Unveiling the Mechanistic Role of Chiral Palladacycles in Pd(II)-Catalyzed Enantioselective C(sp^3)-H Functionalization

Chen-Hui Yuan,[a] Xiao-Xia Wang[a], Keyun Huang[a], and Lei Jiao[a]*

Author Affiliation:
[*] C.-H. Yuan, X.-X. Wang, K. Huang, Prof. L. Jiao
Center of Basic Molecular Science (CBMS), Department of Chemistry, Tsinghua University, Beijing 100084 (China)
Email: leijiao@mail.tsinghua.edu.cn

Keywords: chiral palladacycle; C(sp^3)-H functionalization; palladium catalysis; enantioselectivity; carboxylic acid

Abstract: Palladium-catalyzed enantioselective C(sp^3)-H functionalization reactions has attracted considerable attention due to its ability for the synthesis of enantiomerically enriched molecules and stimulation of novel retrosynthetic disconnections. Understanding the reaction mechanism, especially the stereochemical process of the reaction, is crucial for the rational design of more efficient catalytic systems. Previously, we developed a Pd(II)/sulfoxide-2-hydroxypridine (SOHP) catalytic system for asymmetric C(sp^3)-H functionalization reactions. In this study, our focus is on unraveling the chemistry of chiral palladacycles involved in the Pd(II)-catalyzed enantioselective C(sp^3)-H functionalization. We have isolated key palladacycle intermediates involved in the enantioselective β-C(sp^3)-H arylation of carboxylic acids catalyzed by the Pd(II)/SOHP system. These palladacycles, exhibiting ligand-induced chirality, provided a significant opportunity to investigate the stereochemical process and the ligand effect in this asymmetric C-H functionalization. Our investigation revealed that the C(sp^3)-H palladation step is irreversible, representing the enantioselectivity-determining step to form diastereomeric palladacycles. Ligand exchange experiments and DFT calculations provided insights into the chiral induction in palladacycle formation and the preservation of chirality in the functionalization step. This work highlights the value of chiral palladacycle chemistry in offering mechanistic insights into the Pd(II)-catalyzed asymmetric C(sp^3)-H functionalization reactions.

Introduction

Direct C-H functionalization has emerged as an ideal tool for construction of multifunctional molecules and late-stage modification of complex structures.[1] Due to the abundance of C(sp^3)-H bonds in organic molecules, enantioselective C(sp^3)-H functionalization has received significant attention, owing to its great potential to synthesize enantiomerically enriched molecules and enable novel retrosynthetic disconnections.[2]

Exemplifying this trend, palladium-catalyzed native functional group-directed asymmetric C(sp^3)-H functionalization has witnessed rapid advancement over the past decades (Figure 1a).[3] Yu and coworkers pioneered the early exploration of 2-isopropylpyridine in conjunction with the crucial *N*-monoprotected amino acid (MPAA) ligand, albeit achieving relatively modest yield and enantioselectivity (38% and 37%, respectively).[4] Subsequently, the pivotal role of ligands gradually became recognized, leading to the development of numerous novel ligands that have propelled the field forward.[3a] Representative examples of native functional group-directed enantioselective C(sp^3)-H functionalization have been achieved for amides,[5] sulfonamides,[6] amines,[7] thioamides,[8] and carboxylic acids[9] by the groups of Yu,[4-6,7c,8a,9] Wencel-Delord and Colobert,[5d] Gaunt,[7a-b] and Gong.[8b-c] A variety of chiral ligands, including MPAA,[4-5,6a,7a-b,9b] protected aminosulfides,[5d,7c] protected amino *N*-block ligands,[5b-c,6b,9] chiral phosphoric acids,[8a,8c] and phosphoramidites,[8b] have been developed and effectively utilized in the aforementioned C(sp^3)-H functionalization chemistry. Our own research

efforts have also led to the design of sulfoxide-2-hydroxypyridine (SOHP) ligands,[10] showcasing remarkable efficiency in the enantioselective C(sp^3)–H arylation of aliphatic tertiary amides[11] and primary amines.[12]

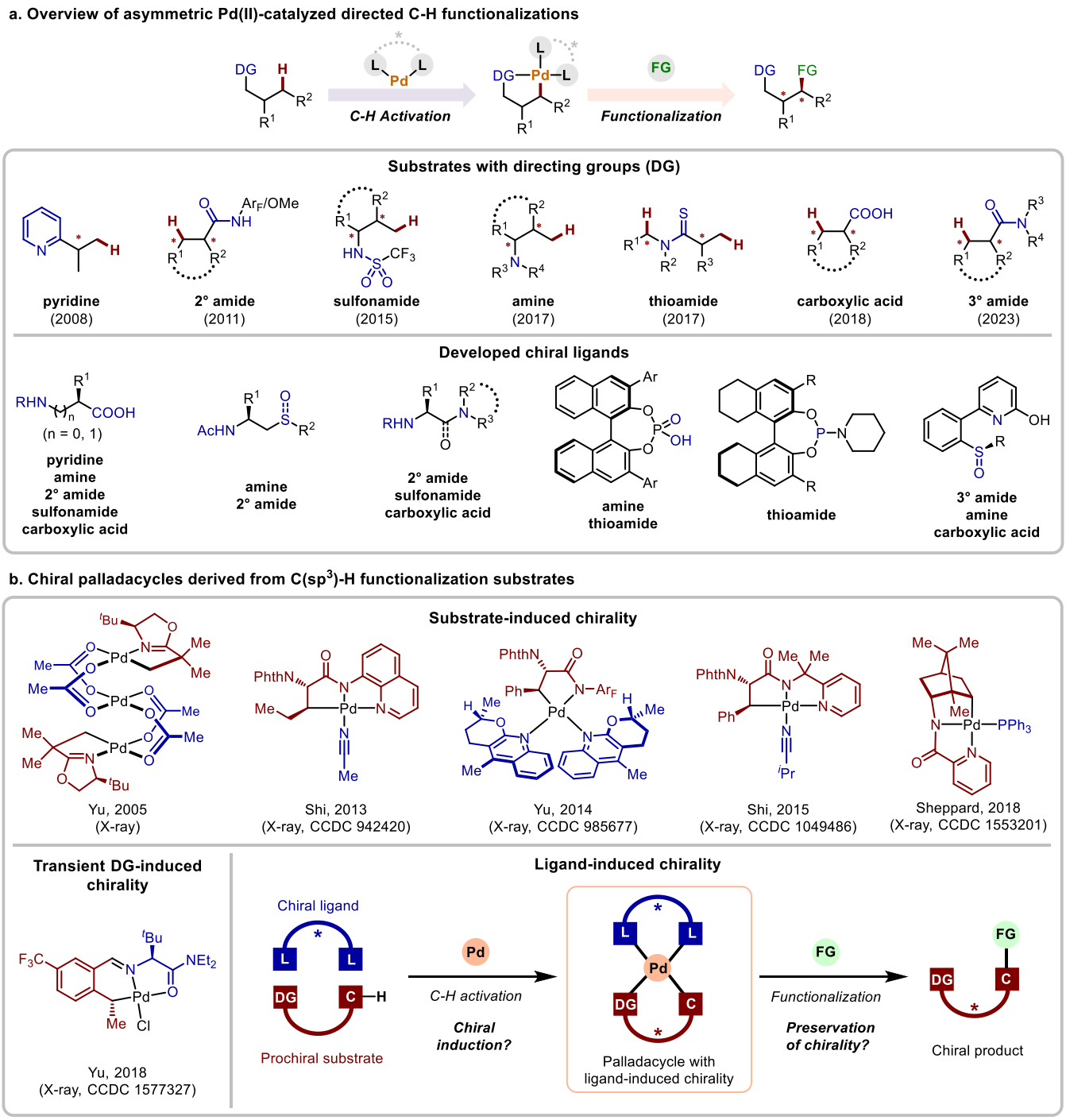


Figure 1. Overview of the Pd(II)-catalyzed native functional group-directed enantioselective C(sp^3)-H Functionalization.

In the Pd-catalyzed enantioselective C-H functionalization, elucidating the reaction mechanism is crucial for the development of efficient and selective catalytic systems through rational design.[3a] A key aspect in mechanistic studies of such reactions is the isolation, characterization, and reactivity elucidation of the proposed chiral palladacycle intermediates. However, although a number of palladacycles have been reported in the reaction between palladium(II) complexes and different types of C(sp^3)-H substrates, only a few of them are chiral (Figure 1b).[13] In most cases, the palladacycles were formed with substrate-induced chirality,[14] and only one example reported the formation of a chiral palladacycle induced by a chiral transient directing group.[15] The case mostly relevant to the asymmetric catalytic C(sp^3)-

H activation, i.e., formation of a palladacycle with ligand-induced chirality, has not yet been exemplified. Although the ligand-enabled asymmetric Pd(II)-catalyzed C(sp^3)-H functionalization reactions have gained significant advances, the isolation and characterization of related chiral palladacycles is still challenging. Key mechanistic questions with regard to the palladacycle, including the chiral induction in the palladacycle formation and the preservation of chirality in the functionalization step of palladacycle, remain to be answered by experimental efforts.

Previously, we accomplished the enantioselective C-H functionalization of aliphatic tertiary amides[11] and primary amines[12] using the Pd(II)/SOHP catalytic system, which implied that the chiral SOHP ligand has a good potential for inducing chirality in palladacycle formation. Due to the observation that SOHP ligands exhibited good coordination ability to Pd(II), we hoped to attempt the isolation of palladacycles with ligand-induced chirality in the Pd(II)/SOHP system. In this work, we successfully isolated SOHP-derived palladacycle intermediates while studying the enantioselective β-C(sp^3)–H arylation of carboxylic acids, and performed the stoichiometric functionalization reactions of the palladacycles with ligand-induced chirality. The first isolation and characterization of these chiral palladacycles allowed for the elucidation of the role of chiral SOHP ligands in different stages of the reaction, and offered direct evidence for the enantioselectivity-determining step in this asymmetric C-H functionalization. This study provides valuable mechanistic information for the Pd(II)-catalyzed directed C(sp^3)-H activation, which is useful for comprehensive understanding and rational design of related reactions.

Results and Discussion

Key mechanistic questions related to chiral palladacycles. In many Pd(II)-catalyzed ligand-enabled asymmetric C(sp^3)-H functionalization reaction, the whole transformation can be divided into two main stages: the C-H activation stage, where the activation of C-H bonds occurs to form a palladacycle intermediate, and the functionalization stage, where the palladacycle reacts with a reagent to introduce the desired functional group (Figure 2a). In this line, two general mechanistic questions arise: (1) What role does the ligand play in these two stages? and (2) Which stage determines the enantioselectivity of the reaction?

In principle, ligand may influence both the C-H activation and the functionalization stages, and either stage could be enantioselectivity-determining depending on the reaction kinetics. In the C-H activation stage, either of the two enantiotopic C-H bonds can be cleaved by the chiral Pd catalyst, giving rise to a pair of diastereomeric palladacycle intermediates **Int-I** and **Int-II**. If the interconversion of these diastereomers is slower than the functionalization step (i.e., k_1, $k_{-1} \ll k_S'$, k_R'), retention of stereochemistry would be expected in the subsequent functionalization step, and the C-H activation step serves as the enantioselectivity-determining step (Mode A). On the other hand, if the interconversion between **Int-I** and **Int-II** is more rapid than the functionalization step (i.e., k_1, $k_{-1} \gg k_S'$, k_R'), the functionalization step becomes the enantioselectivity-determining (Mode B).[16]

In many prior studies, the C-H activation step was assumed to be the enantioselectivity-determining step. Actually, although this step is the enantioinduction step that forges the chiral element of the product, its role as the enantioselectivity-determining step is not unconditional. Previous reports showed that, in C(sp^2)-H and C(sp^3)-H functionalization reactions, the functionalization step could serve as the regio- and site-selectivity determining step when fast and reversible C-H activation process took place.[10,17] For the Pd(II)-catalyzed asymmetric C-H functionalization reactions, however, to date there lacks an explicit experimental study aiming at identifying the role of the ligand in the two stages and distinguishing the mode of enantiocontrol. These mechanistic questions could be answered if a palladacycle incorporating both the ligand and the substrate is available. In the present study, chiral palladacycle derived from SOHP ligand and aliphatic carboxylic acid was obtained, which provided mechanistic insights into this type of reaction (Figure 2b).

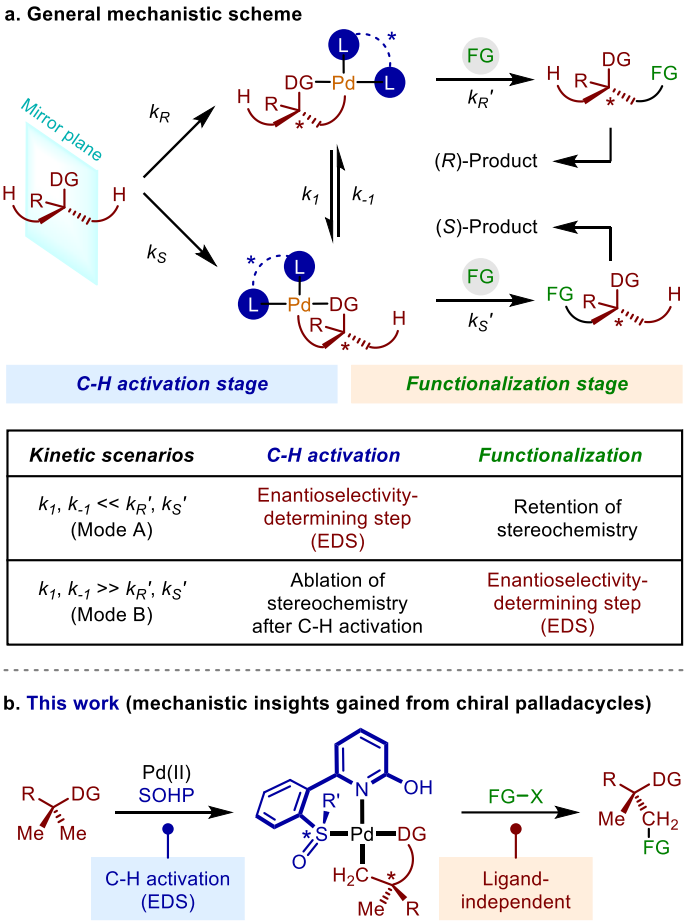


Figure 2. Mode of enantiocontrol in Pd(II)-catalyzed C(sp^3)-H functionalization. DG = directing group, FG = functional group.

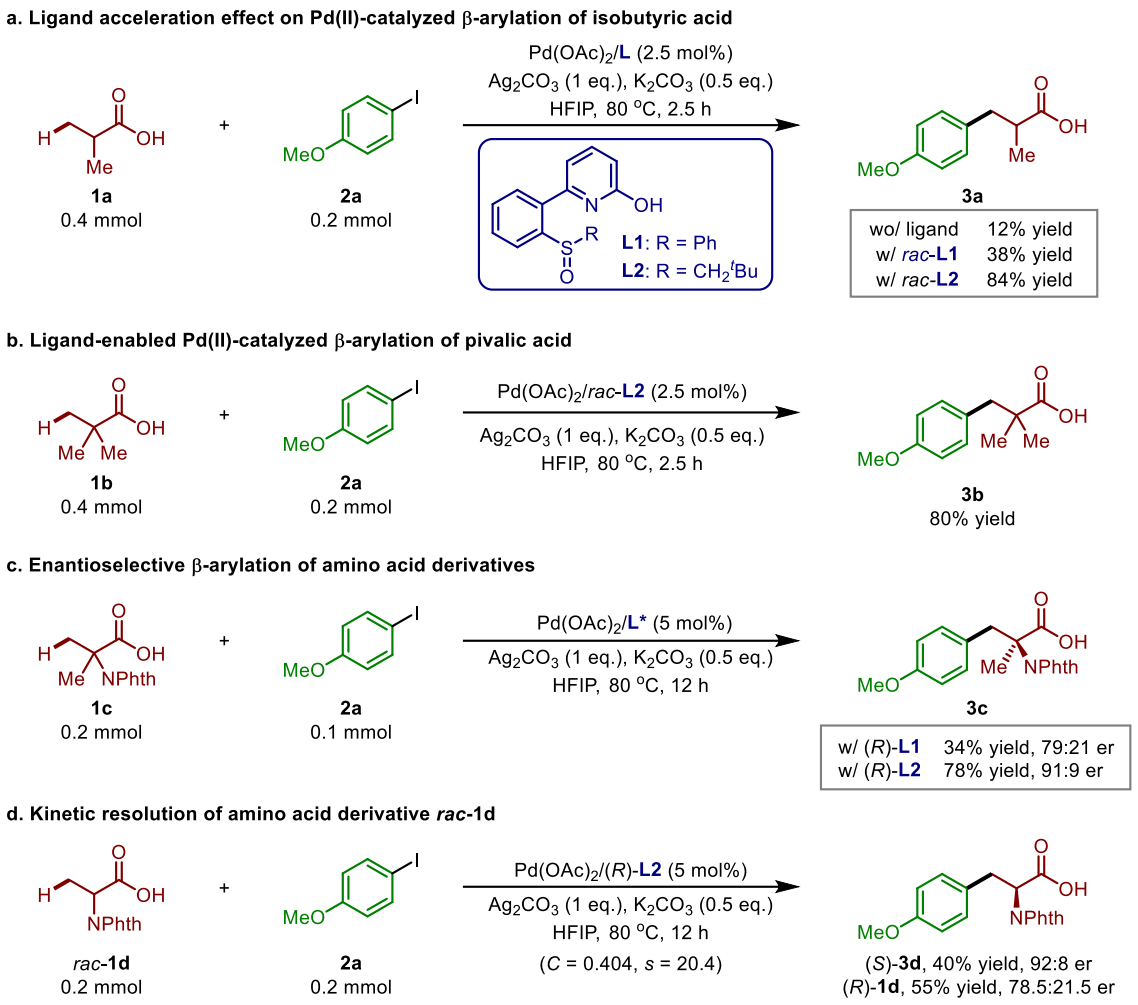
Ligand-enabled C-H arylation of aliphatic carboxylic acids. Among various functional groups that could serve as practical DGs, we selected aliphatic carboxylic acid as the substrate of interest. We reasoned that, the ability of carboxylate to generate relatively stable neutral palladacycle intermediate[13b] may render aliphatic carboxylic acids the substrate of choice for obtaining the desired ligand-associated palladacycle intermediate.

Before our study, there were several reports on the Pd(II)-catalyzed C(sp^3)-H functionalization of aliphatic carboxylic acids. Zhao and coworkers reported a β-C(sp^3)-H arylation reaction with MPAA as ligands in 2017.[18] The Yu group made significant contributions by pioneering enantioselective carboxylic acid-directed C(sp^3)-H functionalization reactions of cyclopropane/cyclobutanecarboxylic acids and 2-aminoisobutyric acids, employing MPAA and mono-protected aminoethyl amine (MPAAM) ligands.[9] However, the key palladacycle intermediate was not isolated in these studies. Our study was aimed at evaluating the suitability of the SOHP ligands for this type of transformation and endeavoring to obtain SOHP-ligated palladacycle intermediates, specifically those with ligand-induced chirality.

We commenced our study with confirming the ligand acceleration effect of SOHP ligands in Pd(II)-catalyzed β-C(sp^3)-H arylation of carboxylic acids. The standard conditions established for Pd(II)-catalyzed C(sp^3)-H functionalization reactions of carboxylic acids,[9,18-19] $Pd(OAc)_2$ with ligand, silver salt, and base in hexafluoroisopropanol (HFIP) solvent, were utilized. We found that, for the β-arylation reaction of isobutyric acid **1a**, both ligands **L1** and **L2** exhibited acceleration effect, and **L2** was found to be superior (Scheme 1a). The results of several other SOHP ligands were listed in Scheme S1. Ligand **L2** was also suitable for catalyzing β-arylation of pivalic acid **1b**, despite the formation of a more sterically congested product **3b** (Scheme 1b). To test whether or not these SOHP ligands were competent for asymmetric C-H functionalization, we employed 2-aminoisobutyric acid derivative **1c** as the substrate and enantiomerically enriched

ligands **L1** and **L2**. To our delight, although the Pd(II)/(*R*)-**L1** catalytic system gave lower yield of the product **3c** with a low enantioselectivity, (*R*)-**L2** performed much better, affording **3c** with a good yield and enantioselectivity (Scheme 1c). Notably, the Pd(II)/(*R*)-**L2** catalytic system achieved the same level of enantioselectivity in the arylation of substrate **1c** as the Pd(II)/MPAAM system developed by the Yu group.[9a] Furthermore, we were pleased to find that the kinetic resolution of *rac*-**1d** catalyzed by the Pd(II)/(*R*)-**L2** system resulted in a decent yield and enantioselectivity, with calculated *s*-factor of 20.4 (Scheme 1d). These experimental findings highlighted the competency of chiral SOHP ligands for promoting enantioselective C-H activation, which are ideal ligands for studying the related palladacycle intermediates.

Scheme 1. SOHP-Enabled Pd-Catalyzed β-C(sp^3)-H Arylation of Carboxylic Acids

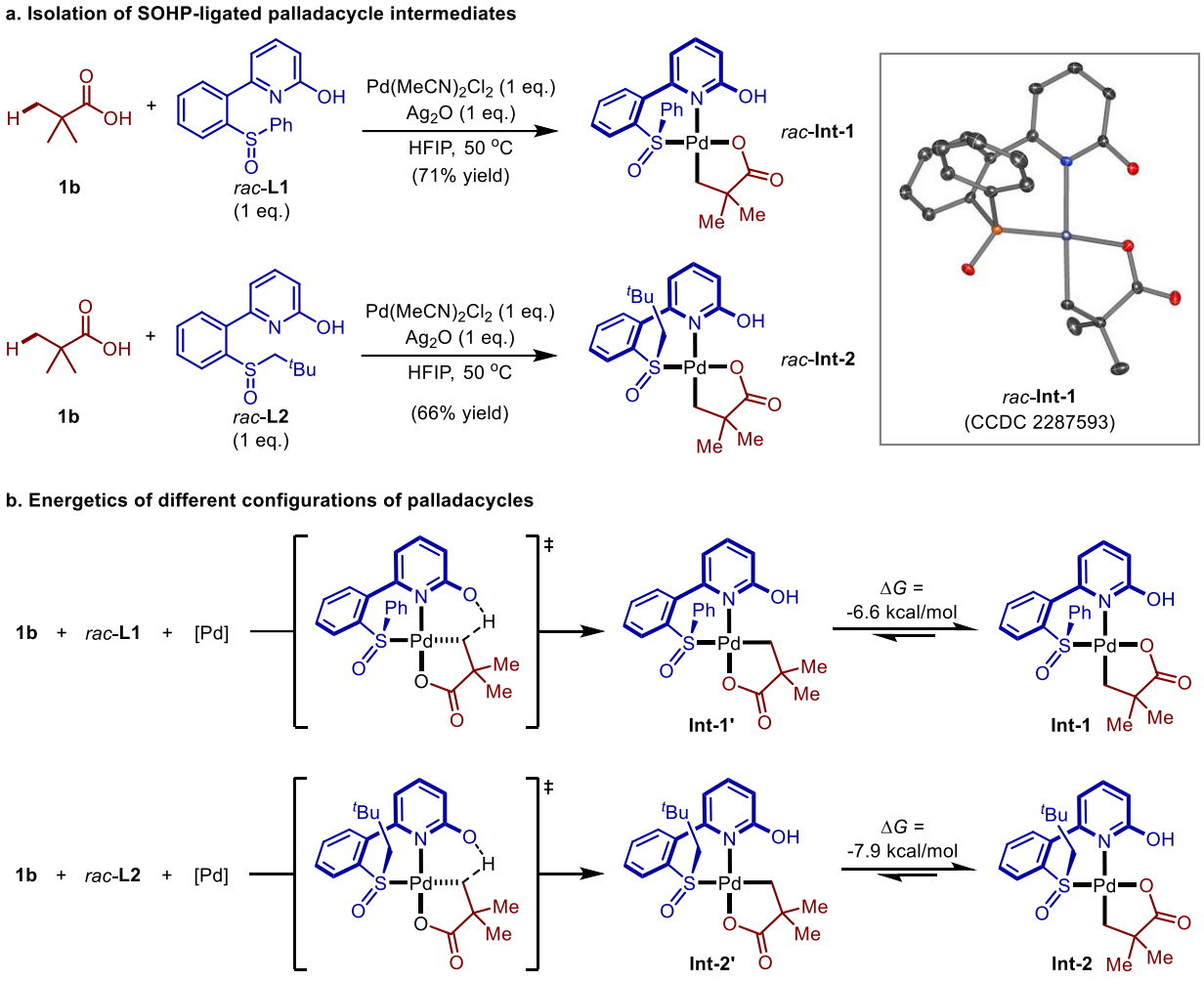


Isolation of SOHP-ligated palladacycle intermediates. We initially examined the possibility of obtaining the palladacycle intermediate derived from pivalic acid **1b** in the presence of SOHP ligands. To our delight, reactions with stoichiometric amounts of Pd(II) and ligands **L1** and **L2** under synthetically-relevant conditions yielded palladacycles **Int-1** and **Int-2** in good yields (Scheme 2a). Intriguingly, these complexes were isolated through column chromatography, affirming their chemical stability. These intermediates comprise an N,S-ligated SOHP ligand and a pivalic acid-derived palladacycle with a C(β)-Pd bond. The structure of palladacycle **Int-1**, derived from phenyl-substituted SOHP ligand **L1**, was determined by single-crystal X-ray diffraction (XRD) analysis.

Notably, the structure of the palladacycle differed from the proposed structure directly generated through the ligand-assisted concerted metalation-deprotonation (CMD) process. As depicted in Scheme 2b, the CMD mechanism would lead to palladacycles **Int-1'** and **Int-2'**, where the β-carbon of the carboxylic acid should be *trans* to the sulfoxide ligand. We

reasoned that this observation did not contradict the CMD mechanism for two reasons. First, DFT calculation indicated that palladacycles **Int-1** and **Int-2** were thermodynamically more stable than **Int-1'** and **Int-2'**, possibly due to the hydrogen bonding interaction between the O atoms of hydroxypyridine and carboxylate moieties in the former. Second, ligand dissociation/association of this type of intermediate could easily occur, as demonstrated by a ligand exchange experiment (*vide infra*). Considering these factors, it is reasonable to deduce that the SOHP-ligated palladacycle intermediates tend to adopt the thermodynamically more favorable configuration (**Int-1** and **Int-2**) after formation, through facile ligand dissociation and re-association. Therefore, the palladacycle intermediate we isolated was, in fact, the thermodynamically more stable configuration.

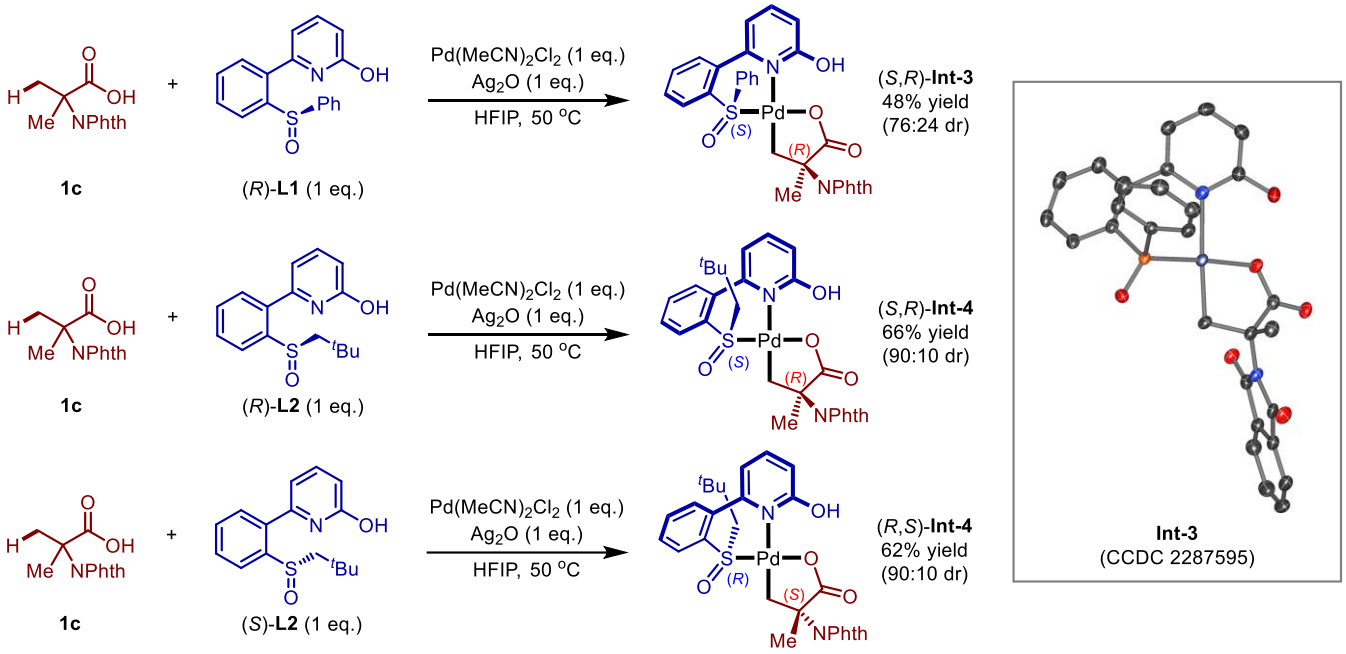
Scheme 2. Preparation of Key Palladacycle Intermediates



Motivated by the successful synthesis of SOHP-ligated palladacycles of carboxylic acid **1b**, we proceeded to investigate the formation of palladacycles with ligand-induced chirality. To achieve this, we utilized 2-aminoisobutyric acid derivative **1c** and enantioenriched SOHP ligands **L1** and **L2**. Under identical conditions, palladacycles **Int-3** and **In-4** were isolated in satisfactory yields as diastereomeric mixtures (Scheme 3). When employing ligand (*R*)-**L1**, palladacycle (*S*,*R*)-**Int-3** was obtained in a moderate diastereomeric ratio (76:24), and the stereochemical assignment was confirmed by XRD analysis of the minor diastereomer. Subsequently, using ligand (*R*)-**L2**, palladacycle (*S*,*R*)-**Int-4** was formed with an improved diastereomeric ratio (90:10). A parallel experiment with (*S*)-**L2** yielded the enantiomeric palladacycle (*S*,*R*)-**Int-4** with a similar yield and diastereoselectivity. The successful isolation and characterization of these chiral palladacycles with ligand-induced chirality represent a remarkable advance in Pd(II)-catalyzed C-H functionalization.

Notably, the diastereomeric ratios corresponded with the enantiomeric ratios of catalytic C-H functionalization product **3c** using **L1** and **L2** as ligands (Scheme 1c), implying the crucial role of the chiral palladacycle in enantiocontrol.

Scheme 3. Preparation of Chiral Palladacycle Intermediates from Acid **1c**

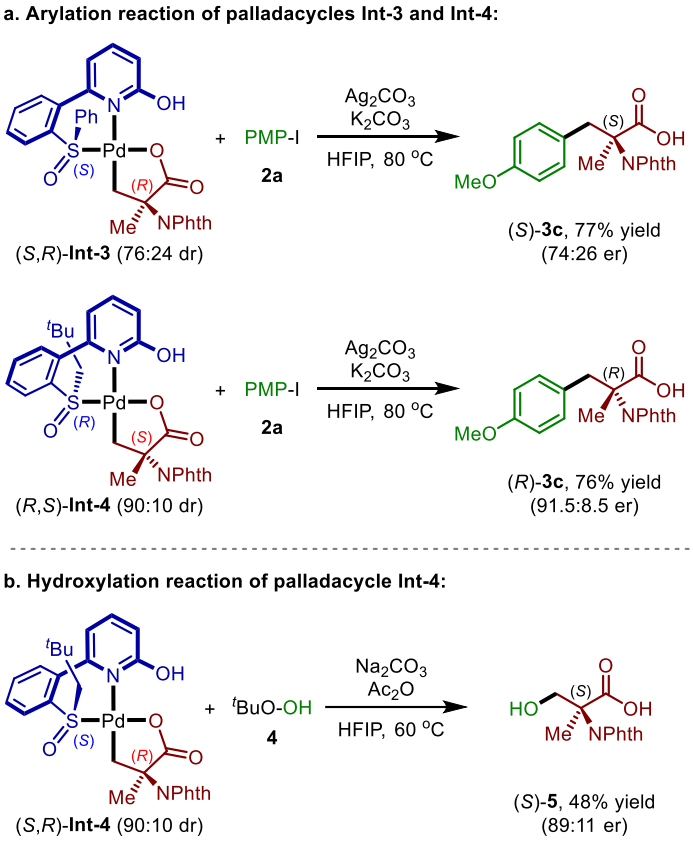


Stoichiometric functionalization reaction of palladacycle intermediates. The isolation and identification of chiral palladacycle intermediates enabled us to elucidate the stereochemical process of the Pd(II)-catalyzed C-H functionalization. If the chiral palladacycle proceeds to the final product with unchanged stereoselectivity, it indicates an irreversible C-H activation step, with the functionalization step simply inhering the stereochemistry of the palladacycle intermediate (Figure 2a, mode A). Conversely, if the chiral palladacycle affords the final product with a significant change in stereoselectivity, it signifies a reversible C-H activation step and a stereoselectivity-determining functionalization step (Figure 2a, mode B).

We performed stoichiometric arylation reactions of **Int-3** and **Int-4** under the reaction conditions identical to the catalytic C(sp^3)-H arylation reaction of **1c** (Scheme 4a). It was found that, (*S*,*R*)-**Int-3** (76:24 dr) was converted into arylation product (*S*)-**3c** with a good yield and moderate enantiomeric ratio (74:26 er), while (*R*,*S*)-**Int-4** (90:10 dr) led to (*R*)-**3c** with a good yield and good enantiomeric ratio (91.5:8.5 er). The diastereomeric ratio of the SOHP-ligated palladacycle and the enantiomeric ratio of the arylation product aligned within the experimental error, indicating that the functionalization step occurred with nearly complete retention of stereochemistry.

Furthermore, we expanded our investigation to the reactivity of the chiral palladacycle beyond arylation (Scheme 4b). It was found that, when subjected to the C(sp^3)-H hydroxylation reaction conditions established by the Yu group,[20] palladacycle (*S*,*R*)-**Int-4** (90:10 dr) was converted to the hydroxylation product (*S*)-**5** with a moderate yield and consistent stereoselectivity (89:11 er). This finding demonstrated that the preservation of stereochemistry in the functionalization of chiral palladacycles extends beyond arylation and may represent a general phenomenon across various reaction types.

Scheme 4. Transformation of Chiral Palladacycle Intermediate

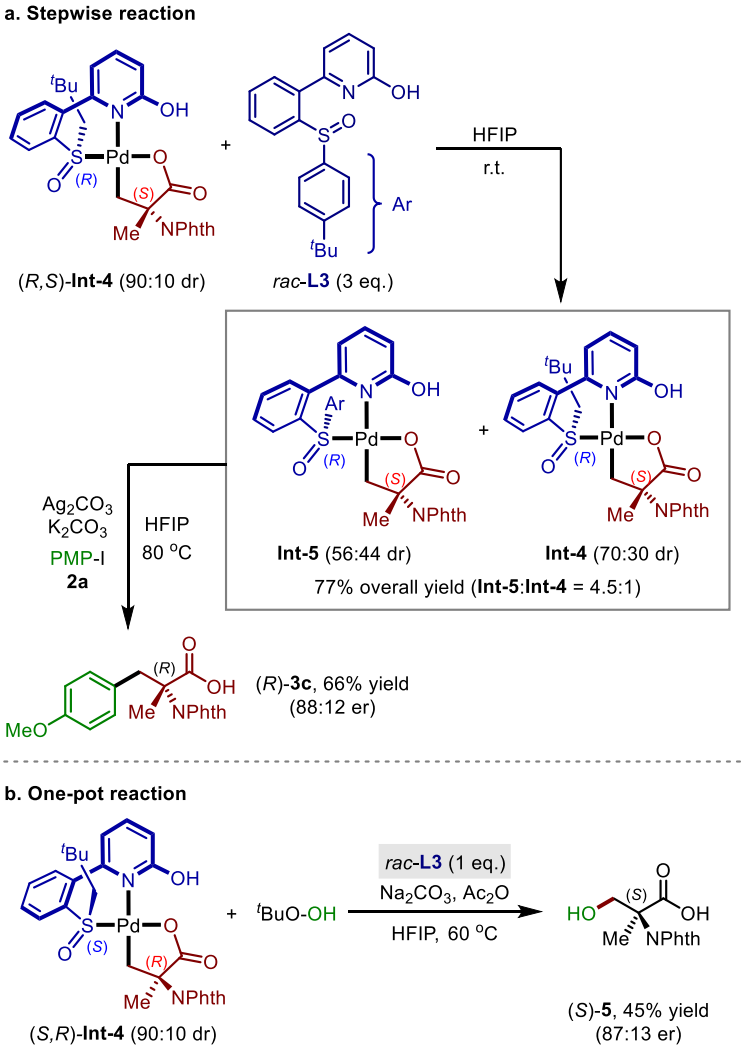


In order to elucidate the role of the chiral SOHP ligand in the functionalization stage, we conducted ligand exchange studies on chiral palladacycles. Our investigations that when (*R*,*S*)-**Int-4** (90:10 dr) was combined with 3 equivalents of *rac*-**L3** in HFIP, rapid ligand exchange took place at room temperature, resulting in the formation of a mixture of palladacycles, as confirmed by ^{1}H NMR analysis. This observation confirmed the facile ligand coordination-dissociation equilibrium on the palladacycle, thus supporting the suggested configuration change following the C-H palladation step (Scheme 2b).

Upon work-up of this ligand exchange mixture, a mixture of **Int-5** (56:44 dr) and **Int-3** (70:30 dr) in a 4.5:1 ratio was obtained, indicating the replacement of approximately 80% of (*R*)-**L1** with **L3**. Since a racemic ligand **L3** was used, the equilibrium mixture led to a shift in the diastereomeric ratios of the resulting palladacycle. Subsequent exposure of this complex mixture of palladacycles to stoichiometric arylation conditions yielded product (*R*)-**3c** with an 88:12 er, consistent with the arylation product directly obtained from (*R*,*S*)-**Int-4**.

Furthermore, a stoichiometric hydroxylation reaction of (*S*,*R*)-**Int-4** was carried out with the addition of equal molar of *rac*-**L3**, resulting in the generation of compound (*S*)-**5** with an 87:13 er (Scheme 5b), which was identical to the reaction outcome without **L3** (Scheme 4b). These findings showed that the chirality of ligand does not influence the stereochemical process of the functionalization stage, implying that the C-H activation step is irreversible and enantioselectivity-determining.

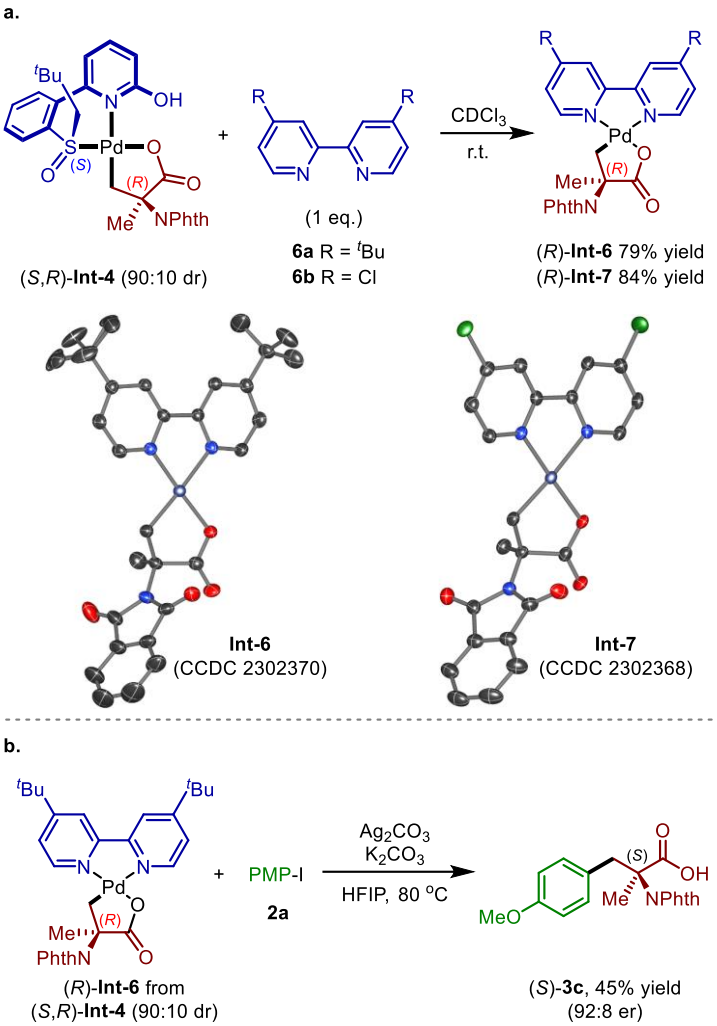
Scheme 5. Ligand Exchange Experiments with Racemic SOHP Ligand **L3**



A remaining question is whether or not the chiral ligand played a crucial role in the functionalization stage. A previous study by Yu and Houk on the methylene C(sp^3)-H bond arylation reactions of aliphatic carboxylic amides, facilitated by the Pd(II)/acetyl-protected aminoethyl quinoline (APAQ) catalytic system,[21] inferred the dissociation of the chiral ligand before the arylation step based on DFT calculations. However, to date there lacks experimental evidence to support this proposed mechanism. The palladacycle intermediate with ligand-induced chirality presents an excellent opportunity to investigate the function of the ligand during functionalization. To address this, we conducted ligand exchange experiments on (*S*,*R*)-**Int-4** with bipyridines, which are *N*,*N*-ligands without a chiral center (Scheme 6a). Treatment of (*S*,*R*)-**Int-4** with equimolar amounts of bipyridine **6a** or **6b** in $CDCl_3$ resulted in the complete displacement of ligand **L2** by the bipyridine ligand (quantitative NMR yield), yielding (*R*)-**Int-6** or (*R*)-**Int-7** in good yields, respectively.

This exchange reaction converted the diastereomeric palladacycle to enantiomeric palladacycle. Subsequently, we carried out the arylation reaction of (*R*)-**Int-6** under established conditions (Scheme 6b). The reaction produced (*S*)-**3c** in a moderate yield with an almost identical enantiomeric ratio (92:8). This result unequivocally demonstrates a ligand-independent arylation step, indicating that enantioselectivity in the arylation product directly originates from the palladacycle intermediate. The experimental finding also supported he previous mechanistic proposal that the chiral ligand is not an essential component for the functionalization stage.

Scheme 6. Ligand Exchange Experiments with 2,2'-Bipyridines



DFT calculations. In order to understand the stereochemistry of the palladacycle formation stage, we performed a DFT computational study on the reaction between **1c**, Pd(II), and (*R*)-**L2**. Because various possible Pd(II) complexes could be formed in the presence of substrate **1c** and ligand **L1**, we first calculated the energetics of various forms of the complex to search for a zero point species (Figure 3). The trimeric $Pd_3(OAc)_6$ is more stable than monomeric $Pd(OAc)_2$, and the exchange of the acetate in $Pd(OAc)_2$ with the anion of **1c** forms **Int-8** and **Int-9** without significant change in free energy. Coordination of (*R*)-**L1** with $Pd(OAc)_2$ was energetically favorable to form **Int-10**. **Int-10** could undergo acetate departure or ligand exchange with **1c** to form **Int-11** to **Int-15**, respectively. Upon analyzing the energetics of these complexes, **Int-14** with two substrate carboxylate ligands was found to be the most stable species and was identified as the zero-point of the potential energy surface.

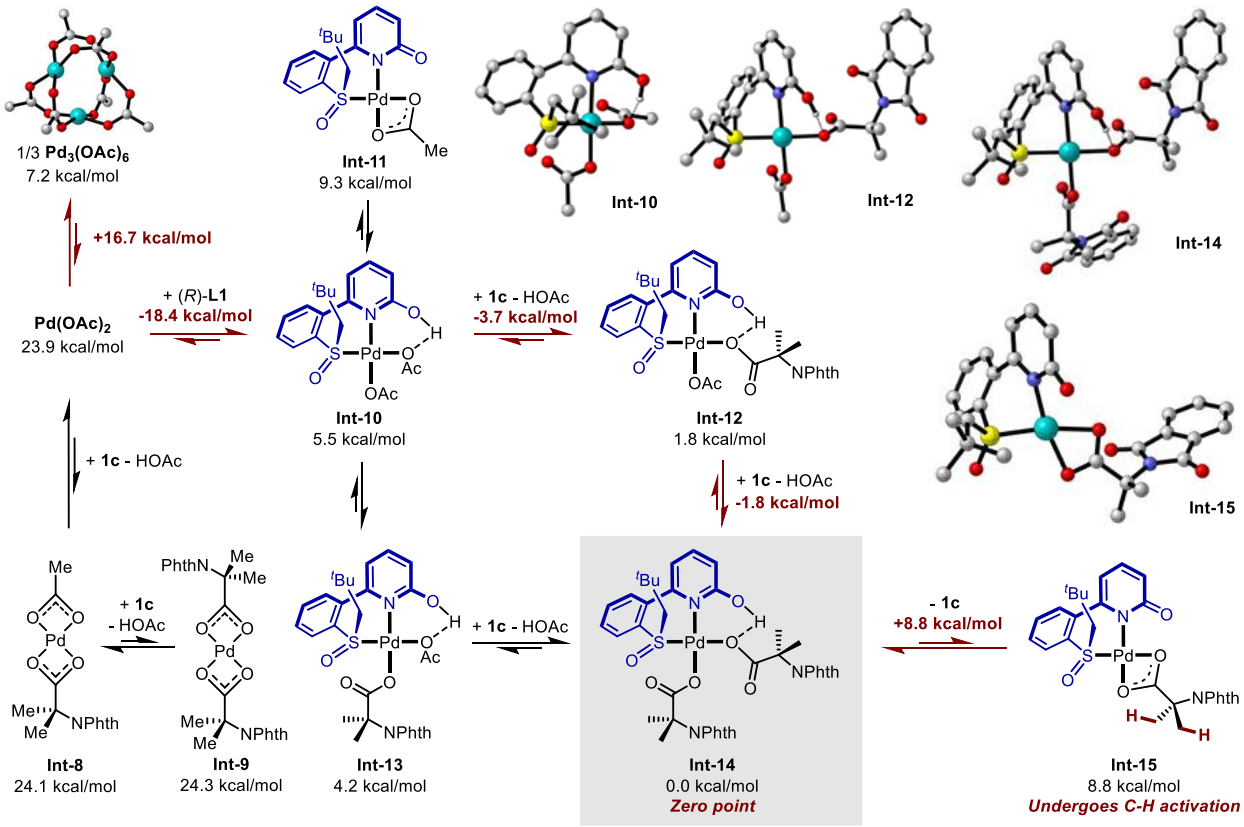


Figure 3. Energetics of the ligand/substrate-ligated Pd(II) complexes. The 3D structures were visualized by CYLview.[22]

Subsequently, the SOHP-ligand promoted C-H activation step was modeled by DFT calculation to rationalize the observed stereoselectivity. The reaction starts from **Int-14** and proceed via **Int-15**, where one carboxylic acid **1c** is dissociated to secure a vacant coordination site for the CMD process. Since the aid of HFIP in facilitating C-H activation has been generally acknowledged in transition metal-catalyzed C-H functionalization,[23] the explicit solvation model is applied. Possible C-H palladation transition states (TSs) arising from **Int-15**, which were associated with different numbers of HFIP molecule by hydrogen bonding, were located and carefully analyzed (Figure 4a).

It was found that, with ligand (*R*)-**L2**, the transition states **TS-1*R*** corresponds to the formation of the (*S*,*R*)-palladacycle are generally favored over **TS-1*R*** in terms of Gibbs free energy, consistent with the experimentally observed stereoselectivity. In particular, the diastereomeric C-H palladation TSs with one HFIP molecule binding to the carboxylate carbonyl group, **TS-1*S*-b** and **TS-1*R*-b**, were figured out as the most stable ones in terms of Gibbs free energy. The structure **TS-1*R*-b** ($\Delta G^{\ddagger}$ = 22.1 kcal/mol) was more favorable than **TS-1*S*-b** ($\Delta G^{\ddagger}$ = 22.7 kcal/mol) by 0.6 kcal/mol. Analysis of their 3D model revealed that the steric repulsion between the *tert*-amyl group and the bulky phthylamide moiety in **TS-1*S*-b** made this TS less stable than **TS-1*R*-b**, where the same interaction does not exist (Figure 4b).

For the TSs without the association of HFIP molecule (**TS-1*S*-a** and **TS-1*R*-a**) and the TSs with one HFIP molecule binding to the sulfoxide moiety (**TS-1*S*-c** and **TS-1*R*-c**) the Gibbs free energies were found to be higher ($\Delta G^{\ddagger}$ > 24 kcal/mol), and they were less likely to make significant contribution to the stereoselectivity. For the TSs with two HFIP molecule associated with both the carboxylate carbonyl and the sulfoxide moiety (**TS-1*S*-d** and **TS-1*R*-d**), the (*R*)-pathway is favored over the (*S*)-pathway by 1.3 kcal/mol, and the free energies were only slightly higher than those of **TS-1*S*-b** and **TS-1*R*-b**, which also contributed to the stereoselectivity, especially given the overestimated entropy in TSs consist of multi components.

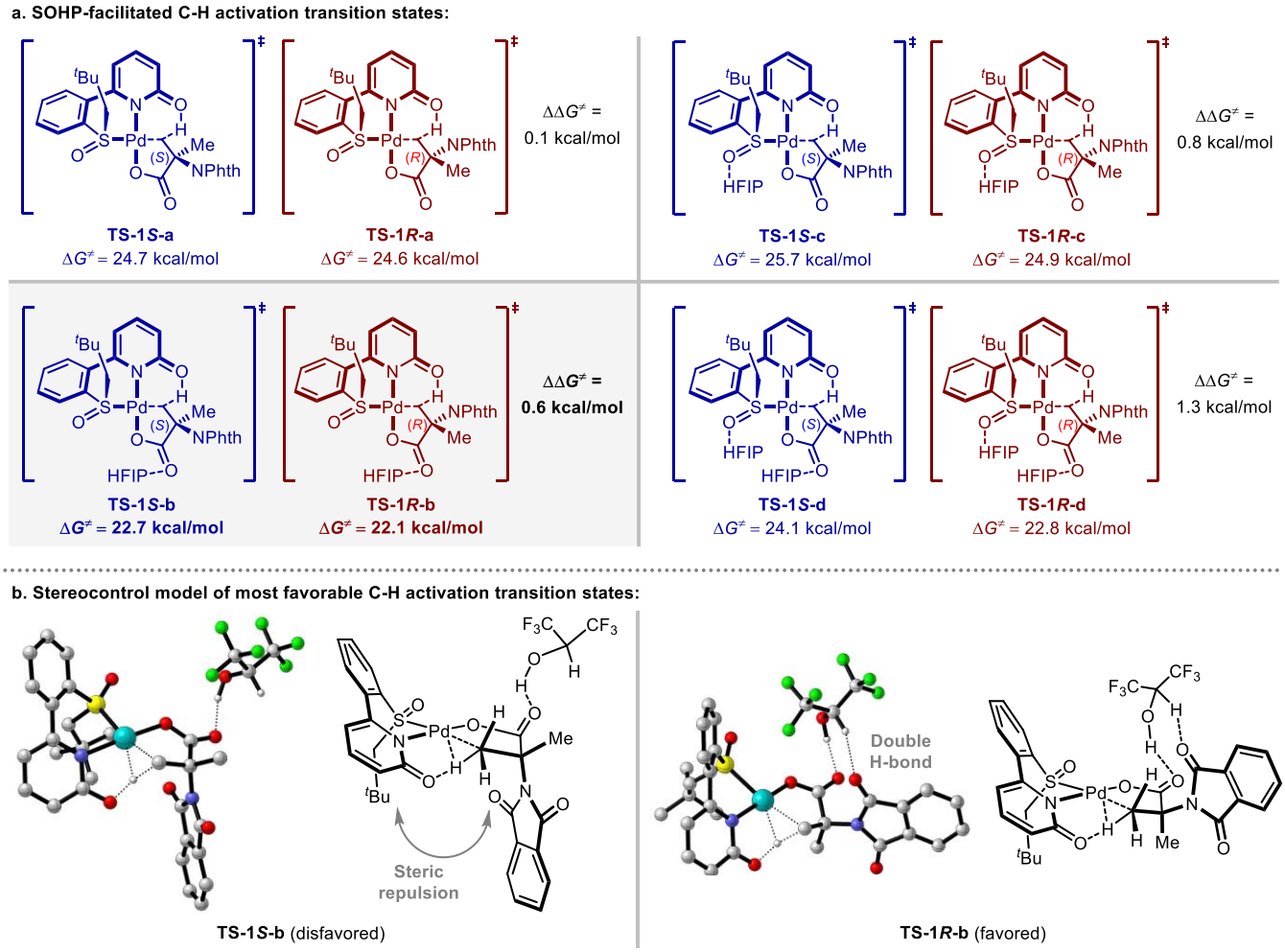


Figure 4. Analysis of the C-H activation transition states.

Based on the above analysis, the potential energy surface of C-H activation of **1c** is constructed, which serves as a reasonable model for rationalizing the stereoselectivity (Figure 5). The C-H activation commences with **Int-14**, which eliminates one **1c** molecule to generate **Int-15**. Starting from this bifurcating species, two TSs **TS-1*S*-b** and **TS-1*R*-b** evolve with one HFIP molecule binding to the carboxylate carbonyl group, exhibiting (*R*)-selectivity. The C-H activation TSs leads to the formation of diastereomeric palladacycle intermediates **Int-16*S*** and **Int-16*R***, which undergo rapid configuration change to form **Int-3*S*** and **Int-3*R*** as the key intermediate for the functionalization step.

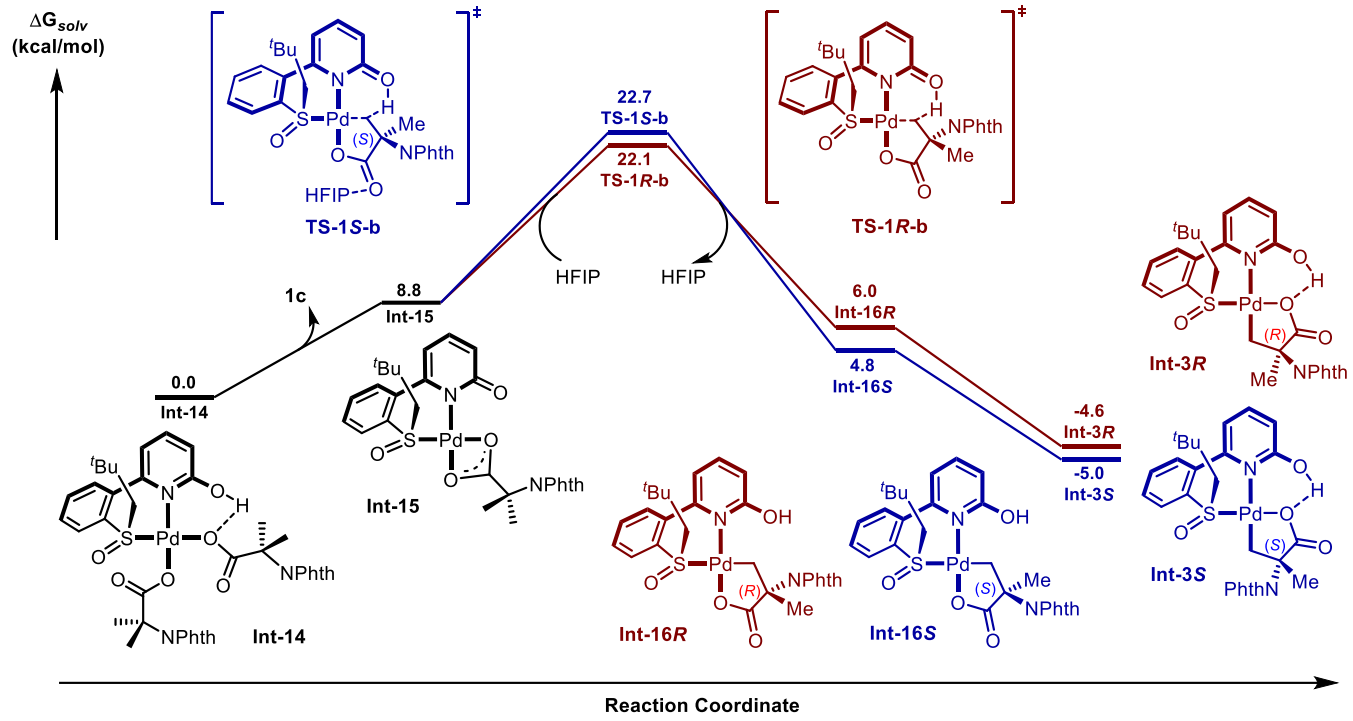


Figure 5. The potential energy surface of the C-H activation of **1c**.

Conclusion

In summary, we have isolated the key palladacycle intermediates involved in the enantioselective β-C(sp^3)-H arylation reaction of carboxylic acids promoted by the Pd(II)/SOHP catalytic system. These palladacycles, with ligand-induced chirality, offered a valuable opportunity to elucidate the stereochemical process and the ligand effect in the Pd(II)-catalyzed C(sp^3)-H functionalization. The diastereoselective formation of the palladacycle in the presence of chiral SOHP ligands, as well as the preservation of chirality during the transformation of palladacycles, enabled us to identify the C-H palladation step as the enantioselectivity-determining step while confirming the ligand-independent nature of the functionalization step. This study highlighted the value of palladacycle intermediate chemistry in providing conclusive experimental evidences to address the mechanistic concerns regarding the ligand effect in Pd(II)-catalyzed asymmetric C(sp^3)-H functionalization.

Acknowledgements

Financial support was provided by the National Natural Science Foundation of China (Grant Nos. 21933007, 21822304). The technological platform of CBMS is acknowledged for providing instrumental and computational resources. The members of Ming-Tian Zhang group are acknowledged for XRD analysis.

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