# Palladium/N-CD3-Xu-Phos-catalyzed enantioselective cascade Heck/remote C(sp2)–H alkylation reaction

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# Abstract

Heck-type C-H bond activation of unactivated alkenes has emerged as a powerful strategy for the construction of synthetically valuable spirocycles over past 30 years, however, the development of asymmetric version has lagged largely behind. Herein we demonstrate a robust Heck-type reaction of a broad range of unactivated alkenes enabled by the first palladium/Xu-Phos-catalyzed tandem Heck/remote C–H bond alkylation. Moreover, the synthesis of both enantiomers of the product using the same enantiomer of a chiral ligand via a position of the phenyl ring-dependent enantiodivergent synthesis. The salient features of this methodology include operational simplicity, high chemo- and enantioselectivity, broad substrate scope. In addition, we first revealed that the C($sp^2$)-H activation, alkene insertion and C–I reductive elimination steps are reversible by experiments.


# Introduction

Chiral spirocycles are key structural skeletons found in a wide of bioactive natural products[1-4], effective chiral ligands and catalysts[5-6]. Owing to its unique three-dimensional orientation and conformational constraints, chiral spirocycles as privileged pharmacophores exist in many drug development programs[7]. Despite a plenty of methods have been developed for the preparation of spiro stereocenters[8-17], most existing methods need to elaborate a preconstructed monocycle[8-9]. Therefore, it is highly desirable to explore novel protocols for the construction of two cycles along with a quaternary stereocenter in one operation.

Functionalizing C-H bonds selectively at various locations in molecules will ultimately afford synthetic chemists transformative tools to modify and construct molecular structures[18-23]. C-H bonds that are remote from functional groups are widespread, and distinguishing these C-H bonds bearing little difference in electronic property is a formidable challenge in C-H activation. To date, much pioneering work utilized the intrinsic steric or electronic properties of the arenes[24-28], or the type of “U”-shaped directing group (DG)[29-30]. Although a large number of brilliant achievements were made with the use of DG, there is one point that the DG needs to be installed on the substrate and removed after the reaction couldn’t be ignored. Instead of using a DG that is covalently bound to a substrate for site-selective C-H activation, an alternative approach that utilizing a transient DG can be generated in situ under the reaction conditions would open the door to new reactivities (Fig. 1a, 1b)[31-40]. As a pioneering study, Grigg et al. successfully implemented this strategy in the Pd-catalyzed remote-C-H functionalization of the heteroaromatic tethered alkene moiety through carbopalladation of alkenes to form neopentyl-type $\sigma$-alkylpalladium intermediate as the DG[32]. This marks that the direct and selective functionalization of remote C-H alkylation of arenes has been successfully applied to the construction of spirocycles. Utilizing the same concept, Ruck et al. have accomplished the expansion of the C($sp^2$)-H scope to an unactivated aryl C-H bond[33]. Subsequently, Zhu et al. demonstrated that the σ-alkylpalladium intermediate can activate the C($sp^3$)-H bond, thereby leading to the 5,6-spiroheterocycles[36]. Notably, continued interest in

this reaction has recently culminated with the highly strained spiro-fused benzocyclobutene derivatives by Lautens[39]. Very recently, Beller's group combines selective nucleophilic substitution ($S_N2'$), Pd-catalyzed Heck and C-H activation reaction in a cascade manner, affording the highly strained racemic 5,4-spiroheterocycles in good to high yields[40]. In the classic domino Heck/intramolecular C-H alkylation reaction, the carbopalladation step is a chiral-determining step, but this step is reversible[31,33].

Nowadays much progress has been made in racemic domino Heck/intramolecular C-H alkylation reaction to construct complex molecular architectures. However, due to no solid experiment evidence, there remain some unresolved issues relating to the mechanism of this kind of reaction, such as: (1) whether the carbopalladation step is reversible; (2) whether the C($sp^2$)-H activation step is reversible; (3) whether the C–I reductive elimination is reversible. Moreover, the development of an enantioselective version remains extremely challenging, due to the following issues: (1) various competitive side reactions such as reductive Heck reaction, carboiodination reaction, 1,4-Pd migration/C($sp^2$)–H functionalization[41-43]; (2) when having two different *ortho*-position C-H of aromatic ring, how to control the site-selectivity; (3) the high temperature was required in previous work[39-40], which easily lead to the ring-opening byproduct (Fig. 1a). Inspired by the good performance of

Xu-Phos in asymmetric Heck and related cascade reactions[44-53], we became very interested in addressing this long-standing unsolved asymmetric tandem Heck reaction/C-H alkylation, which, if successful, would provide an immediate access to synthetically-valuable optically active 5,4- and 5,5-spirocycle derivatives[54]. Herein, we present a robust palladium/Xu-Phos catalyst system for asymmetric tandem Heck reaction/C-H alkylation via a palladacycle intermediate (Fig. 1c). Synthesis of both enantiomers of the product can be accomplished depending on the site of the substituent on the aromatic or heteroaromatic ring (Fig. 1d). Moreover, this reaction exhibits a broad scope of the unactivated aryl tethered alkene moiety while under operationally simple and mild reaction conditions.

# Results And Discussion

We began our investigation by revisiting our previously developed catalytic system for enantioselective cascade Heck-type reactions of alkene-tethered aryl iodides[44-48]. With the *ortho*-iodophenol-derived allyl ether **1a** as the model substrate, we conducted a preliminary study in isopropyl ether (120 $^oC$) for 24 h with $Pd_2(dba)_3$•$CHCl_3$ as the precatalyst, *N*-Me-Xu-Phos (*N*-Me-**Xu3**) as the chiral ligand and $Cs_2CO_3$ as the base (Table 1). Our initial efforts resulted in poor yield of the desired product **4a** with moderate enantiomeric ratio (e.r.) (67% conversion, 22% yield with 88:12 e.r.) together with a series of byproducts **2**, **3** and **5** (Table 1, entry 1), indicating that the synthesis of the highly strained chiral 5,4-spirocycles is indeed very challenging. Subsequently, further evaluation of the reaction conditions revealed that all of bases, additives, Pd salts, and temperature were the key factors to obtain a robust reaction.

Several points are noteworthy: (1) this reaction is very sensitive to the bases (Table 1, entries 2–6). For example, when PMP was chosen as the base, the byproduct **2** was given as the main product via

carboiodination of alkene (Table 1, entry 3). Nevertheless, changing to CsOAc, a 1,4-Pd shift of palladacycle followed by *ortho*-C-H activation led to the fused polycycle **6** (Table 1, entry 4). (2) In Lauten's work, **1a** quickly converts to the target compound **4a** in good yield by using the racemic ligand ($P^tBu_3$) at 100 °C for 1 hour (entry 9)[39]. By a huge margin, the rate of reaction is greatly reduced under current conditions without $P^tBu_3$ (Table 1, entry 8). Even extending to 72 hours and warming up to 110 °C, the desired product **4a** was obtained in only 48% yield (63% conversion). Indeed, adding the racemic ligand was beneficial to the conversion of the reaction (Table 1, entries 2 vs 3, and 7 vs 8). However, such a strong racemic background reaction poses a great challenge to the high enantioselectivity. (3) The potassium bases are beneficial to the enantioselectivity (Table 1, entries 5, 6 vs 2). (4) Reducing the temperature to 110 °C could inhibit the formation of the ring-opening by-product **5** (Table 1, entries 1–6 vs 7, 8). After an extensive evaluation of the reaction conditions, the current conditions were not satisfactory (Table 1, entry 7). Not only the desired product **4a** was provided with 92.5:7.5 e.r., but also the conditions have poor universality (more detail see the supporting information, Table S1–S9).

Then, we focused our attention on screening of chiral ligands (Table S10–S12). Firstly, various commercially available chiral ligands such as biphosphines (**L1**–**L7**), monophosphine (**L8**), phosphoramidite (**L9**), ferrocene-derived P,N-ligands (**L10**–**L11**), bis(oxazoline) (**L12**) were tested occasionally together with the byproduct **7**. The biphosphine ligands (**L1**–**L4**, **L6**, **L7**), ferrocene-derived P,N-ligands (**L10**–**L11**) failed to give the desired product **4a**. Both a bulky biarylphosphine (**L5**) and monophosphine (**L8**) gave **4a** in good yield without any enantioselectivity. Only the phosphoramidite (**L9**) delivered **4a** but with low enantioselectivity. Subsequently, we examined the performance of a Sadphos kit (including Ming-Phos[55], Xu-Phos[44-48], Xiang-Phos[56], PC-Phos[57], Xiao-Phos[58], Wei-Phos[59] and TY-Phos[60] etc.). The dicyclohexyl phosphine ligands (Xu-Phos) remained the most effective for enantioselective induction. Inspired by these results, other Xu-Phos such as *N*-Me-**Xu4** (Table 1, entry 11) and *N*-$CD_3$-**Xu4** (Table 1, entry 10) were then examined under previous reaction conditions. Of which, the better results could be obtained by using the newly indentified *N*-$CD_3$-**Xu4** as the chiral ligand. To the best of our knowledge, the introduction of deuterium atom in the chiral ligand to increase the enantioselectivity are rarely reported.

With the optimal reaction conditions established, we next examined the generality of this enantioselective tandem Heck reaction/C-H alkylation. First, the effect of allyl substituents was examined, and the results are shown in Table 2. A broad series of allyl substituted aryl iodides **1** including monosubstituted phenyl rings with electron-donating or -withdrawing groups at different positions (*ortho*, *meta* or *para*-), a disubstituted phenyl ring, worked smoothly to afford **4a**–**4l** in 65–96% yields with 91:9–96.5:3.5 ers. The absolute configuration of the product was confirmed by the X-ray diffraction analysis of **4b**. In addition, highly strained 5,4-spiro-fused 2,3-dihydrobenzofurans **4m**–**4n** that contain medicinally relevant heterocycles, such as 9,9-dimethyl-9H-fluorene and 9-phenyl-9H-carbazol-1-yl were isolated in 70–71% yields with 95:5–96:4 ers. The effect of substituents on the benzene ring of the 2- iodophenoxy moiety was then investigated under the optimal reaction conditions. The desired products **4o**–**4ad** were also obtained in 44–86% yields with 92.5:7.5–97:3 ers for the reactions with substrates bearing

monosubstituted phenyl rings with either electron-rich or electron-deficient group at C4 or C5, a disubstituted phenyl ring and a naphthalene ring. When using *N*-Me-**Xu4** as a chiral ligand, except in one particular case (**4e**), no better enantioselectivities were given. It is general phenomenon that the introduction of deuterium atom is beneficial to increase the enantioselectivity.

To gain deep insight into the reaction mechanism, several control experiments were carried out (Fig. 2). Although a series of byproducts had been inhibited under the standard conditions, a key mechanistic question is: how does the relative rate of σ-alkyl palladium compare reductive elimination with Sonogashira coupling, Suzuki coupling, reductive Heck and alkyne insertion? To probe this question, several competing reactions were performed (Fig. 2a). Note that no desired product **4a** was detected with using $PhB(OH)_2$, cyclohexenylboronic acid or phenylacetylene as the second substrates. These results supported that the C($sp^3$)-C($sp$)and C($sp^3$)-C($sp^2$) cross-coupling of the domino Heck/Suzuki or Sonogashira reaction is more favored than this present domino Heck/remote C-H alkylation reaction. However, the C($sp^3$)-C($sp^3$) cross-coupling is obviously unfavored. Subsequently, adding $HCO_2Na$ or ethyl 3-phenylpropiolate to the reaction mixture, roughly the same amount of the reductive Heck product **3** or alkyne insertion[61] product **9** with the spirocycle **4a** were furnished, indicating that the rates of these reactions are similar. All these results further confirmed that the realization of domino Heck/remote C-H alkylation reaction is extremely challenging[31, 39-40], especially in an enantioselective manner. It's worth noting that er of **3**, **8**, **9**, **12** and **13** are different, which might indicate that the transmetalation step taking place prior to the alkene insertion. Experiments with $D_2O$ instead of $H_2O$ were conducted under the optimal conditions by using **1a** and **1g** as the substrates (Fig. 2b), respectively. 75% D-labeled **4a** was obtained in 85% yield with 94:6 er. Nevertheless, *ortho*-methyl aryl group derived **1g** could not afford D-labeled **4g**. Deuterium (D)-labeling experiments confirmed our assumption that the step of C-H bond activation is reversible. Moreover, the five-membered palladacycle of C($sp^2$)-H bond activation was favored comparing with the less-strained six-membered palladacycle of C($sp^3$)-H bond activation under the reaction conditions[35]. Despite overcoming the high barriers was required to construct the highly strained 5,4-spirocycle, the C-C bond of **4a** could be cleaved to give the ring-opening byproduct **5a** at 120 $^oC$ (Fig. 2c). Nonlinear effect studies on the enantiomeric composition of the chiral ligand *N*-$CD_3$-**Xu4** and product **4a** indicated there is a clear first-order dependence was observed for the catalyst (Fig. 2d). These results are consistent with an active catalyst/ligand being of a monomeric nature and the reaction possessing a first-order dependence on catalyst. When carboiodination compound **2ae** (5-*exo*) was subjected to the catalysis of $Pd(dba)_2$/QPhos or $Pd_2(dba)_3$•$CHCl_3$/*N*-Me-**Xu3**, 6-*endo*-products **16a** and **16a'** could be obtained, which indicates that the alkene insertion and carboiodination steps are reversible. Subsequently, we examined the progress of the reaction as a function of time and temperature with *ortho*-iodophenol-derived allyl ether **1ae** as the model substrate (Fig. 2f). At 100 $^oC$, the reaction proceeded smoothly and gave the 5-*exo*-product **2ae** with 93% *ee* and 95:5 rr. With the increase of reaction time, the ratio of 5-*exo*-product and 6-*endo*-product, and *ee* value hardly changes. However, the proportion of 6-*endo*-product increased significantly with increasing of the temperature (120 $^oC$ and 150 $^oC$). Meanwhile, the *ee* value of 5-exo-product decreased obviously.

Based on the results of the above experiment and previous works, a reasonable pathway for this palladium-catalyzed Heck/intramolecular C-H alkylation reaction is shown in Fig. 3. First, the arylpalladium species **I** was generated by oxidative addition of **1** or **14** with Pd(0) complex. Then, followed by an intramolecular 5-*exo*-Heck-type or 6-*endo*-Heck-type reactions form chiral *σ*-alkylpalladium species **II** or **II'**. Next, aryl ($Ar^2$) C-H bond activation via the *σ*-alkylpalladium intermediate **II** deprotonation gave a spiropalladacycle **III**, which produces the corresponding product **4** or **15** and regenerates the Pd(0) catalyst to the next catalyzed cycle from reductive elimination. Nevertheless, *σ*-alkylpalladium species **II** through C-I elimination also afforded the iodide **2**. The *β*-H elimination of 6-*endo*-cyclization *σ*-alkylpalladium species **II'** could delivered the *endo*-products **16a** and **16a'**. Here, it is worth noting that the C($sp^2$)-H activation, the carbopalladation and the C–I reductive elimination steps are reversible.

Encouraged by these excellent results, we applied this method to the construction of the optically active 5,5-spirocycles. Both enantiomers of a chiral molecule are often required in organic synthesis, biological chemistry, and the medicinal and pharmaceutical industries. Generally, the synthesis of the enantiomer of a chiral molecule could be obtained by using the enantiomer of chiral ligands. Herein, we envisaged that the synthesis of a pair of enantiomers might be achieved by changing the position of the aromatic or heteratomic aromatic rings (Table 3). Using a variety of aryl iodides **14** bearing electron-donating/withdrawing groups at the *para*- and *meta*-positions of phenyl rings, both (*R*)- and (*S*)-enantiomers of the spiro-indane-dihydrobenzofuran products **15a**–**15f** were obtained in high yields (80–99% for the (*R*)-enantiomers and 82–98% for the (*S*)-enantiomers) with excellent enantioselectivity (95:5–97:3 ers for the (*R*)-enantiomers and 95:5–97.5:2.5 ers for the (*S*)-enantiomers) under the standard condition, respectively. When the linker at C2 or C3 of heteratomic aromatic rings, such as thiophene, benzothiophene and furan, the corresponding 5,5-spirocycle products **15g**–**15n** were also afforded with good results (93–99% yields with 95:5–98.5:1.5 ers for the (*R*)-enantiomers and 94–>99% yields with 95:5–98.5:1.5 ers for the (*S*)-enantiomers).

Then, we further extended the scope of alkene-tethered aryl iodides **14** (Table 4). In more than 40 examples, the desired products **15o**–**15bc** were synthesized exclusively in good yields with excellent enantioselectivity (up to 98.5:1.5 er). Substrates bearing monosubstituted phenyl rings with electron-donating or -withdrawing groups at different positions (ortho or para), a disubstituted phenyl ring, a trisubstituted phenyl ring, a naphthalene, a pyrene and medicinally relevant heterocycles (dibenzo[*b*,*d*]thiophene, benzofuran, thiophene and indole) could be well tolerated. Notably, the present asymmetric catalytic system is applicable to BocN as a tether, delivering the indolines **15al**–**15am** in good yields and with good *ee* values.

# Conclusions

In summary, we have developed the first highly enantioselective palladium-catalyzed domino Heck/intramolecular C-H alkylation of alkenes with excellent chemo- and regioselectivities. The mothed not only constructs various chiral 5,4-and 5,5-spirocycles including one challenging all-carbon quaternary stereocenter, but also exhibits superior catalytic properties of Xu-Phos, which open up new avenues for

the asymmetric domino Heck/intramolecular C-H activation reaction. Moreover, this work also provides an alternative solution that a position of the phenyl ring-dependent enantiodivergent synthesis, enabling the synthesis of both enantiomers of the product using the same enantiomer of a chiral catalyst. Moreover, this protocol works with a wide range of substrates and tolerates a series of functional groups under operationally simple and mild reaction conditions. In addition, the reversibility of the C($sp^2$)-H activation, alkene insertion and C–I reductive elimination steps was revealed by experiment. Further direction will focus on the development of asymmetric functionalization of palladacycles and will be reported in the due course.

# Methods

**General procedure for the 5,4-spirocycle derivatives (4).** To a 10 mL oven-dried sealed tube was added substrate **1** (0.20 mmol, 1.0 equiv.), Pd-P$^t$Bu$_3$-G3 (11.4 mg, 0.02 mmol, 10 mol%), *N*-$CD_3$-**Xu4** (31 mg, 0.044 mmol, 22 mol%), $Cs_2CO_3$ (65.2 mg, 0.2 mmol, 1.0 equiv.), KOAc (19.6 mg, 0.2 mmol, 1.0 equiv.). The flask was evacuated and refilled with argon. Then, $H_2O$ (36 mg, 2.0 mmol, 10.0 equiv.), MTBE (2 mL), and $^i$Pr$_2$O (2 mL) was added to the tube, and stirred at room temperature for 1 h. Then the mixture was stirred at 110 °C for 12-24 h. After the reaction was complete (monitored by TLC), solvent was removed under reduced pressure. The crude product was then purified by flash column chromatography on silica gel to afford the desired product **4**.

**General procedure for the 5,5-spirocycle derivatives (15).** To a sealed tube was added substrate **14** (0.2 mmol), $Pd_2(dba)_3$•$CHCl_3$ (0.01 mmol, 5 mol%), *N*-Me-**Xu3**

(0.04 mmol, 20 mol%) and $Cs_2CO_3$ (0.4 mmol). The flask was evacuated and refilled with argon. Then, MTBE (2 mL) was added to the tube, and stirred at room temperature for 1 h. Then the mixture was stirred at 90 °C for 12-24 h. After the reaction was complete (monitored by TLC), solvent was removed under reduced pressure. The crude product was then purified by flash column chromatography on silica gel to afford the desired product **15**.

# Declarations

### Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2058479. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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### Author contributions

X.B. and Z.-M.Z. carried out the experimental and data-analysis work. D.J., L.Z., and L.W. performed the synthesis of the chiral ligands and materials. Z.-M.Z. and J.Z. designed the reaction, directed the project and wrote the paper with the assistance of L.Y.

### Competing interests

The authors declare no competing interests.

### Additional information

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## References

1. Posner, G. H., Hamill, T. G. An Asymmetric Total Synthesis of Fragrant Spiro[4.5]decane Sesquiterpene (-)-*β*-Vetivone via an Enantiomerically Pure Vinylic Sulfoxide. *J. Org. Chem.* **53**, 6031–6035 (1988).
2. Kita, Y., Fujioka, H. Enantioselective constructions of quaternary carbons and their application to the asymmetric total syntheses of fredericamycin A and discorhabdin A. *Pure Appl. Chem.* **79**, 701–713 (2007).
3. Nicolaou, K. C., Vourloumis, D., Winssinger, N. & Baran, P. S. The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century. *Angew. Chem. Int. Ed.* **39**, 44–122 (2000).
4. Shirai, F. et al. Discovery of novel spiroindoline derivatives as selective tankyrase inhibitors. *J. Med. Chem.* **62**, 3407–3427 (2019).
5. Ding, K., Han Z. & Wang, Z. Spiro Skeletons: A Class of Privileged Structure for Chiral Ligand Design. *Chem.– Asian J.* **4**, 32–41 (2009).
6. Xie, J. & Zhou, Q. Magical Chiral Spiro Ligands. *Acta Chim. Sinica.* **72**, 778–797 (2014).
7. Zheng, Y., Tice, C. M., Singh, S. B. The use of spirocyclic scaffolds in drug discovery. *Bioorg. Med. Chem. Lett.* **24**, 3673–3682 (2014).
8. Rios, R. Enantioselective methodologies for the synthesis of spiro compounds. *Chem. Soc. Rev.* **41**, 1060–1074 (2012).
9. Ding, A., Meazza, M., Guo, H., Yang J. W. & Rios, R. New development in the enantioselective synthesis of spiro compounds. *Chem. Soc. Rev.* **47**, 5946–5996 (2018).
10. Narayan, R. *et al.* Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides for Biology-Oriented Synthesis. *Acc. Chem. Res.* **47**, 1296–1310 (2014).

11. Tan, B., Candeias N. R. & Barbas III, C. F. Construction of bispirooxindoles containing three quaternary stereocentres in a cascade using a single multifunctional organocatalyst. *Nat. Chem.* **3**, 473–477 (2011).
12. Godfrey, R. C., Green, N. J., Nichol G. S. & Lawrence A. L. Total synthesis of brevianamide A. *Nat. Chem.* **12**, 615–620 (2020).
13. Han, T., Yao, Z., Qiu, Z. *et al.* Photoresponsive spiro-polymers generated in situ by C–H-activated polyspiroannulation. *Nat. Commun.* **10**, 5483 (2019).
14. Zhou, Z., Wang, Z.-X., Zhou, Y.-C. *et al.* Switchable regioselectivity in amine-catalysed asymmetric cycloadditions. *Nat. Chem.* **9**, 590–594 (2017).
15. Moerdyk, J. P. & Bielawski, C. W. Diamidocarbenes as versatile and reversible [2+1] cycloaddition reagents. *Nat. Chem.* **4**, 275–280 (2012).
16. Antonchick, A. P. *et al.* Highly enantioselective synthesis and cellular evaluation of spirooxindoles inspired by natural products. *Nat. Chem.* **2**, 735–740 (2010).
17. Rauniyar, V., Lackner, A. D., Hamilton, G. L., Toste, F. D. Asymmetric Electrophilic Fluorination Using an Anionic Chiral Phase-Transfer Catalyst. *Science* **334**, 1681–1684 (2011).
18. Chen, X., Engle, K. M., Wang, D.-H. & Yu, J.-Q. Palladium(II)-catalyzed C–H activation/C–C cross-coupling reactions: versatility and practicality. *Angew. Chem. Int. Ed.* **48**, 5094–5115 (2009).
19. Colby, D. A., Bergman, R. G. & Ellman, J. A. Rhodium-catalyzed C–C bond formation via heteroatom-directed C–H bond activation. *Chem. Rev.* **110**, 624–655 (2010).
20. Engle, K. M., Mei, T.-S., Wasa, M. & Yu, J.-Q. Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions. *Acc. Chem. Res.* **45**, 788–802 (2012).
21. Huang, Z., Lim, H. N., Mo, F., Young, M. C. & Dong, G. Transition metal-catalyzed ketone-directed or mediated C–H functionalization. *Chem. Soc. Rev.* **44**, 7764–7786 (2015).
22. Gensch, T., Hopkinson, M. N., Glorius, F. & Wencel-Delord, J. Mild metal-catalyzed C–H activation: examples and concepts. *Chem. Soc. Rev.* **45**, 2900–2936 (2016).
23. Hartwig, J. F. Borylation and silylation of C–H bonds: a platform for diverse C–H bond functionalizations. *Acc. Chem. Res.* **45**, 864–873 (2012).
24. Cho, J.-Y., Tse, M. K., Holmes, D., Maleczka, R. E. Jr & Smith, M. R. III. Remarkably selective iridium catalysts for the elaboration of aromatic C–H bonds. *Science* **295**, 305–308 (2002).
25. Chen, C. & Hartwig, J. F. Rhodium-catalyzed intermolecular C–H silylation of arenes with high steric regiocontrol. *Science* **343**, 853–857 (2014).
26. Phipps, R. J. & Gaunt, M. J. A meta-selective copper-catalyzed C–H bond arylation. *Science* **323**, 1593–1597 (2009).
27. Duong, H. A., Gilligan, R. E., Cooke, M. L., Phipps, R. J. & Gaunt, M. J. Copper(II)-catalyzed meta-selective direct arylation of α-aryl carbonyl compounds. *Angew. Chem. Int. Ed.* **50**, 463–466 (2011).
28. Zhang, Y.-H., Shi, B.-F. & Yu, J.-Q. Pd(II)-catalyzed olefifination of electron-defificient arenes using 2,6-dialkylpyridine ligands. *J. Am. Chem. Soc.* **131**, 5072–5074 (2009).

29. Leow, D., Li, G., Mei, T.-S. & Yu, J.-Q. Activation of remote meta-C–H bonds assisted by an end-on template. *Nature* **486**, 518–522 (2012).
30. Tang, R.-Y., Li, G. & Yu, J.-Q. Conformation-induced remote meta-C–H activation of amines. *Nature* **507**, 215–220 (2014).
31. Ping, Y., Li, Y., Zhu, J. & Kong, W. Construction of quaternary stereocenters by palladium-catalyzed carbopalladation-initiated cascade reactions. *Angew. Chem. Int. Ed.* **58**, 1562–1573 (2019).
32. Grigg, R., Meerholtz, P. F. C. & Sridharan, V. Palladium catalysed synthesis of spiroindolines. *Tetrahedron* **50**, 359–370 (1994).
33. Ruck, R. T. *et al*. Palladium-catalyzed tandem Heck reaction/C-H functionalization-preparation of spiro-indane-oxindoles. *Angew. Chem. Int. Ed.* **47**, 4711–4714 (2008).
34. Satyanarayana, G., Maichle-Mossmer, C. & Maier, M. E. Formation of pentacyclic structures by a domino sequence on cyclic enamides. *Chem. Commun.* 1571–1573 (2009).
35. Piou, T., Neuville, L. & Zhu, J. Spirocyclization by palladium-catalyzed domino heck-direct C-H arylation reactions: synthesis of spirodihydroquinolin-2-ones. *Org. Lett.* **14**, 3760–3763 (2012).
36. Piou, T., Neuville, L. & Zhu, J. Activation of a C($sp^3$)-H bond by a transient sigma-alkylpalladium(II) complex: synthesis of spirooxindoles through a palladium-catalyzed domino carbopalladation/C($sp^3$)-C($sp^3$) bond-forming process. *Angew. Chem. Int. Ed.* **51**, 11561–11565 (2012).
37. Franzoni, I., Yoon, H., García-López, J. A., Poblador-Bahamonde, A. I. & Lautens, M. Exploring the mechanism of the Pd-catalyzed spirocyclization reaction: a combined DFT and experimental study. *Chem. Sci.* **9**, 1496–1509 (2018).
38. Pèrez-Gómez, M. et al. Synthesis and Reactivity of Model Intermediates Proposed for the Pd-Catalyzed Remote C–H Functionalization of *N*-(2-Haloaryl)acrylamides. *Organometallics* **36**, 4465–4476 (2017).
39. Ye, J. et al. Remote C-H alkylation and C-C bond cleavage enabled by an in situ generated palladacycle. *Nat. Chem.* **9**, 361–368 (2017).
40. Ye, F., Ge, Y., Spannenberg, A., Neumann H., & Beller M. The role of allyl ammonium salts in palladium-catalyzed cascade reactions towards the synthesis of spiro-fused heterocycles. *Nat. Commun.* **11**, 5383–5390 (2020).
41. Huang, Q., Fazio, A., Dai, G., Campo, M. A. & Larock, R. C. Pd-Catalyzed Alkyl to Aryl Migration and Cyclization: An Efficient Synthesis of Fused Polycycles via Multiple C-H Activation. *J. Am. Chem. Soc.* **126**, 7460–7461 (2004).
42. Sickert, M., Weinstabl, H., Peters, B., Hou, X. & Lautens, M. Intermolecular domino reaction of two aryl iodides involving two C-H functionalizations. *Angew. Chem. Int. Ed.* **53**, 5147–5151 (2014).
43. Bunescu, A., Piou, T., Wang, Q. & Zhu, J. Pd-Catalyzed Dehydrogenative Aryl–Aryl Bond Formation via Double C($sp^2$)–H Bond Activation: Efficient Synthesis of [3,4]-Fused Oxindoles. *Org. Lett.* **17**, 334–337 (2015).

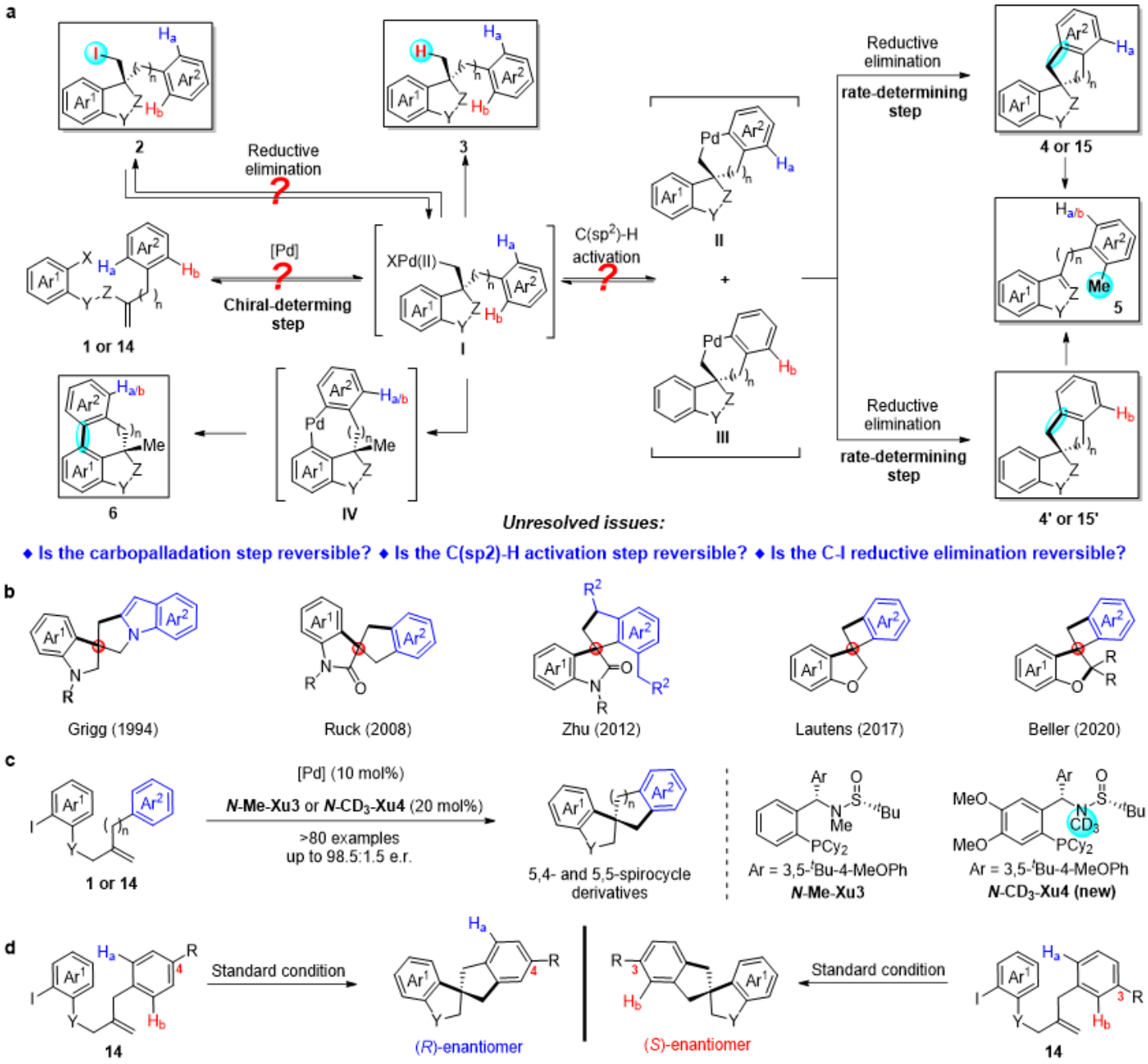
44. Zhang, Z.-M. *et al.* Palladium-Catalyzed Enantioselective Reductive Heck Reactions: Convenient Access to 3,3-Disubstituted 2,3-Dihydrobenzofuran. *Angew. Chem. Int. Ed.* **57**, 10373–10377 (2018).
45. Zhang, Z.-M. *et al.* Enantioselective Dicarbofunctionalization of Unactivated Alkenes by Palladium-Catalyzed Tandem Heck/Suzuki Coupling Reaction. *Angew. Chem. Int. Ed.* **58**, 14653–14659 (2019).
46. Zhang, Z.-M., Xu, B. *et al.* Palladium/XuPhos-Catalyzed Enantioselective Carboiodination of Olefin-Tethered Aryl Iodides. *J. Am. Chem. Soc.* **141**, 8110–8115 (2019).
47. Zhou, L., Li, S. *et al.* Enantioselective Difunctionalization of Alkenes by a Palladium-Catalyzed Heck/Sonogashira Sequence. *Angew. Chem. Int. Ed.* **59**, 2769–2775 (2020).
48. Whyte, A. *et al*. Sequential Pd(0) and Pd(II)-Catalyzed Cyclizations: Enantioselective Heck and Nucleopalladation Reactions. *Angew. Chem. Int. Ed.* **60**, DOI: 10.1002/anie.202106518 (2021).
49. Jones, D. J., Lautens, M. & McGlacken, G. P. The emergence of Pd-mediated reversible oxidative addition in cross coupling, carbohalogenation and carbonylation reactions. *Nat. Catal*. **2**, 843–851 (2019).
50. Marchese, A. D., Larin, E. M., Mirabi, B. & Lautens. M. Metal-Catalyzed Approaches toward the Oxindole Core. *Acc. Chem. Res.* **53**, 1605–1619 (2020).
51. Newman, S. G. & Lautens, M. Palladium-Catalyzed Carboiodination of Alkenes: Carbon-Carbon Bond Formation with Retention of Reactive Functionality. *J. Am. Chem. Soc.* **133**, 1778–1780 (2011).
52. Yoon, H., Marchese, A. D. & Lautens, M. Carboiodination Catalyzed by Nickel. *J. Am. Chem. Soc.* **140**, 10950–10954 (2018).
53. Liu, H., Li, C., Qiu, D. & Tong, X. Palladium-Catalyzed Cycloisomerizations of (Z)-1-Iodo-1,5-dienes: Iodine Atom Transfer and Mechanistic Insight to Alkyl Iodide Reductive Elimination. *J. Am. Chem. Soc.* **133**, 6187–6193 (2011).
54. Carreira, E. M. & Fessard, T. C. Four-membered ring-containing spirocycles: synthetic strategies and opportunities. *Chem. Rev.* **114**, 8257–8322 (2014).
55. Zhang, Z.-M., Chen, P. *et al.* A New Type of Chiral Sulfinamide Monophosphine Ligands: Stereodivergent Synthesis and Application in Enantioselective Gold(I)-Catalyzed Cycloaddition Reactions. *Angew. Chem. Int. Ed.* **53**, 4350–4354 (2014).
56. Wang, L. et al. Enantioselective Synthesis of Isoxazolines Enabled by Palladium-Catalyzed Carboetherification of Alkenyl Oximes. *Angew. Chem. Int. Ed.* **59**, 4421–4427 (2020).
57. Wang, Y. et al. Gold-Catalyzed Asymmetric Intramolecular Cyclization of N-Allenamides for the Synthesis of Chiral Tetrahydrocarbolines. *Angew. Chem. Int. Ed.* **56**, 15905–15909 (2017).
58. Dai, Q. et al. P-Chiral Phosphines Enabled by Palladium/Xiao-Phos-Catalyzed Asymmetric P–C Cross-Coupling of Secondary Phosphine Oxides and Aryl Bromides. *J. Am. Chem. Soc.* **141**, 20556–20564 (2019).
59. Zhou, W. et al. Chiral Sulfinamide Bisphosphine Catalysts: Design, Synthesis, and Application in Highly Enantioselective Intermolecular Cross-Rauhut-Currier Reactions. *Angew. Chem. Int. Ed.* **54**, 14853–14857 (2015).

60. Lin, T.-Y. et al. Design and Synthesis of TY-Phos and Application in Palladium-Catalyzed Enantioselective Fluoroarylation of gem-Difluoroalkenes. *Angew. Chem. Int. Ed.* **59**, 22957–22962 (2020).
61. Yoon, H., Rolz, M., Landau, F. & Lautens, M. Palladium-catalyzed spirocyclization through C-H activation and regioselective alkyne insertion. *Angew. Chem. Int. Ed.* **56**, 10920–10923 (2017).

# Tables

Tables 1-4 are available in the Supplementary Files.

# Figures




## Figure 1

Domino Heck/Intramolecular C-H Alkylation reaction. a, The classic domino Heck/Intramolecular C-H alkylation reaction, the carbopalladation step is a chiral-determing step which is reversible. Various competitive side reactions such as carboiodination reaction (2), reductive Heck reaction (3) and 1,4-Pd migration/C(sp2)−H functionalization (6). The high temperature (≥ 120 oC) easily lead to the ring-opening by-product 5. When Ha and Hb are different, the regioselective product 4’ may be given. b. Reported elegant racemic examples. Grigg et al. successfully developed Pd-catalyzed remote-C-H functionalization of the heteroaromatic tethered alkene moiety. Ruck et al. have accomplished the expansion of the C(sp2)-H scope to an unactivated aryl C-H bond. Zhu et al. demonstrated that the σ-alkylpalladium intermediate can activate the C(sp3)-H bond. The highly strained spiro-fused

benzocyclobutene derivatives have been developed by Lautens. Beller's group combines selective nucleophilic substitution (SN2'), Pd-catalyzed Heck and C-H activation reaction in a cascade manner. c. This work presents a robust palladium/Xu-Phos catalyst system for enantioconvergent tandem Heck reaction/C-H alkylation via a palladacycle intermediate. d. Synthesis of both enantiomers of the product can be accomplished depending on the site of the substituent on the aromatic or heteroaromatic ring.

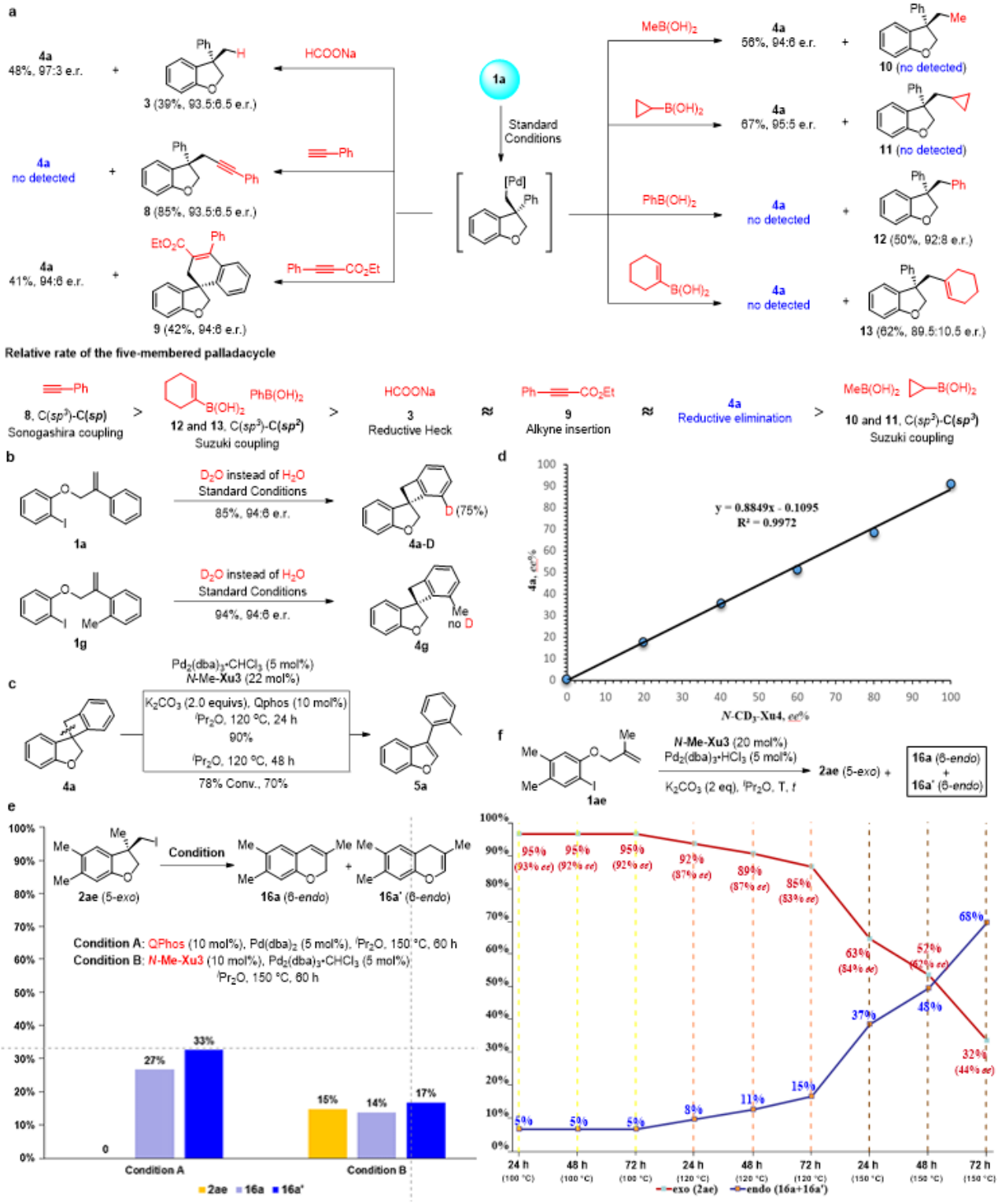



Figure 2

Mechanistic studies. a. Using HCO2Na, PhB(OH)2, MeB(OH)2, cyclopropylboronic acid, cyclohexenylboronic acid, ethyl 3-phenylpropiolate or phenylacetylene as the second substrates. b. Deuterium (D)-labeling experiments of 1a and 1g. c. The ring-opening side reaction. d. Nonlinear effect studies on the enantiomeric composition of the chiral ligand N-CD3-Xu4 and product 4a. e. 6-endo-Heck product 16a and 16a' could be obtained from 5-exo-product 2ae. f. The ratios of 5-exo-product (2ae) with 6-endo-product (16a and 16a') change with time at 100 oC, 120 oC and 150 oC.

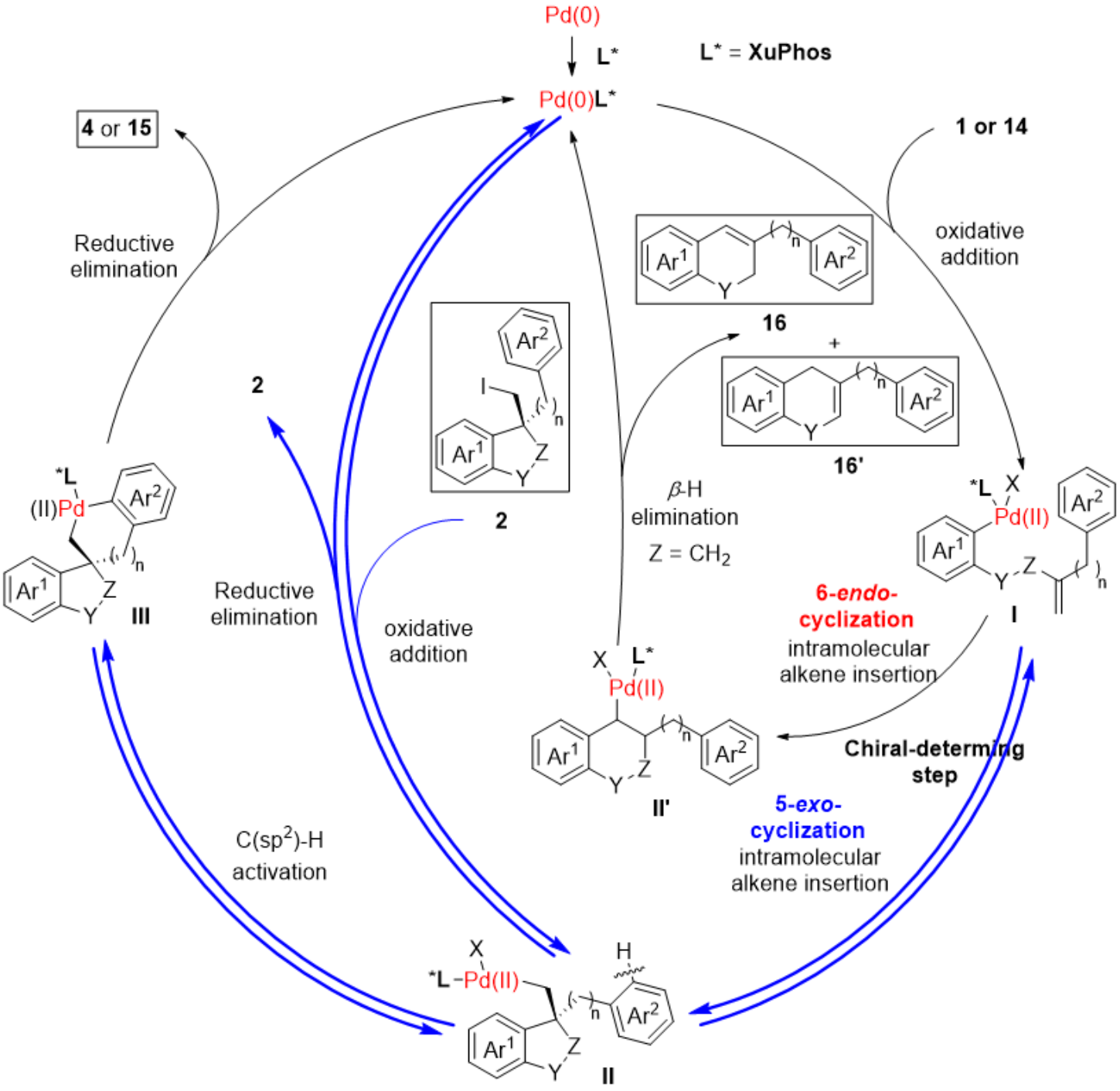



Figure 3

Proposed Mechanism.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupportingInformation.pdf
- Table1.png
- Table2.png
- Table3.png
- Table4.png