The Stereochemistry of the Reactions between Palladacycle Complexes and Primary Alkyl Iodides

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Abstract: As an important elementary step in organometallic chemistry, the alkylation reaction of palladacycle complexes and alkyl halides has attracted much attention in recent years due to their presence as key step in palladium catalyzed C-H alkylation reactions. In principle, several alkylation mechanisms, such as the stereoinvertive S_N2-type mechanism and the stereoretentive oxidative addition (OA) mechanism can be operated, and mechanistic insights can be obtained from the stereochemical outcomes of these alkylation reactions. Previous stereochemical investigations on the alkylation reaction of palladacycle complexes mainly focused on the use of chiral secondary alkyl halides as stereochemical probes, leaving more synthetically relevant primary alkyl iodides untouched. In this work, deuterium-labeled primary alkyl iodides were selected as a stereochemical probe, and their reaction with C,C- and C,X-type palladacycle complexes, namely Catellani-type palladacycle intermediates and directing group (DG)-coordinated palladacycle complexes, were investigated both experimentally and computationally to elucidate the alkylation mechanism. We found that, the C,C-ligated palladacycle intermediates undergo alkylation through the S_N2-Pd mechanism, while the C,X-ligated 8-aminoquinolin-derived palladacycle complex favors an OA mechanism. In addition, the 2-phenylpyridine-derived C,X-type palladacycle dimer complex was found to react through the S_N2-Pd mechanism due to its stable dimer structure and the d^8-d^8 interaction between two palladium atoms.

Introduction

A deep mechanistic understanding of the elementary steps can facilitate the rational design of new catalytic systems. An important elementary step in organometallic chemistry is the reaction between organometallics and alkyl electrophiles to form alkyl-metal complexes, which function as active species in various transition metal-catalyzed alkylation reactions.[1] Specifically, the reaction between palladacycle complexes and alkyl halides has gained much attention in recent years due to its presence as key step in the palladium catalyzed C-H alkylation reactions, with the Catellani reactions (Figure 1a)[2] and directed C-H alkylation reactions (Figure 1b)[3] being the most representative reactions of this type.

Mechanism of the reaction between palladacycle complexes and alkyl halide electrophiles has been of interest to organometallic chemists for long,[4] as mechanistic insights from these reactions can both deepen our fundamental understanding on palladacycle intermediates and guide future development of new synthetic methodologies. Such mechanistic insights can be obtained from the stereochemical outcome of these alkylation reactions, and previous stereochemical investigations mainly focused on the reaction of chiral secondary alkyl halides with isolated or in-situ formed palladacycle complexes. For C,C-ligated palladacycles produced in the Catellani-type reaction, electrophile-dependent stereochemical outcomes were observed (Figure 1a). In 2007, the Lautens group reported a Catellani reaction that utilized chiral secondary alkyl iodides or bromides as intramolecular electrophiles, and the corresponding alkylation

product was formed through a stereoinvertive pathway.[5] Chiral aziridines, which can be viewed as an analogue of secondary alkyl halide, have also been employed as alkylation reagents in the Catellani-type C-H alkylation reactions, in which the alkylation product was also formed through a stereoinvertive pathway.[6] Interestingly, when chiral glycosyl chlorides were introduced as electrophiles in a similar Catellani-type C-H glycosylation reaction, stereodivergent alkylation products were observed: although selective formation of stereoretentive glycosylation product was observed in most cases, formation of ca. 1:1 α/β anomeric mixture was observed when Bn protected α-glucosyl chloride was utilized as the glycosylation reagent.[7]

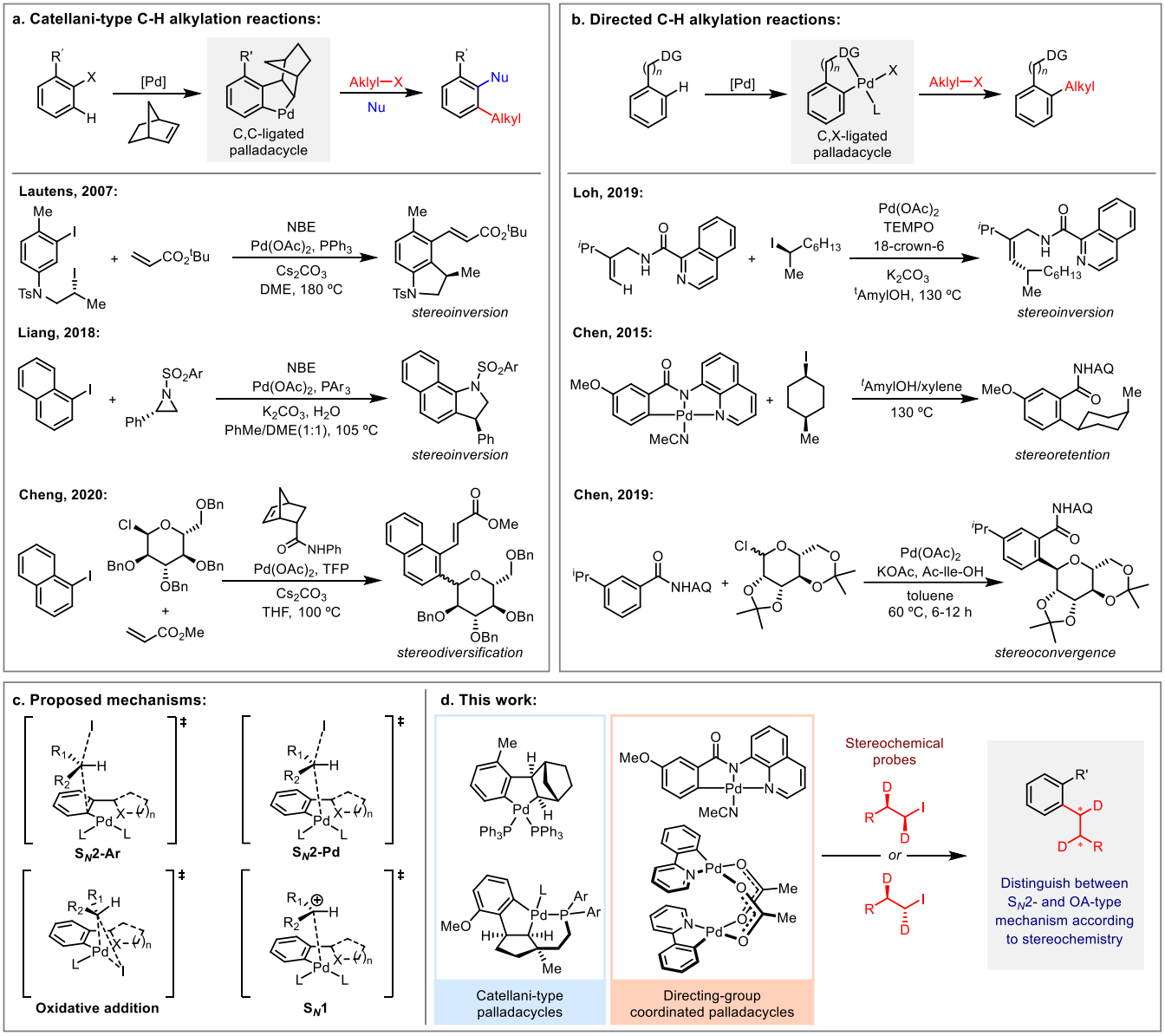


Figure 1. Study on the mechanism of the alkylation of palladacycle intermediates.

Similar stereochemical investigations have also been carried out in directed C-H alkylation reactions, which involved C,X-ligated palladacycle complexes as the key intermediates (Figure 1b). In 2019, a palladium catalyzed, isoquinoline directed alkenyl C-H alkylation reaction was reported by Loh and coworkers, in which the alkylation product was formed through stereoinvertive pathway.[8] In contrary, alkylation products with retention of configuration were observed by the Chen group during their mechanistic study on the palladium catalyzed *ortho*-C-H alkylation reaction of *N*-quinolyl

benzamides.[9] In addition, a stereoconvergent directed C-H glycosylation reaction was recently developed by Chen group, in which a diastereomeric α/β glycosyl chloride mixture produced the corresponding alkylation product with exclusive α-selectivity.[10]

Based on these experimental observations and DFT computational studies, several alkylation mechanisms have been postulated, including the stereoinvertive S_N2-type mechanisms (S_N2-Ar and S_N2-Pd),[5,6,8,11] the stereoretentive oxidative addition (OA) mechanism,[9] and the stereodivergent/convergent S_N1-type mechanism (Figure 1c).[7,10] Despite these advances, precise factors leading to different alkylation mechanisms and stereochemical outcomes remain elusive. Whether these differences are caused by the structural feature of palladacycle complexes or that of the alkylation reagents is still unclear, since in the aforementioned studies structurally diverse secondary alkyl halides were employed as probes, and it is well-known that the mechanism of nucleophilic substitution reactions is dependent on the nature of alkyl electrophile.[12] To our surprise, stereochemical investigation involving synthetically relevant primary alkyl electrophiles has not been reported so far.

In this work, we performed a study on the stereochemistry of the reactions between palladacycle complexes and primary alkyl iodides, aiming to systematically investigate the alkylation mechanism and to provide a more comprehensive understanding of the transition metal-catalyzed C-H alkylation process. Two types of palladacycle complexes, namely Catellani-type palladacycle intermediates (C,C-ligated type)[13] and directing group (DG)-coordinated palladacycle complexes (C,X-ligated type),[9,14] were selected as model complexes, and vicinal dideuterium-labeled primary alkyl iodides with specific relative configuration were employed as stereochemical probes. We have identified two different alkylation reaction modes depending on the structural feature of the palladacycle complex, and the factors dictating the alkylation mechanism were further elucidated by DFT calculations.

Results and Discussion

Selection of Probe Molecules. Carefully-designed stereochemical probes should be used to study the alkylation mechanism of primary alkyl derivatives. To achieve this goal, vicinal dideuterium-labeled stereochemical probes were developed by Whitesides and co-workers (Figure 2a).[15] Stereocenters were successfully introduced by deuterium-labeling in these stereochemical probes, which can be used to indicate the stereochemical outcome of S_E2 reactions and Suzuki coupling. In this study, primary alkyl iodides with similar vicinal-dideuteration were selected as stereochemical probes to investigate how they interact with the palladacycle complexes (Figure 2b). The relative stereochemistry of the probe alkyl moiety will serve as an indicator for the stereochemical process of the palladacycle-alkyl halide interaction, assuming that the reductive elimination step is stereoretentive. This probe is expected to distinguish between the S_N2-type mechanism (with inversion of the stereocenter) and the OA mechanism (with the retention of the stereocenter).

Selecting the suitable R- substituent is the key to the design of those probes. The *t*-Bu substituted alkyl iodide **1**, which has been utilized to probe the oxidative addition mechanism of rhodium[15c] and iron[15e] complexes, was employed in this study (Figure 2c, left). Due to the presence of bulky *t*-Bu substituent, the conformation of this molecule was locked in *anti*-conformation,[16] which facilitates the determination of the relative configurations of both the probe molecule and the alkylation product, while with diminished reactivity. The less sterically encumbered, TBS protected stereochemical probe **2** exhibits enhanced reactivity, but its conformation is relatively flexible, resulting in some difficulty in determining the diastereomeric ratio (Figure 2c, right). The relative configuration of the vicinal-dideuterated moiety could be identified by the coupling constants of the neighboring protons measured by the $^1H\{^2H\}$ NMR

spectroscopy (see SI for further details).

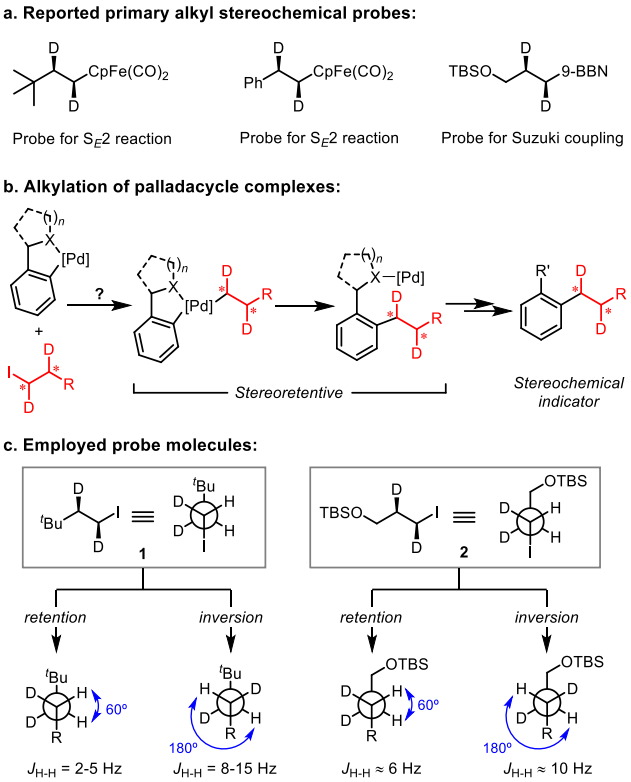
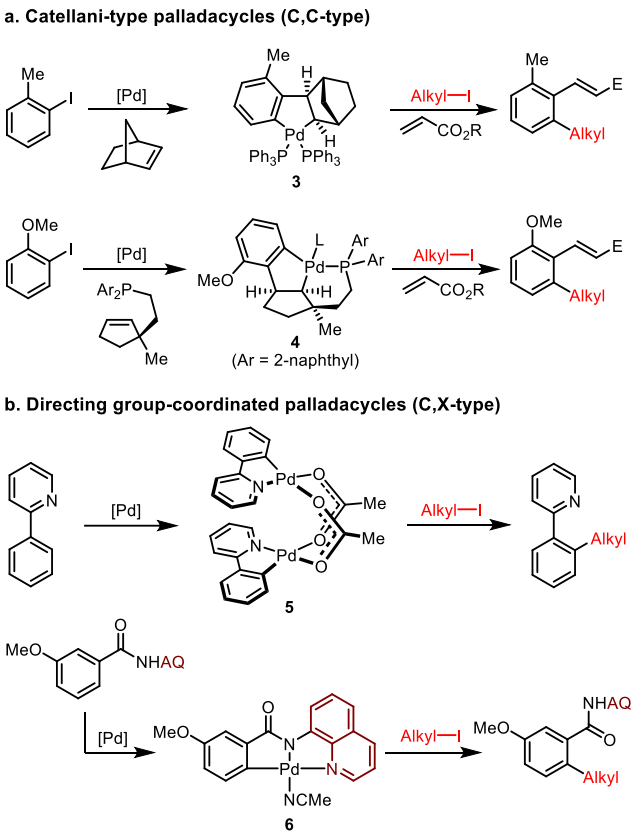


Figure 2. Stereochemical probes for alkylation.

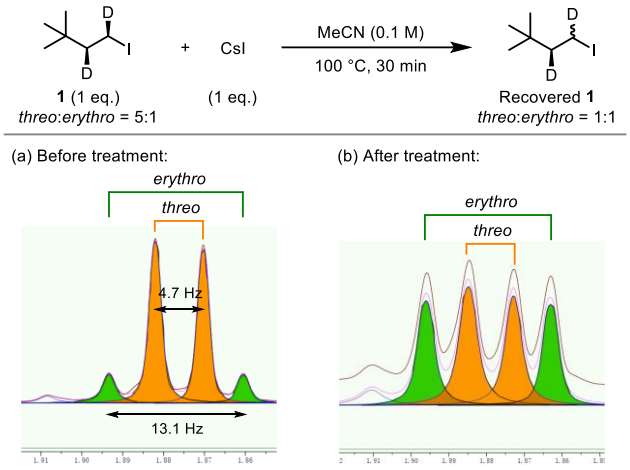
Two different classes of palladacycle complexes were selected as model complexes in this study. The first one is the Catellani-type palladacycle intermediates with two carbanion ligands, including the classical norbornene-derived palladacycle complex **3**[13a] and the cycloolefin ligand-derived palladacycle complex **4**[13b] recently developed by our group (Scheme 1a). The second class is the directing group (DG)-coordinated palladacycle complexes with a carbanion ligand and a heteroatom ligand, including the pyridine-coordinated palladacycle complex **5**[14] and the 8-aminoquinoline (8-AQ)-coordinated palladacycle complex **6**[9] (Scheme 1b). These directing group-coordinated palladacycle complexes represent the C,X-type palladacycle complexes, while the Catellani-type palladacycle intermediates represent the electron-rich, C,C-type palladacycle complexes. These palladacycle complexes reflect the general situation involved in Pd-mediated C-H alkylation chemistry.

Scheme 1. Palladacycle complexes involved in this study.



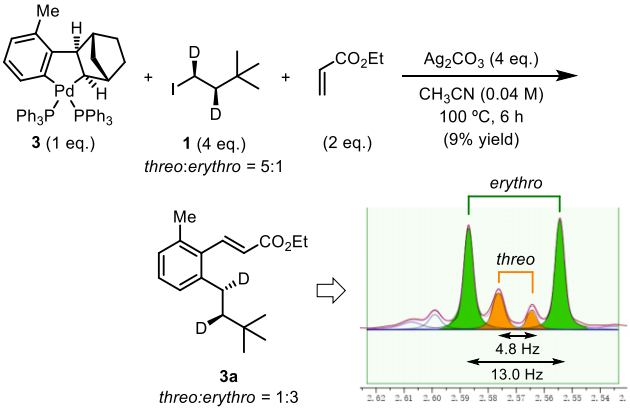
Suitable Reaction Conditions. It would be most convenient to run the C-H alkylation reactions in a catalytic manner employing the probe molecule as the alkylation reagent, and then determine the relative configuration of the product alkyl moiety. However, we realized that this simple solution is not feasible, since primary alkyl halides tend to undergo S_N2 reaction with the iodide anion generated in the reaction system, which may lead to epimerization of the probe molecule and thus interfere with the stereochemical study.[8] Unfortunately, this was found to be true by a control experiment, in which treatment of the probe alkyl iodide **1** (*threo*:*erythro* = 5:1) with CsI under synthetically relevant conditions resulted in complete epimerization (*threo*:*erythro* = 1:1) of the probe in only 30 min (Scheme 2). Therefore, we planned to do the study by performing stoichiometric reactions between the synthesized palladacycles and the probe molecules. Meanwhile, in order to eliminate the affection of the iodide anion generated as a byproduct after alkyl substitution, silver salts should be used as an iodide trapper.

Scheme 2. Epimerization of the stereochemical probe **1** in the presence of iodide anion.



Reaction Mechanism of the Catellani-Type Palladacycle Intermediates. With suitable reaction conditions in hand, we first investigated the stereochemical outcome of the alkylation reaction between norbornene derived palladacycle complexes **3** and alkyl iodide **1** (*threo*:*erythro* = 5:1). The synthesized norbornene-embedded palladacycle **3** was reacted with probe molecule **1** under the standard reaction conditions, with ethyl acrylate as the termination reagent. In the presence of excess Ag_2CO_3, the alkylation product **3a** was isolated in a low yield, possibly due to the steric hindrance of the *tert*-butyl group. Nevertheless, this did not affect our stereochemical investigation. $^1H\{^2H\}$ NMR analysis showed that the alkyl moiety in **3a** existed as a diastereomeric mixture (*threo*:*erythro* = 1:3), indicating the inversion of configuration at the reaction center (Scheme 3). We attributed the decrease of diastereomeric ratio to the epimerization of the probe molecule under the reaction conditions due to trace amount of iodide anion, as supported by the decreased diastereomeric ratio of the recovered **1** (*threo*:*erythro* = 3:1). This served as the first stereochemical experimental evidence for the Catellani reaction involving a primary alkyl electrophile. The stereochemical outcome supported the S_N2-type mechanism of the reaction between norbornene-derived palladacycle complex **3** and stereochemical probe **1**, in agreement with the mechanism proposed by DFT computational study.[11c,d]

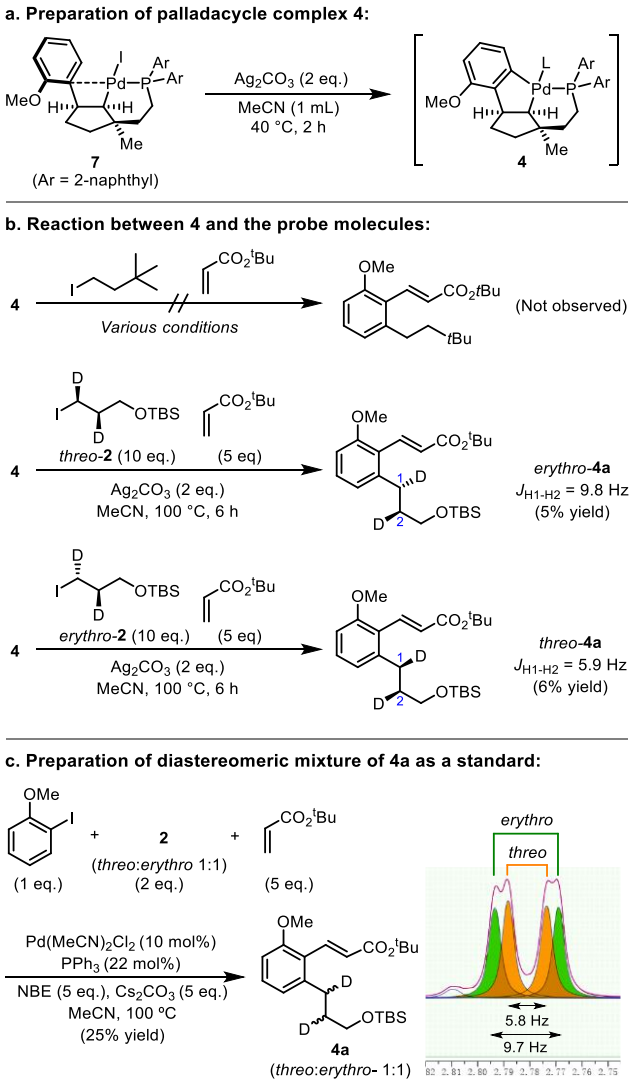
Scheme 3. Stereochemical investigation on norbornene-derived palladacycle complex **3**.



We then turned to investigate the alkylation mechanism of alkene-ligand derived palladacycle complex **4** by testing

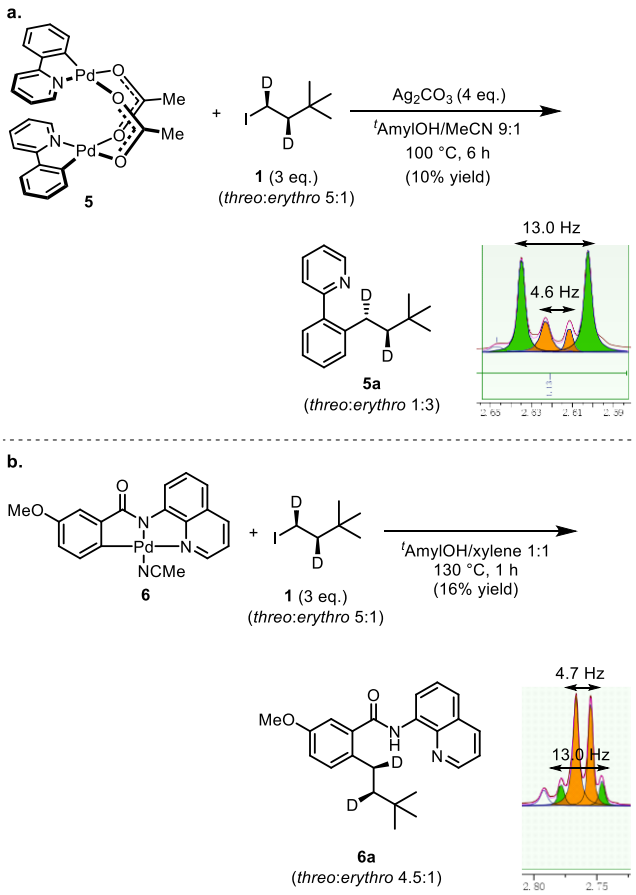
the reactivity of this complex at first. Based on our previous work, this palladacycle complex can be successfully formed in situ by heating the MeCN solution of complex **7** with Ag_2CO_3 (Scheme 4a).[13b] However, we observed that 1-iodo-3,3-dimethyl butane, the undeuterated derivative of stereochemical probe **1**, failed to react with complex **4** under various conditions (Figure 6b, see SI for detailed conditions), possibly due to the steric hinderance of the *tert*-butyl group. To our delight, when less sterically encumbered, TBS protected stereochemical probe **2** was used as the alkylation reagent, the corresponding alkylation product **4a** can be successfully isolated in 5-6% yield (Scheme 4b). Because for this probe molecule the preference for *anti*-conformation is not as strong as that for molecule **1**, the coupling constants for *threo*- and *erythro*-isomers of product **4a** have little difference. To identify these isomers clearly, a standard 1:1 diastereomeric mixture sample of **4a** was synthesized under standard Catellani conditions (Scheme 4c), and the relationship between the magnitude of H_1-H_2 coupling constant and the relative configuration of compound **4a** was assigned based on the previous investigation of Biscoe *et al.*[17] Careful overlay of the $^1H\{^2H\}$ NMR spectra confirmed that *threo*-**2** afforded *eythro*-**4a**, and *eythro*-**2** afforded *threo*-**4a** (Figure S12), indicating that complete inversion of configuration at the reaction center occurred at palladacycle complex **2**. Thus, we can conclude that both Catellani-type palladacycles tend to undergo an S_N2 reaction with primary alkyl iodides.

Scheme 4. Stereochemical investigation on palladacycle complex **4**.



Reaction Mechanism of the Directing Group-Coordinated Palladacycle Complexes. Following the established procedure for stereochemical investigation, we found that when the pyridine coordinated palladacycle complex **5** reacted with probe molecule **1** (*threo*:*erythro* = 5:1), the alkylation product **5a** with inverted configuration was isolated (*threo*:*erythro* = 1:3, Scheme 5a), implying an S_N2-type mechanism. In contrast, when 8-aminoquinoline-coordinated palladacycle complex **6** reacted with the same probe molecule, alkylation product **6a** with retention of configuration was produced (*threo*:*erythro* = 4.5:1, Scheme 5b), supporting an OA-type alkylation mechanism in consistent with the previous result of Chen et al.[9,18]

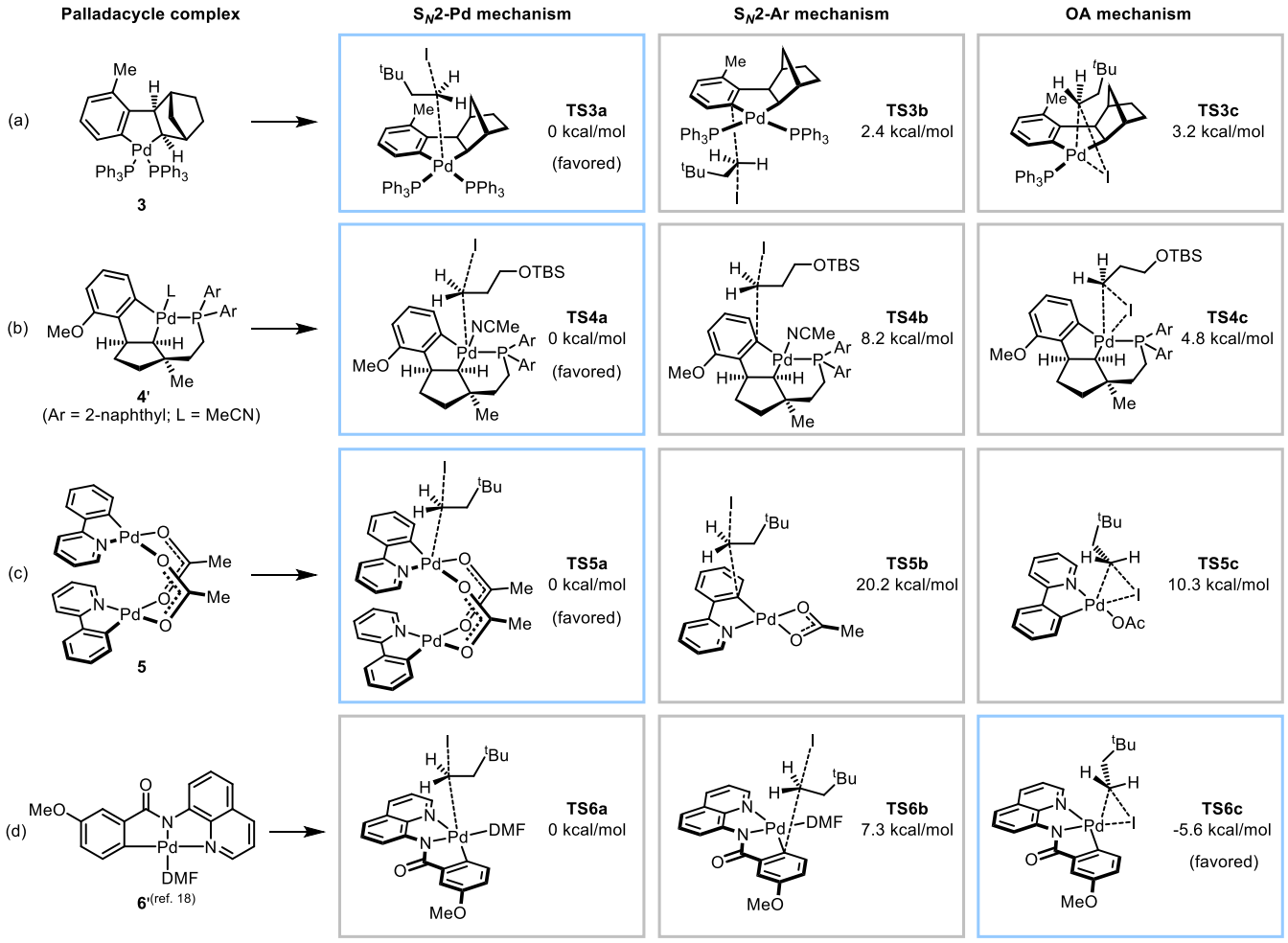
Scheme 5. Stereochemical investigations on directing group-coordinated palladacycle complexes



Computational Studies. To elucidate the mechanistic details of the reaction, density functional theory (DFT) calculations were carried out at the M06-SMD(solvent)/SDD-6-311++G(d,p)//B3LYP-D3(BJ)-SMD(solvent)/Lan2ldz-6-31G(d) level of theory (see SI for detailed computational methods).[19-27] Relative Gibbs free energy of various alkylation transition states (Figure 1c) was evaluated at first and calculation results were summarized in Scheme 6.

It is clear that the S_N2-Pd mechanism leading to stereoinvertive alkylation products was favored with complex **3**, **4′** and **5**, while the OA mechanism was favored with complex **6′**, which will lead to stereoretentive alkylation products. The computational results are consistent with our experimental observations. It is notable that, in no case the S_N2-Ar mechanism favors, indicating that the reaction mechanism of alkyl halide with different palladacycles mainly switches between S_N2-Pd and oxidative addition.

Scheme 6. Relative Gibbs free energies of various alkylation transition states (S_N2-Pd mechanism was selected as the reference)



In order to further understand the different preferences of the palladacycles, charge decomposition analysis (CDA) developed by the Frenking group was performed.[28,29] The transition structures for S_N2-Pd (**TS3a**) and OA (**TS3c**) pathways were chosen as the model, and several important donor-acceptor interactions involved in these two TSs can be unraveled. It was found that, the major donor-acceptor interaction involved in **TS3a** is the electron donation from the d_z^2-type orbital of Pd center to the σ*(C-I)-type orbital of the alkyl iodide (Figure 3a). Similar donor-acceptor interaction was proposed by Ariafard and co-workers in an S_N2-type oxidative addition TS of a phenol carbamate-derived palladacycle complex with *N*-chlorosuccinimide.[30] In contrary, in **TS3c** both the donation from the Pd d_z^2-type orbital to σ*(C-I)-type orbital and the back donation form the nonbonding electron pair of iodine to the empty d_x^2-$_y^2$-type orbital of Pd are significant, with the latter being more profound (Figure 3b).[31]

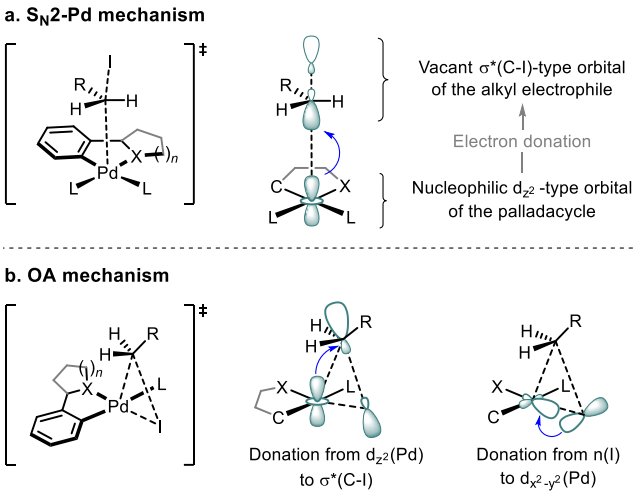


Figure 3. Dondor-acceptor interactions involved in the S$_N$2-Pd and OA mechanisms

Based on the above analysis, we purpose that the σ-donation ability of the ligands is a key factor affecting the alkylation mechanism, which is supported by the computed energy levels of the palladacycles of interest (Figure 4).[32] The C,C-ligated Catellani-type palladacycle intermediates **3** and **4** have two strongly σ-donating carbanion ligands, which result in high-lying d_z^2-type and d_x^2-y^2-type orbitals with a highly nucleophilic Pd center and thus favored the stereoinvertive S$_N$2-Pd pathway. In contrast, in the C,N-ligated complex **6** a weakly σ-donating amide ligand lowers the energy levels of both d_z^2-type and d_x^2-y^2-type orbitals, rendering the stereoretentive OA mechanism predominate. Interestingly, in a recently reported computational work of Ehara *et al.*, an norbornene-embedded palladacycle bearing an electron-withdrawing CO_2Me substituent was also found to prefer the OA mechanism, compared with the palladacycle without this substituent.[11c]

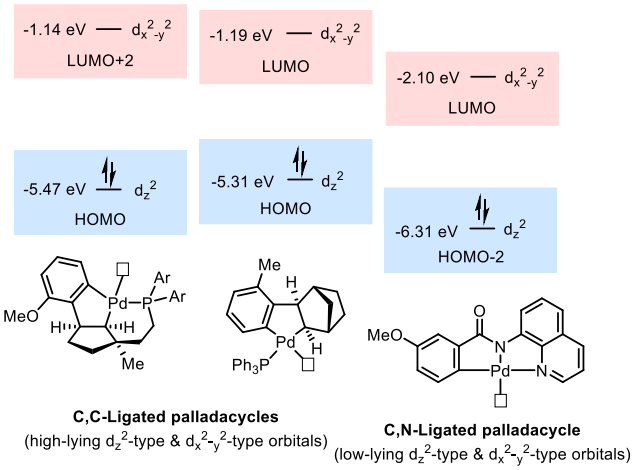


Figure 4. Computed energy levels of the molecular orbitals of palladacycle complexes.

However, the above rationalization could not account for the observed mechanistic preference of the pyridine-coordinated palladacycle **5**, which is a C,N-ligated complex but still favors the S$_N$2-Pd mechanism. We hypothesized that this unusual phenomenon was caused by the unique dimer structure of complex **5** (Figure 5). Due to the stable dimer

structure of this complex, it is difficult to substitute one of the acetate ligands by alkyl iodide electrophile, thus disfavoring the OA mechanism. On the other hand, the d^8-d^8 interaction between two palladium atoms increases the nucleophilicity of this complex, as demonstrated by the elevated energy of the d_z^2-type orbital compared with that in the thermodynamically disfavored monodentate palladacycle.[33] As a result, in the reaction of this palladacycle and alkyl iodide, the S_N2-Pd mechanism is favored and stereoinversion on the electrophilic carbon center was observed (see SI for a more detailed discussion).

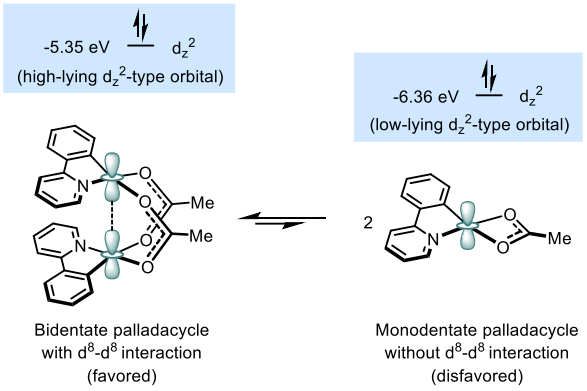


Figure 5. Influence of the ligand dissociation equilibrium and d^8-d^8 interaction on the alkylation mechanism.

Summary

In summary, the alkylation mechanism of palladacycle complexes with primary alkyl iodides was investigated through the combination of experimental efforts and DFT calculations. By utilizing vicinal dideuterium-labeled primary alkyl iodides as the stereochemical probe, we have elucidated the stereochemical outcomes of the alkylation reactions of several representative palladacycle complexes. For the Catellani-type palladacycle intermediates coordinated with strongly σ-donating carbanion ligands, the stereoinvertive S_N2-Pd mechanism is the key step of the alkylation process. For the directing group-coordinated palladacycle complex which bears a weakly σ-donating amide ligand, the stereoretentive OA mechanism was found to predominate. The dimeric pyridine-coordinated palladacycle complex **5** serves as an exception, whose alkylation was found to proceed through the S_N2-Pd mechanism due to its unique dimer structure and the d^8-d^8 interaction between two Pd atoms, which increased the nucleophilicity of the Pd center. The present work provides a comprehensive understanding of the alkylation mechanism of the palladacycles with primary alkyl iodides, and we hope that this work can facilitate the rational design of new reactions involving palladacycle intermediates.

Supporting Information

Detailed experimental procedure, NMR spectra, and DFT computational results are available.

Funding

The National Natural Science Foundation of China (Grant No. 21822304) are acknowledged for financial support.

Notes

The authors declare no competing financial interest.

Acknowledgements

The technology platform of CBMS is acknowledged for providing instrumentation and computational resources.

Reference

1. (a) Labinger, J. A. Tutorial on Oxidative Addition. *Organometallics* **2015,** *34,* 4784−4795. (b) Ankade, S. B.; Shabade, A. B.; Soni, V.; Punji, B. Unactivated Alkyl Halides in Transition-Metal-Catalyzed C-H Bond Alkylation. *ACS Catal.* **2021,** *11,* 3268−3292.

2. (a) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. Pd/Norbornene: A Winning Combination for Selective Aromatic Functionalization *via* C−H Bond Activation. *Acc. Chem. Res.* **2016,** *49,* 1389−1400. (b) Wang, J.; Dong, G. Palladium/Norbornene Cooperative Catalysis. *Chem. Rev.* **2019,** *119,* 7478−7528.

3. (a) Tremont, S. J.; Rahman, H. U. Ortho-Alkylation of acetanilides using alkyl halides and palladium acetate. *J. Am. Chem. Soc.* **1984,** *106,* 5759−5760. (b) Auxiliary-Assisted Palladium-Catalyzed Arylation and Alkylation of sp^2 and sp^3 Carbon-Hydrogen Bonds" Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965-3972. (c) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. Ligand-Promoted Alkylation of C(sp3)-H and C(sp2)-H Bonds. *J. Am. Chem. Soc.* **2014,** *136,* 13194−13197. (d) Le, K. K. A.; Nguyen, H.; Daugulis, O. 1-Aminopyridinium Ylides as Monodentate Directing Groups for sp3 C−H Bond Functionalization. *J. Am. Chem. Soc.* **2019,** *141,* 14728−14735.

4. (a) Byers, P. K.; Canty, A. J.; Skelton, B. W.; White, A. H. The Oxidative Addition of Iodomethane to [$PdMe_2$(2,2'-bipyridyl)] and the X-ray Structure of the Organopalladium(IV) Product fac-[$PdMe_3$(2,2'-bipyridyl)L]. *J. Chem. Soc., Chem. Commun.* **1986,** 1722−1724. (b) Byers, P. K.; Canty, A. J.; Crespo, M.; Puddephatt, R. J.; Scott, J. D. Reactivity and mechanism in oxidative addition to palladium(II) and reductive elimination from palladium(IV) and an estimate of the palladium methyl bond energy. *Organometallics* **1988,** *7,* 1363−1367.

5. (a) Rudolph, A.; Rackelmann, N.; Lautens, M. Stereochemical and mechanistic investigations of a palladium-catalyzed annulation of secondary alkyl iodides. *Angew. Chem. Int. Ed.* **2007,** *46*, 1485−1488. (b) Rudolph, A.; Rackelmann, N.; Turcotte-Savard, M.-O.; Lautens, M. Application of Secondary Alkyl Halides to A Domino Aryl Alkylation Reaction for the Synthesis of Aromatic Heterocycles. *J. Org. Chem.* **2009,** *74,* 289− 297.

6. Liu, C.; Liang, Y.; Zheng, N.; Zhang, B. S.; Feng, Y.; Bi, S.; Liang, Y. M. Synthesis of indolines via a palladium/norbornene-catalyzed reaction of aziridines with aryl iodides. *Chem. Commun.* **2018,** *54*, 3407−3410.

7. Lv, W.; Chen, Y.; Wen, S.; Ba, D.; Cheng, G. Modular and Stereoselective Synthesis of C-Aryl Glycosides via Catellani Reaction. *J. Am. Chem. Soc.* **2020,** *142*, 14864−14870.

8. Luo, Y.-C.; Yang, C.; Qiu, S.-Q.; Liang, Q.-J.; Xu, Y.-H.; Loh, T.-P. Palladium(II)-Catalyzed Stereospecific Alkenyl C-H Bond Alkylation of Allylamines with Alkyl Iodides. *ACS Catal.* **2019,** *9,* 4271−4276.

9. Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. Pd-Catalyzed Monoselective ortho-C–H Alkylation of N-Quinolyl Benzamides: Evidence for Stereoretentive Coupling of Secondary Alkyl Iodides. *J. Am. Chem. Soc.* **2015,** *137*, 531−539.

10. Wang, Q.; An, S.; Deng, Z.; Zhu, W.; Huang, Z.; He, G.; Chen, G. Palladium-catalysed C−H glycosylation for synthesis of C-aryl glycosides. *Nat. Catal.* **2019,** *2*, 793−800.

11. (a) Ye, J., Shi, Z.; Sperger, T.; Yasukawa, Y.; Kingston, C.; Schoenebeck, F.; Lautens, M. Remote C−H alkylation and C−C bond cleavage enabled by an *in situ* generated palladacycle. *Nat. Chem.* **2017,** *9,* 361–368. (b) Zhang, H.; Wang, H. Y.; Luo, Y. X.; Chen, C. H.; Cao, Y. M.; Chen, P. H.; Guo, Y. L.; Lan, Y.; Liu, G. S. Regioselective Palladium-Catalyzed C-H Bond Trifluoroethylation of Indoles: Exploration and Mechanistic Insight. *ACS Catal.* **2018,** *8,* 2173−2180. (c) Yang, T.; Kong, C.; Yang, S.; Yang, Z.; Yang, S.; Ehara, M. Reaction mechanism, norbornene and ligand effects, and origins of meta-selectivity of Pd/norbornene-catalyzed C–H activation. *Chem. Sci.* **2020,** *11*, 113−125. (d) Qi, X.; Wang, J.; Dong, Z.; Dong, G.; Liu, P. Compatibility Score for Rational Electrophile Selection in Pd/NBE Cooperative Catalysis. *Chem.* **2020,** *6,* 2810−2825.

12. E. V. Anslyn and D. A. Dougherty, Chapter 11-Organic Reaction Mechanisms, Part 2: Substitutions at Aliphatic Centers and Thermal Isomerizations/Rearrangements, in *Modern Physical Organic Chemistry*, University Science, **2005,** pp. 637–668.

13. (a) Lei, C.; Jin, X.; Zhou, J. S. Palladium-Catalyzed Heteroarylation and Concomitant ortho-Alkylation of Aryl Iodides. *Angew. Chem. Int. Ed.* **2015,** *54,* 13397−13400. (b) Zheng, Y.-X., Jiao, L. Hybrid cycloolefin ligands for palladium–olefin cooperative catalysis. *Nat. Synth.* **2022,** *1,* 180−187.

14. Wang, X.; Ji, X.; Shao, C.; Zhang, Y.; Zhang, Y. Palladium-Catalyzed C−H Alkylation of 2-phenylpyridines with Alkyl Iodides. *Org. Biomol. Chem.* **2017,** *15,* 5616−5624.

15. (a) Bock, P. L.; Whitesides, G. M. Stereoselective synthesis of 1-substituted organometallic derivatives of 3,3-dimethylbutane-1,2-d_2. *J. Am. Chem. Soc.* **1974,** *96*, 2826−2829. (b) Bock, P. L.; Boschetto, D. J.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. Stereochemistry of reactions at carbon-transition metal .sigma. bonds. .pi.-Cyclopentadienyldicarbonyliron erythro-and threo-3,3-dimethylbutyl-1,2-d_2. *J. Am. Chem. Soc.* **1974,** *96*, 2814−2825. (c) Collman, J. P.; Brauman, J. I.; Madonik, A. M. Oxidative Addition Mechanisms of a Four-Coordinate Rhodium (I) Macrocycle. *Organometallics* **1986,** *5,* 310−322. (d) Igau, A.; Gladysz, J. A. Reactions of the neohexyl iodide complex [(.eta.5-C_5H_5)Re(NO)(PPh_3)($ICH_2CH_2C(CH_3)_3$)]$^+BF_4^-$ and nucleophiles: stereochemistry of carbon-iodine bond cleavage in highly accelerated S_N2 reactions. *Organometallics* **1991,** *10*, 2327−2334. (e) Rummelt, S. M.; Peterson, P. O.; Zhong, H.; Chirik, P. J. Oxidative Addition of Aryl and Alkyl Halides to a Reduced Iron Pincer Complex. *J. Am. Chem. Soc.* **2021,** *143,* 5928−5936. (f) Slack, D. A.; Baird, M. C. Stereochemistry of alkyl transfer and olefin elimination reactions of transition-metal phenethyl complexes. *J. Chem. Soc., Chem. Commun.* **1974,** 701−702. (g) Slack, D. A.; Baird, M. C. Halogen cleavage reactions of dicarbonyl-.eta.5-cyclopentadienyl-threo-.alpha.,.beta.-dideuteriophenethyliron(II). *J. Am. Chem. Soc.* **1976,** *98,* 5539−5546. (h) Ridgway, B. H.; Woerpel, K. A. Transmetallation of Alkylboranes to Palladium in the Suzuki Coupling Reaction Proceeds with Retention of Stereochemistry. *J. Org. Chem.* **1998,** *63,* 458−460.

16. Whitesides, G. M.; Sevenair, J. P.; Goetz, R. W. Conformation Isomerism in 1-Substituted 3,3-Dimethylbutane *J. Am. Chem. Soc.* **1967,** *89,* 1135−1144.

17. Murray, B.; Zhao, S.; Aramini, J. M.; Wang, H.; Biscoe, M. R. The Stereochemical Course of Pd-Catalyzed Suzuki Reactions Using Primary Alkyltrifluoroborate Nucleophiles. *ACS. Catal.* **2021,** *11,* 2504−2510.

18. To identify whether this shift in alkylation mechanism was caused by the structural feature of palladacycle complexes or diminished polarity of the ^{t}AmylOH/xylene hybrid solvent system, the same reaction was also carried out in DMF solvent with otherwise identical reaction conditions. Stereoretentive alkylation product was still observed, albeit with a

lower distereomeric ratio (*threo*:*erythro* = 1.5:1; see SI for more detailed discussions). Based on similar reasons, DMF was chosen as co-ligand and implicit solvent in the DFT calculation of this reaction.

19. Gaussian 16, Revision A.03, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

20. Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008,** *120,* 215−241.

21. Marenich A. V.; Cramer C. J.; Truhlar D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **2009,** *113,* 6378−6396.

22. (a) Dolg, M.; Wedig, U.; Stoll, H.; Preuss, H. Energy-adjusted ab initio pseudopotentials for the first row transition elements. *J. Chem. Phys.* **1987,** *86,* 866−872. (b) Andrae, D.; Häußermann, U.; Dolg, M.; Stoll, H.; Preuß, H. Energy-adjusted ab initio pseudopotentials for the second and third row transition elements. *Theor. Chem. Acc.* **1990,** *77,* 123−141.

23. Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. *J. Chem. Phys.* **1980,** *72,* 650−654.

24. (a) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993,** *98,* 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988,** *37,* 785−789. (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.* **1994,** *98,* 11623−11627.

25. (a) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **2010,** 132, 154104−154119. (b) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the damping function in dispersion corrected density functional theory. *J. Comput. Chem.* **2011,** *32,* 1456−1465.

26. (a) Hay, P. J.; Wadt, W. R. Ab initio effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals. *J. Chem. Phys.* **1985,** *82,* 299−310. (b) Ehlers, A. W.; Bö hme, M.; Dapprich, S.; Gobbi, A.; Höllwarth, A.; Jonas, V.; Köhler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett.* **1993,** *208,* 111−114. (c) Roy, L. E.; Hay, P. J.; Martin, R. L. Revised Basis Sets for the LANL Effective Core Potentials. *J. Chem. Theory Comput.* **2008,** *4,* 1029−1031.

27. (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. Self-Consistent Molecular-Orbital Methods. IX. An Extended Gaussian-Type Basis for Molecular-Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1971,** *54,* 724−728. (b) Hehre, W. J.;

Ditchfield, R.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian—Type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1972,** *56,* 2257−2261. (c) Hariharan, P. C.; Pople, J. A. The influence of polarization functions on molecular orbital hydrogenation energies. *Theor. Chim. Acta.* **1973,** *28,* 213−222.

28. Dapprich, S.; Frenking, G. Investigation of Donor-Acceptor Interactions: A Charge Decomposition Analysis Using Fragment Molecular Orbitals. *J. Phys. Chem.* **1995,** *99,* 9352−9362.

(b) Meng Xiao, Tian Lu, Generalized Charge Decomposition Analysis (GCDA) Method, *Journal of Advances in Physical Chemistry,* **2015,** *4,* 111-124.

29. Tian Lu, Feiwu Chen, Multiwfn: A Multifunctional Wavefunction Analyzer, *J. Comput. Chem.* **2012,** *33,* 580-592.

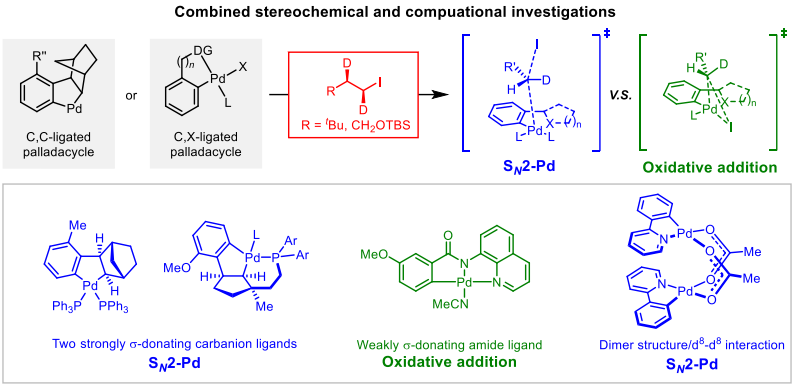
30. Farshafar K.; Tizhoush, S. K.; Ariafard, A. Role of Brønsted Acids in Promoting $Pd(OAc)_2$-Catalyzed Chlorination of Phenol Carbamates Using N-Chlorosuccinimide. *ACS Catal.* **2022,** *12,* 2681−2693.

31. In addition to the results shown in Figure 3b, the back-donation from σ(C-I)-type orbital to the empty $d_{x^2-y^2}$-type orbital of Pd was also found to be significant in **TS6c** (Figure S27), which we attribute to the lower $d_{x^2-y^2}$-type orbital energy level of complex **7**.

32. Börgel, J.; Campbell, M. G.; Ritter, T. Transition Metal d-Orbital Splitting Diagrams: An Updated Educational Resource for Square Planar Transition Metal Complexes. *J. Chem. Educ.* **2016,** *93,* 118−121.

33. Bercaw, J. E.; Durrell, A. C.; Gray, H. B.; Green, J. C.; Hazari, N.; Labinger, J. A.; Winkler, J. R. Electronic Structures of Pd^{II} Dimers. *Inorg. Chem.* **2010,** *49,* 1801−1810.

TOC


Combined stereochemical and compuational investigations
C,C-ligated palladacycle
or
C,X-ligated palladacycle
R = tBu, CH2OTBS
SN2-Pd
V.S.
Oxidative addition
Two strongly σ-donating carbanion ligands
SN2-Pd
Weakly σ-donating amide ligand
Oxidative addition
Dimer structure/d8-d8 interaction
SN2-Pd