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Article

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# SKP ligands in Pd-catalyzed asymmetric allylic amination of MBH adducts: Exceptionally high efficiency and new mechanism

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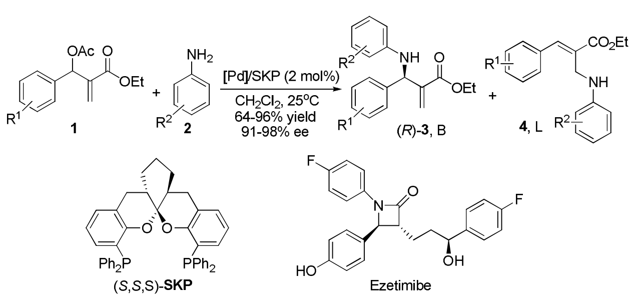
***Supporting Information***

**ABSTRACT:** Exceptionally high activity (with a TON up to 4750) of the palladium complexes of SKP ligand was discovered in the catalysis of asymmetric allylic amination of MBH adducts with aromatic amines. A comprehensive mechanistic study indicates that the unique structural features of the SKP ligand, with a long P···P distance in its solid state structure, was favorable for allowing two P atoms to play a bifunctional role in the catalysis. Herein, one of the P atom forms a C-P σ–bond with the terminal carbon atom of allyl moiety as a Lewis base and an alternative P atom coordinates to Pd atom. The cooperative action of organo- and organometallic catalysis discovered in the present catalytic system is most likely responsible for its high activity, as well as excellent regio and enantioselectivities. The mechanism disclosed in the present catalytic system is distinct from most of the currently recognized mechanisms for Pd-catalyzed allylic substitutions.

## I. INTRODUCTION

Palladium-catalyzed asymmetric allylic substitutions have gained great successes in organic synthesis.[1] However, it is still a great challenge in terms of the efficiency and adaptability of catalysis for the application in industry.[1,2] Moreover, the regioselective formation of a branched product at the sterically more hindered position of allylic substrate is also particularly difficult in this Pd-catalyzed transformation.[3]

**Scheme 1.** SKP/Pd catalyzed regio and enantioselective allylic amination of MBH adducts.

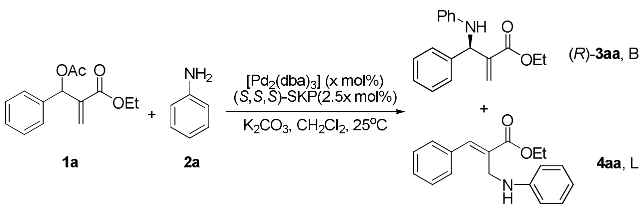



Very recently, a type of chiral spiroketal-based diphosphine ligands (SKP)[4] have been developed in our lab and their palladium complexes have been discovered to be effective to address the challenging issues of asymmetric allylic amination of racemic Morita-Baylis–Hillman (MBH) adducts with aromatic amines, affording the β-aryl amino acid esters with excellent enantio- and regioselectivities (Scheme 1).[4d] This catalytic system has also provided a facile approach for the synthesis of a chiral drug, Ezetimibe.[4d] In this work, we would like to report our new results on the discovery of exceptionally high activity of the catalysis, a long-standing challenge in this type of reaction, and the disclosure of a new mechanism based on the bifunctional role of SKP ligand.

## II. RESULTS AND DISCUSSION

**1. The exceptionally high efficiency**: The research was initiated by following the reaction profile of **1a** and **2a** with a ReactIR in order to understand the kinetic behaviors of the catalysis in the presence of 1 mol% of $Pd_2(dba)_3$/SKP catalyst. It was surprising to find that the complete conversion of MBH adduct has been observed in a couple of minutes. This remarkably serendipitous discovery allowed us to further reduce the catalyst loading. As shown in Table 1, the complete conversion of substrate can be realized in 1.5-2 h when the catalyst loading of [$Pd_2(dba)_3$]/SKP was reduced to 0.1-0.05 mol%, affording the corresponding β-arylamino acid ester with 93-92% *ee* and 96/4 regioselectivity (entries 1-2). These exciting results stimulated us to further diminish the catalyst loading to 0.01%, 95% conversion of substrate has been achieved in this case by extending the reaction time to 12 h with comparable regio- and enantioselectivities with a TON of 4750 (entry 3). We believe this loading should be among the lowest records in Pd-catalyzed asymmetric allylic substitutions.[1] The remarkable activity, excellent regio and enantioselectivity of this catalyst system coupled with the practical importance of this reaction prompted us to further undertake mechanistic stuty to reveal the underlying reasons for its unique performance.

**Table 1.** The exceptionally high efficiency of the SKP/Pd catalyst for the allylic amination of MBH adduct **1a** with aniline **2a**.[a]




| entry | x(mol %) | t (h) | conv. (%)[b] | yield (%)[c] | 3aa/4aa[b] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | 0.1 | 1.5 | >99 | 90 | 96/4 | 93 |
| 2 | 0.05 | 2.0 | >99 | 89 | 96/4 | 92 |
| 3 | 0.01 | 12 | 95 | 91 | 97/3 | 92 |

[a] For details, see SI. [b] Determined by $^1$H NMR. [c] The yield of isolated (*R*)-**3aa**. [d] The *ee* value of (*R*)-**3aa** is determined by HPLC on a chiral stationary phase.

**2. The nature of the catalysis**: Since it has been established that both Lewis bases (typically tertiary amines or phosphines)[5,6] and the transition metal complexes[7] are able to catalyze the allylic substitutions of MBH adducts with various nucleophiles, control experiments were thus carried out in the presence of either Pd precursor or (*S*,*S*,*S*)-SKP alone to clarify whether the reaction proceed via organo or organometallic catalysis. The results showed that no reaction occurs in either case (Figure S1), clearly indicating both SKP ligand and Pd metal are essential for the catalysis. Furthermore, reaction profile measurement in the presence of several different Pd precursors, including $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, $Pd_2(dba)_3$ and $[Pd(\eta^3\text{-allyl})Cl]_2$, showed that $Pd_2(dba)_3$ is superior to other Pd sources in terms of both activity and selectivity, suggesting that the catalytic process might be triggered by a Pd(0) species (Figure S4). The exposure of the reaction system to $O_2$ results in an immediate inhibition of the reaction, supporting that some low-valence Pd species is involved in the catalytic cycle (Figure S5). Since the in situ formation of Pd(0) nanoparticles have often been found to be genuine active species in some Pd-catalyzed reactions,[8] we also proceeded to clarify whether the catalysis is homogeneous or heterogeneous in nature by Hg(0)-test.[9] As shown in Figure S5, reaction profile accumulation indicated the progress is scarcely affected by addition of an excessive amount of Hg(0) to the reaction mixture, consistent with the homogeneous nature of the active species. Moreover, non-linear effect[10] study disclosed a linear relationship between the ee of **3aa** and the enaniopurity of SKP ligand, indicating only one SKP ligand being most likely involved in the active Pd species in the enantio-determining step (see Figure S9).

**3. Structural features of the SKP ligand with a long P…P distance**: A quantitative comparison of impact of the ligand structure on the catalytic activity and regio selectivity of the catalysis was also carried out with several well-established diphosphine ligands, including (*R*)-BINAP, D$^t$BPF, Xantphos, and (*S*,*S*,*S*)-SKP, respectively, in the reaction of **1a** with **2a**. The catalysis with (*S*,*S*,*S*)-SKP/Pd demonstrated a much faster rate than other cases (Figure S6) under the otherwise identical conditions. This dramatic activity difference prompted us to probe into the structural features of the SKP ligand. As shown in Figure 1a, X-ray structural analysis of (*S*,*S*,*S*)-SKP revealed an intramolecular P,P distance of 6.293(8) Å, much larger than those reported for analogous ligands SPANphos (4.991 Å)[11] or Xantphos (4.080 Å).[12] Such an extremely large inter P,P distance in SKP ligand is probably not favorable for adopting an intramolecular *cis*-chelating mode with metallic ions, but might provide the opportunity to interact with metal ions in a *trans*-coordination, or in a coordination with metals as a monodentate ligand.[13] Indeed, a $PdCl_2$ complex of (*S*,*S*,*S*)-SKP, (*S*,*S*,*S*)-**5**, was prepared in 90% yield by reaction of (*S*,*S*,*S*)-SKP with $[Pd(CH_3CN)_2Cl_2]$, and its X-ray structural analysis showed the complex adopted a distorted square-planar geometry, featuring a *trans*-spanned chelating coordination with a P-Pd-P angle of 160.08 (2)° (Figure 1b).[13,14] The distance between two P atoms 4.583(7) Å in the complex (*S*,*S*,*S*)-**5** is much shorter than that in free (*S*,*S*,*S*)-SKP, indicating that a substantial conformational flexibility exists in the spiroketal backbone of SKP ligand. Unfortunately, complex (*S*,*S*,*S*)-**5** only showed very poor activity and selectivities in the reaction (Figure 2b vs 2a), implying that this complex is not responsible for this highly selective and efficient catalysis.

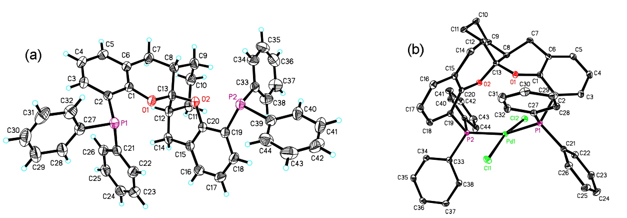


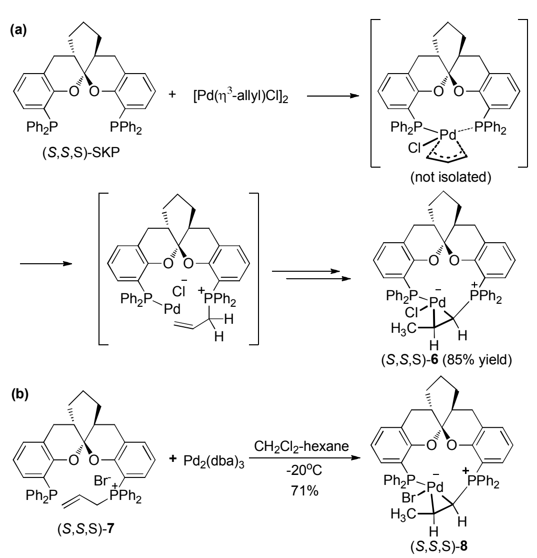

**Figure 1.** X-Ray crystal structure of (*S*,*S*,*S*)-SKP (a), and its $PdCl_2$ complex (*S*,*S*,*S*)-**5** (b), hydrogen atoms are omitted for clarity.

We next proceeded to investigate the solution behavior by $^{31}$P-NMR (Figure S10) and the catalytic performance (Figure S7) of (*S*,*S*,*S*)-**5** and mixtures of $Pd(CH_3CN)_2Cl_2$ with different ratio of (*S*,*S*,*S*)-SKP. The results showed that upon in situ mixing $[Pd(CH_3CN)_2Cl_2]$ with SKP ligand, a dynamic mixture of (*S*,*S*,*S*)-**5** and some Pd species coordinated with a single P atom of SKP ligand co-existed in the solution, and the monodentate SKP-coordinated Pd species might be responsible for the formation of active species in the catalysis.[13,15] Based on these observations, a question about whether both P moieties are necessary for the catalysis is raised. To address this issue, monoxide of SKP ((*S*,*S*,*S*)-SKPO'), a monodentate SKP ligand analogue,[16] was synthesized and examined in the catalysis. The reaction catalyzed by 1 mol% of (*S*,*S*,*S*)-SKPO'/$Pd_2(dba)_3$ at a ratio of 2/1 or 4/1 showed poor performance (Table S2), indicating that SKP ligand does not simply act as a monophosphine ligand, and both P atoms of the ligand should be involved in the catalysis.

**4. Bifunctional role of SKP ligand**: To gain some information of the possible intermediates in the catalysis, we turned our attention to study π-ally Pd complexes of

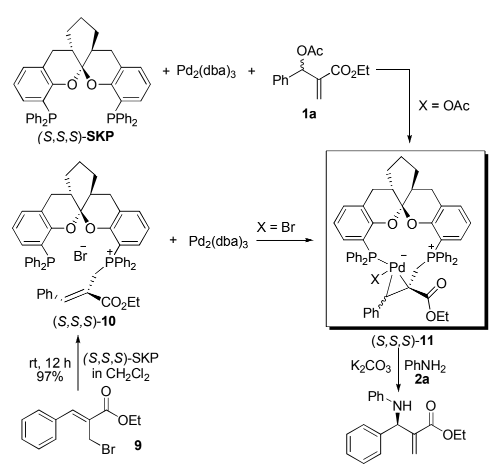
(*S,S,S*)-SKP. Intriguingly, the reaction of [Pd(η³-allyl)Cl]$_2$ precursor with (*S,S,S*)-SKP ligand gave a crystalline complex (*S,S,S*)-**6** (85% yield), with a molecular composition of (*S,S,S*)-SKP/Pd(ally)Cl but not the expected π-allyl Pd(II) structure (Scheme 2a).[17] To our surprise, X-ray crystallographic analysis of this complex revealed that two P atoms of (*S,S,S*)-SKP do not coordinate to Pd simultaneously (see Figure S29 in SI). Instead, a σ bond is observed between the allyl moiety and one of the P atoms of SKP ligand, to form an alkenylphosphonium cation with its C=C double bond coordinating to a palladium atom in an η² fashion.[18] The formation of the complex (*S,S,S*)-**6** is probably caused by an intramolecular nucleophilic attack of phosphorus atom at the terminal carbon of a nascent η³-allyl Pd intermediate, to lead to the formation of the phosphorus-carbon bond, followed by C=C bond rearrangement via a hydrogen shift (Scheme 2a).[19] In-situ $^{31}$P NMR monitoring of the reaction of (*S,S,S*)-SKP with [Pd(η³-allyl)Cl]$_2$ provided further support of the proposed process (Figure S11), and an analogous η²-propenyl Pd complex (*S,S,S*)-**8** has been isolated in 71% yield from the reaction of an allyphosphonium salt of SKP (*S,S,S*)-**7** with Pd$_2$(dba)$_3$ (Scheme 2b, for its crystal structure, see Figure S30 in SI)). However, tests of (*S,S,S*)-**6** and (*S,S,S*)-**8** in the catalysis indicated both complexes are less active than the catalyst prepared in-situ from (*S,S,S*)-SKP with Pd$_2$(dba)$_3$ although their regio and enantioselectivities were essentially same (Figure 2c,d vs 2a). From the structural information and catalytic performance of (*S,S,S*)-**6** and (*S,S,S*)-**8**, it is clear that (*S,S,S*)-SKP ligand likely behaves as a “bifunctional ligand” in the catalysis. However, these complexes are only catalyst precursors rather than the direct active species involved in the catalytic cycle .

**Scheme 2**. The reactions of (*S,S,S*)-SKP with [Pd(η³-allyl)Cl]$_2$ (a), and an allyphosphonium salt of SKP (*S,S,S*)-**7** with Pd$_2$(dba)$_3$ to give unexpected complexes (*S,S,S*)-**6** and (*S,S,S*)-**8**.




After some efforts to prepare a crystalline Pd complex of (*S,S,S*)-SKP with MBH adduct **1a** failed, we were finally successful to obtain a phosphonium salt of (*S,S,S*)-SKP with analogous MBH adduct ((*S,S,S*)-**10**) (Scheme 3). It is assumed that (*S,S,S*)-**10** might react with a Pd(0) presursor to form the active species ((*S,S,S*)-**11**), which may immediately undergo the amination with aniline. Comparison of the catalytic performance of (*S,S,S*)-SKP/Pd$_2$(dba)$_3$ and (*S,S,S*)-**10**/Pd$_2$(dba)$_3$ indicated that both catalyst systems resulted in the essentially same activity, regio- and enantioselectivities in the catalysis (Figure 2e vs 2a). ESI-MS analysis of the catalyst system generated from (*S,S,S*)-**10** and Pd$_2$(dba)$_3$ indicated the presence of species with the composition of [((*S,S,S*)-**11**)-Br]$^+$ (m/z 953.2291, see SI), supporting the formation of an intermediate of (S,S,S)-**11**. A stoichiometric reaction of phosphonium salt (*S,S,S*)-**10** and Pd$_2$(dba)$_3$ with **2a** in the presence of AgOAc (1.2 equiv) indeed gave the expected amination product (*R*)-**3aa** in 80 % yield with 89/11 regioselectivity and 92% *ee* (see SI), directly reproducing the scenario of catalytic system. These results strongly suggested that an intermediate (*S,S,S*)-**11** should most likely be involved in the catalysis, although we were unable to get direct evidence of its exact molecular structure.

**Scheme 3.** The proposed pathway for the formation of active species (*S,S,S*)-**11**.




The difficulties associated with the isolation and characterization of intermediate (*S,S,S*)-**11** are probably due to its unstability and high reactivity. Fortunately, we obtained an analogous complex (*S,S,S*)-**13** by reacting a triethoxylcarbonyl substituted allylic chloride (**12**) with (*S,S,S*)-SKP and Pd$_2$(dba)$_3$ (Scheme 4). X-ray single crystal structural analysis of (*S,S,S*)-**13** clearly showed that the complex adopts a structure analogous to that proposed for intermediate (*S,S,S*)-**11**. A square-planar coordination geometry is found in this structure, wherein the tetrasubstituted C=C bond coordinates in a *η*²-fashion to Pd atom which in turn bonded with one P atom of the SKP ligand. The terminal carbon of allylic unit forms a C-P σ-bond with the alternative P atom of the ligand, to generate an allyl phosphonium moiety (Scheme 4). Under such a circumstance, hydrogen shift as that in the formation of complex (*S,S,S*)-**6** or (*S,S,S*)-**8** did not occur. The C46-C47 distance [1.532(6) Å] is very close to that of a C-C single bond, and the bond lengths of Pd1-C46 [2.056(8) Å] and Pd1-C47 [2.059(5) Å] are also within the range of common Pd-C($sp^3$) σ-bond lengths (2.04-2.08 Å),[20] indicating that the palladium atom in the complex can be regarded as a Pd(II), likely as a result of the very strong tendency of back electron transfer from electron rich Pd atom to electron-deficient olefinic moiety.[18,21] The distance (3.174(5) Å) between carbonyl oxygen (O7) and P1 atom of ligand is shorter than the sum of their van der Waals radii (3.3 Å),[22] indicating the presence of some weak intramolecular interaction of carbonyl O7 atom with P atom of phosphonium salt. Such kind of intramolecular interaction has been also proposed in the phosphine-catalyzed allylic substitution of MBH adducts.[23]

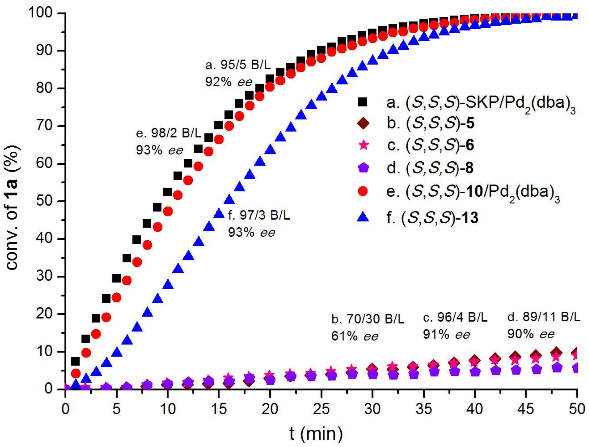
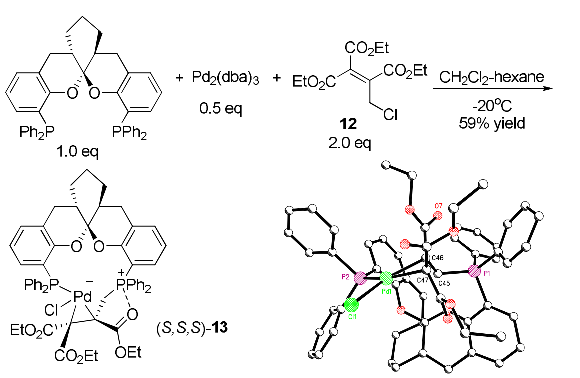



**Figure 2.** Comparison of reaction profiles of model substrates **1a** and **2a** using various catalyst precursors (at a 0.1 mol% [Pd]).

**Scheme 4.** The preparation and X-ray crystal structure of (*S,S,S*)-**13** (Hydrogen atoms are omitted for clarity).



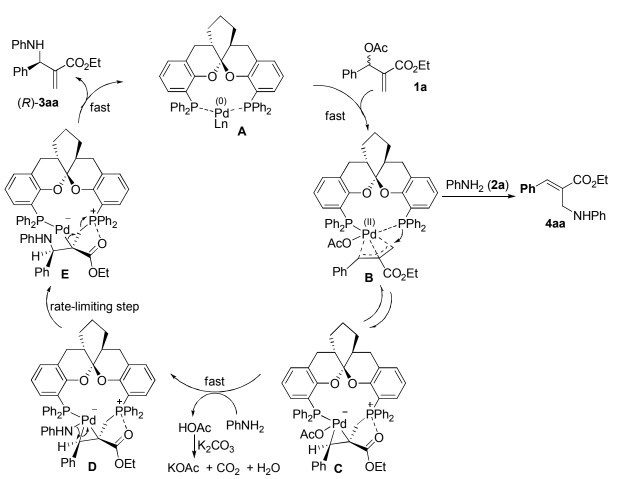

As shown in Figure 2, complex (*S,S,S*)-**13** showed activity, regio and enantioselectivities very similar to those of (*S,S,S*)-SKP/$Pd_2(dba)_3$, albeit a short incubation period (about 5 min.) was observed in the catalysis (Figure 2f vs 2a). These results suggested that the complex (*S,S,S*)-**13** should be a competent active species for the allylic amination. Accordingly, the preparation, characterization and catalytic activity studies of (*S,S,S*)-**13** have provided strong albeit circumstantial evidences for the assumed active species (*S,S,S*)-**11**. Moreover, the evaluation of the reactions of several allylic acetates with distinct structural patterns(Figure S8), clearly demonstrated that 1-phenyl and 2-$CO_2Et$ substituents in **1a** were critically important for its high reactivity. This was probably caused by the stabilization of the transition state in the rate-limiting step, gained from the formation of phosphonium salt and the ensuing interaction of 2-$CO_2Et$ with phosphonium moiety,[23] as well as the further stabilization by benzyl carbon-Pd bond[24] as that in the assumed active species (S,S,S)-**11**.

**5. Kinetic studies and Hammett plots**: Further kinetic studies indicated the reaction follows a first order dependence on the Pd catalyst and zero-order for **1a** and **2a** (see Figure S19-22 in SI). Although the kinetic studies showed that the rate was independent of the concentrations of both substrates, the studies of the Hammett plots[25] showed that electronic features of the substituents in substrates obviously impacts the reactivity (see Figure S23-S26 in SI). These results demonstrated that one catalyst molecule has been involved in the rate-limiting step, and both MBH adduct (**1a**) and aniline (**2a**) substrates probably have been readily embraced into the catalytic center before the rate-determining step. Such kind of kinetic behavior obviously favors a mechanism of dual activation of both substrates and thereby allows a subsequent intramolecular reaction of the activated species to realize high catalytic activity and fine control of the selectivity.[26,27] Moreover, the best correlation of $\log(k_X/k_H)$ of arylamines with $\sigma^-$ (see Figure S24 in SI) reflected the higher possibility of the involvement of aniline anion, and the best correlation of $\log(k_Y/k_H)$ of MBH adducts with σ (see Figure S26 in SI) indicated no obvious positive charge is developed at the benzyl carbon of allylic component in the rate-limiting transition state. Both of them afforded a straight line with negative slope. Suppose that the reductive elimination of amido and allyl moieties from the Pd(II) key intermediate is involved in the rate-limiting step, the high electron distribution at both amido and allyl moieties would be favorable for their reductive-elimination to form the new C-N bond.[28,29] Thus, all the kinetic data of catalysis and Hammett plots of substituent effect support the hypothesis of reductive elimination mechanism for C-N bond formation.

**6. The proposed mechanism:** Based on these results, a plausible reaction mechanism was proposed. As outlined in Scheme 5, the catalysis is initiated by a Pd(0) species (**A**), in which the SKP ligand either takes a hemilabile *trans*-chelating coordination or coordinates to Pd(0) as a monodentate ligand. Complex **A** is assumed to quickly undergoes oxidative addition with MBH adduct, to form the corresponding π-allylic Pd intermediate **B** coordinated by one P atom of SKP ligand owing to the steric repulsion of allyl moiety and the long distance of P, P atoms. This intermediate may exist an equilibrium with complex **C**,[30,31] formed by an intramolecular nucleophilic attack of the noncoordinating P atom of SKP at the terminal allyl carbon. The structure of **C** has been further evidenced by X-ray diffraction analysis of an analogous $\eta^2$-propenyl Pd complex (*S,S,S*)-**13** with comparable catalytic activity (Figure 2f vs 2a). Alternatively, the π-allylic Pd complex **B** may also accept the intermolecular nucleophilic attack of aniline on the less hindered end of the allyl moiety to give the linear amination product **4aa**

directly by following the usual process of Pd-catalyzed allylic amination. Thanks to the weak nucleophilicity of aromatic aniline and priority of intramolecular nucleophilic attack of standby P atom, amination of complex **B** only plays a minor role in the catalysis. Complex **C** is expected to react readily with aniline to form key intermediate **D** by elimination of HOAc under basic conditions. Although we are unable to isolate **D**, the formation of analogous Pd(II) amido complexes have been reported by Hartwig and Buchwald, respectively.[29] On the basis of Hammett plots of substituent effect in substrates **1** and **2**, a reductive elimination for the formation of C($sp^3$)-N bond seems to be more feasible. Considering the spatial proximity of amido N-Pd and benzyl C-Pd bond in intermediate **D**, the reductive elimination accordingly occurs at benzyl C-Pd bond to yield the branched isomer with simultaneous regeneration of C=C double bond in the product and release of species **A**.[32] The kinetic studies suggested the reductive elimination of **D** to be the rate-determining step in the catalysis.

**Scheme 5.** The proposed mechanism for SKP/Pd-catalyzed asymmetric allylic amination of MBH adducts.




On the basis of the proposed mechanism mentioned above, the unique performance of this catalytic system can be rationalized. The appropriate distance of P, P coordinating atoms in SKP ligand is essentially important for playing a bifunctional role in catalysis,[33] in which one P atom forms a C-P bond as a Lewis base with the terminal carbon atom of allyl moiety, and the other P atom coordinates to Pd for organometallic catalysis. From the view point of stereochemistry, 1-phenyl and 2-$CO_2Et$ substituents at allyl moiety in intermediates **C** and **D** are apt to take a *cis* arrangement and were extruded in the opposite direction of central metal and SKP ligand, because of the steric congestion between the 1-Ph group of allyl moiety and aromatic sprioketal backbone of ligand (see Scheme S2).[7b,23] On the basis of the proposed configuration (*R*) at benzyl carbon bound to palladium atom and the observed configuration of benzyl carbon in product **3aa** (*R*), reductive elimination for the formation of C-N bond would proceed via a concerted process, although an ionic pathway would be also possible.[29a] It has been known that the use of aromatic amines as nucleophiles in Pd-catalyzed allylic amination were rarely reported, presumably due to the weak nucleophilicity of arylamines.[1i] In fact, the commonly used diphosphine ligands such as BINAP, Xantphos, DtBPF only showed modest activity in the reaction system (Figure S6), indicating the critical importance of structural feature of SKP ligand. Accordingly, the origin of the acceleration of the catalysis using SKP ligands should come from the changes of the reaction mechanism in comparison with that observed in conventional nucleophilic allylic amination, thus avoiding the less efficient nucleophilic attack step. On the other hand, the novel multisite interaction pattern between catalyst and substrates (D and E shown in Scheme 5) led to the formation of a more tight reaction assembly somewhat like enzyme, which thus facilitates the intramolecular transformation and excludes the potential product inhibition that observed in some metal-catalyzed reactions.[32,34] Moreover, the formal charge separation developed in intermediates D and E might be an inherent driving force to facilitate the reductive elimination and formation of C=C bond in the product with the regeneration of the catalyst. To the best of our knowledge, such kind of ligand/metal/substrate interaction pattern (Figure 3a) is unprecedented although various coordination modes of diphosphine ligands with metal ions (Figure 3b) have been extensively studied.[13,35] The cooperative action of both organo and organometallic catalysis discovered in the present catalytic system is most likely responsible for its exceptionally high efficiency and excellent regioselectivity.

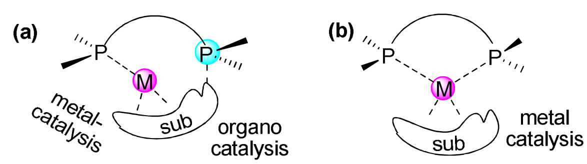



**Figure 3.** Comparison of the present bifunctional catalysis involving cooperative actions of a metal and a Lewis base (a), and conventional metal catalysis where both phosphine moieties behaving as 'spectator' ligands (b).

## III. SUMMARY AND CONCLUSIONS

In summary, the palladium complexes of spiroketal-based diphosphine ligand (SKP) have been disclosed to show remarkably high activity (with a TON up to 4750) in the catalysis of asymmetric allylic amination of racemic MBH adducts with aromatic amines, which is extremely important for the practical synthesis of β-aryl amino acid derivatives, as well as a chiral drug, Ezetimibe. The unique structures of the SKP ligand, the related Pd complexes with allylic substrates and their corresponding performance indicate that SKP ligand plays a bifunctional role in the catalysis. The cooperative action of both organo and organometallic catalysis discovered in the present catalytic system is most likely responsible for its exceptionally high efficiency and excellent regioselectivity. The reaction pathway revealed in this study contrasts sharply with most of the currently recognized mechanistic understandings on the scenarios of allylic substitutions,[1] and thus might stimulate future work for the development of new catalytic reactions involving the cooperative effect of organo and organometallic catalysis with diphosphine ligands.

## ASSOCIATED CONTENT

### Supporting Information

Experimental details for data acquisition and additional discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## Keywords

asymmetric catalysis, allylic amination, cooperative catalysis, palladium, phosphine ligand, spiro

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(32) The addition of product **3aa** (0.5 equiv.) to the catalytic system at the beginning of the reaction of **1a** with **2a** did not result in observable negative effect on the outcome of catalysis (see SI).

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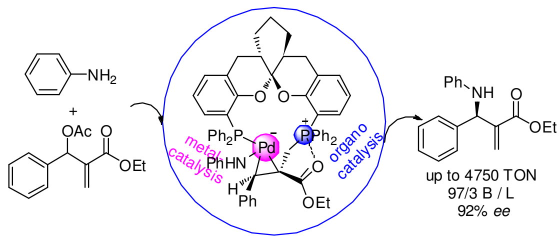
NH2
OAc
O
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Ph2P
Pd
PPh2
metal catalysis
organo catalysis
PhHN
H
Ph
O
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Ph
NH
O
OEt
up to 4750 TON
97/3 B / L
92% ee