and regioselectivities. The aminals bearing halides (**2b**−**2f**) flourished the corresponding chiral 1,3-diamines in high yields with excellent enantioselectivities as well as good regioselectivities (Table 2, entries 2−6). However, the reaction with strong electron-withdrawing aminal (**2g**) provided lower yield and regioselectivity due to the lower nucleophilicity of the corresponding amine, but a higher enantioselectivity (Table 2, entry 7). Comparing with the results of the substrates bearing an electron-withdrawing group, the presence of an electron-donating group such as methoxyl (**2h**) led to a moderate yield with good regio- and enantioselectivity (Table 2, entry 8). Aminals derived from simple aliphatic amines (**2i**−**2k**) were incorporated into the conjugated diene with this catalytic system, however, the corresponding 1,3-diamine products were obtained with moderate yields and moderate ee values (Table 2, entries 9−11), albeit excellent regioselectivities were observed.

We next examined the scope with respect to the dienes (Table 3). The substrate scope of 1,3-diene was explored by reaction of a variety of substituted butadienes **1** with aminal **2d**. In theory, four kinds of regiomers could be generated from the reaction. However, thanks to the efficient catalytic protocol, the application of the optimized reaction conditions to the reaction of different conjugated dienes with **2d** was quite successful, and almost only two regiomers (1,3-diamine and 1,2-diamine) were observed. As shown in Table 3, the desired chiral 1,3-diamines were obtained in high enantioselectivities ranging from 77% to 99% ee and up to 91% yield as well as >20:1 regioselectivity. It is noteworthy that the arylbutadienes with a variety of substituents, such as alkyl, methoxyl, trifluoromethoxyl, fluoro, chloro, bromo, and nitro, were all compatible with this protocol. Obviously, both the reactivities and regioselectivities suffer from the steric hindrance of the alkenes. For instance, the sterically hindered *ortho*-substituted arylbutadienes **1f** and **1r** were subjected to the catalytic system to afford the desired products in 86% and 99% ee, respectively, but with a relatively lower regioselectivities and yields (Table 3, entries 6 and 18). This lower regioselectivities probably due to the fact that *ortho*-substituted groups influenced the stability of the π-allyl-Pd intermediates **I**, thereby accelerated the steps of β-hydride elimination and reinsertion to form the unusual 1,2-diamines. In addition, naphthyl substituted arylbutadiene **1m** and **1n** were also compatible with this reaction, affording the corresponding 1,3-diamines with high regio- and enantioselectivities (up to 92% ee, Table 3, entry 14). In addition, the products **3df**, **3ef**, **3pf** were isolated with higher ee values when aminal **2f** instead of **2d** was used as the reaction partner (Table 3, entries 19−21). Moreover, the challenging alkyl substituted butadienes **1s** and **1t** can also be transformed into the desired products in moderate yields with high regioselectivities and good enantioselectivities when **5c** was utilized as a chiral ligand. Furthermore, the heteroaromatic 2-(buta-1,3-dien-1-yl)furan also worked well in the reaction, generating the desired product in good yield and excellent enantioselectivity (96% ee for **3ud** and 85% ee for **4ud**, Table 3, entry 24). It was important to mention that the reactivity regio- and enantioselectivity of this reaction were not affected by the (*E*/*Z*) ratio of the corresponding dienes (see SI). Pleasingly, the reaction underwent smoothly on 10 mmol scale, affording the desired product with high yield and excellent stereoselectivity (5.98 g of **3ad** was obtained in 89% yield, with 92%ee and >20:1 regioselectivity, see SI). The absolute configuration of **3qd** was determined as (*S*) by its X-ray crystallographic analysis, and the other products were tentatively assigned as (*S*) by analogy.

To rationalize the observed enantioselectivity of the present reaction, a Pd(II) complex of chiral ligand **5e** has been isolated and characterized by X-ray crystallography to have the formula of [Pd(*R*-**5e**) (allyl)]ClO_4 (Figure 1). The cationic complex contains one ligand **5e**, coordinated to Pd through the P atom. All four phenyl rings attached to the P atom of the ligand locate at four different quadrants, respectively. On the basis of the catalyst structure and the absolute configuration of the products, we proposed the chiral induction model shown in Figure 1. Assuming all of the diastereomeric π-allylic-Pd intermediates are in equilibrium by reversible β-H elimination, the allylic moiety adopts the *exo-syn-syn* configuration (W-type) and is

Table 3. Substrate Scope of 1,3-Butadienes[a]



entry	R^1	yield (%)	ee (%)[b]	ratio (**3**/**4**)[c]
1	C_6H_5	**3ad** (91)	93	>20:1
2	3-MeC_6H_4	**3bd** (86)	92	93:7
3	4-MeC_6H_4	**3cd** (75)	95	>20:1
4	4-^{t}BuC_6H_4	**3dd** (79)	88	>20:1
5	4-FC_6H_4	**3ed** (81)	88	>20:1
6	2-ClC_6H_4	**3fd** (40)	86	76:24
7	3-ClC_6H_4	**3gd** (72)	83	92:8
8	4-ClC_6H_4	**3hd** (81)	81	>20:1
9	4-BrC_6H_4	**3id** (84)	87	>20:1
10	4-$CF_3OC_6H_4$	**3jd** (86)	83	88:12
11	4-$NO_2C_6H_4$	**3kd** (82)	81	75:25
12	4-PhC_6H_4	**3ld** (84)	93	89:11
13	1-naphthyl	**3md** (48)	89	>20:1
14	2-naphthyl	**3nd** (91)	92	91:9
15	3,4-$(Me)_2C_6H_3$	**3od** (74)	96	>20:1
16	3,5-$(Me)_2C_6H_3$	**3pd** (76)	88	>20:1
17	3,4-$(OMe)_2C_6H_3$	**3qd** (73)	92(79)	48:52
18	2,3-$(Me)_2C_6H_3$	**3rd** (26)	99(92)	62:38
19[d]	4-^{t}BuC_6H_4	**3df** (71)	94	88:12
20[d]	4-FC_6H_4	**3ef** (68)	92	91:9
21[d]	3,5-$(Me)_2C_6H_3$	**3pf** (70)	91	90:10
22[e]	$PhCH_2CH_2$	**3sd** (33)	80	>20:1
23[e]	*n*-Oct	**3td** (56)	77	>20:1
24	2-furyl	**3ud** (65)	96(85)	47:53

[a]Reaction conditions: **1** (0.24 mmol), aminal **2** (0.2 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %), **5h** (5.5 mol %), $AgClO_4$ (5.5 mol %), CH_2Cl_2 (0.5 mL), 10 °C, 48 h, isolated yield for **3** and **4**. [b]Determined by HPLC analysis, the data in bracket were for **4**. [c]Determined by ^{1}H NMR analysis. [d]**2f** was used. [e]**5c** was used as ligand.

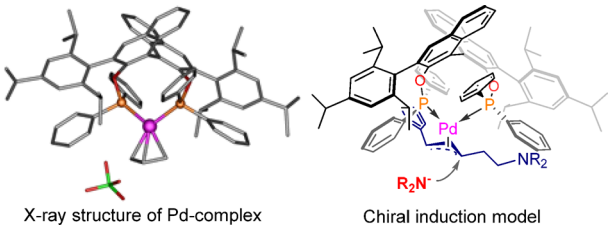


Figure 1. Structure of the cationic Pd-complex and chiral induction model.

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attacked by R_2N^- from the less-hindered *Si* face, affording the product with an *S* configuration.

To gain some insights into the mechanism of this novel reaction, isotope effect experiments were conducted by the reaction of d_2-3,4-dimethoxylphenylbutadiene (**1q-d$_2$**) with aminal **2d** (see SI). Similar to the results obtained by Gong,[7v] the deuterium migration was observed in the regiomer **4qd-d$_2$**. In addition, the regioselectivity of the reaction was improved from 48:52 to 75:25. The reason may be attributed to that the β-deuteride elimination and reinsertion steps underwent much slower than the similar reactions with **1q**, thus result in the formation of allylic-Pd intermediate **IV** is much more slower than **III**. On the basis of these results, we speculated that β-hydride elimination and reinsertion to form allylic-Pd intermediate were most likely involved in this reaction.

In summary, we have developed a new type of Pd-catalyzed enantioselective aminomethylamination of conjugated dienes with aminals via C−N bond activation. The palladium complex coordinated with BINAPO-type ligand efficiently catalyzed the difunctionalization reaction with high regioselectivity and enantioselectivity, where a series of synthetically useful chiral 1,3-diamines were obtained as the reaction products. The present transformation is the first example of an enantio- and regioselective difunctionalization of conjugated dienes via C−N bond activation. Further exploring of efficient chiral catalysts for regio- and enantioselectively providing the chiral 1,2-diamines with this novel catalytic protocol and applying this cyclopalladated complex in other asymmetric catalysis are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00976.

■ AUTHOR INFORMATION

Corresponding Author

*hmhuang@licp.cas.cn

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

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