Non-innocent hybrid cycloolefin ligands for palladium/olefin cooperative catalysis

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Abstract: Catalyst design is a key research area in modern synthetic chemistry. Engineering of molecular catalysts in homogeneous catalysis brings about new catalytic modes that enable efficient synthetic transformations. In this regard, design of novel ligands for transition-metal catalysis have played a major role. Olefins have been emerging as a significant class of steering ligands in transition-metal catalysis, which are known to serve as innocent ligands that provide electronic and steric tuning of the metal center. However, it is unknown whether a distinct type of olefin ligand that contrasts the common innocent feature is possible. Here we show that a novel type of heteroatom-cycloolefin hybrid ligand functions as a non-innocent ligand in palladium catalysis, which exhibits covalent catalytic function that enables efficient *ipso*,*ortho*-difunctionalization of iodoarenes. Detailed mechanistic study revealed that this ligand undergoes reversible covalent bonding between the substrate and the cycloolefin unit, which forms key organopalladium intermediates to enable new reactivity. Our results demonstrate a novel design concept that utilizes unstrained cycloolefin as a covalent catalytic module, opening an avenue to a more general transition metal/olefin cooperative catalysis.

Main:

Introduction

Homogeneous transition-metal (TM) catalysis has made great contributions to modern synthetic chemistry[1]. Engineering of TM-based molecular catalysts played a crucial role, which enabled new catalytic modes that lead to useful synthetic reactions with enhanced selectivity and efficiency. In this regard, design of novel ligands for TM catalysis with specific functions is of great significance[2].

The majority of ancillary ligands utilize one or more heteroatom (e.g., N, O, S, or P) as the coordination site to form the metal-ligand bond. In the past decades, olefins have been recognized as unique steering ligands in TM-catalysis[3-7]. Owing to elegant design, in these systems olefins do not behave as unsaturated reactants as usual, but act as spectator ligands to provide electronic and steric tuning of the metal center. A variety of diene and hybrid heteroatom/olefin ligands have been developed and used in combination with transition metals to promote many synthetically useful reactions (Fig. 1a). This great success led us to think of an interesting question contrasting the established concept of olefin ligand: is it possible to develop an olefin ligand that is reactive towards organometallic intermediates for transition metal catalysis, [i.e., a non-innocent (or cooperative) ligand[8-11]]? With this question in mind, we imagined to explore the possibility of developing a fundamentally new type of olefin ligand that makes use of the reactivity of the carbon-carbon double bond.

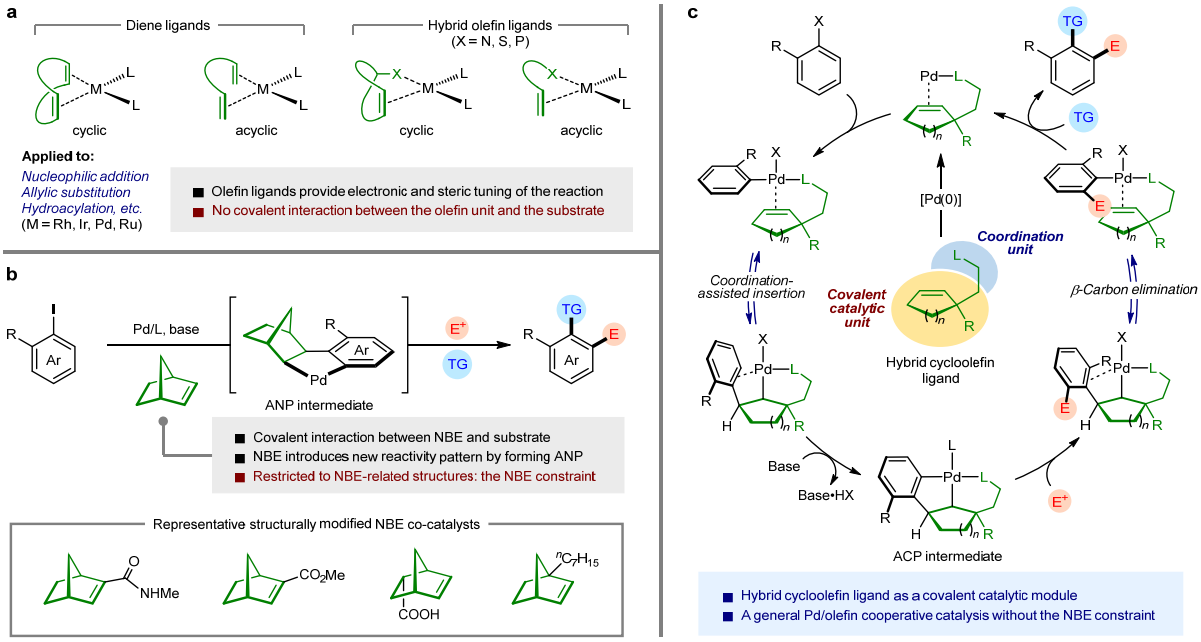


Fig. 1. Olefin ligands and co-catalysts. a, Olefins serve as stirring ligands to tune transition-metal-catalyzed reactions electronically and sterically without covalent interaction with substrates. **b**, In the Pd/NBE cooperative catalysis NBE serves as a covalent transient mediator to enable *ipso*,*ortho*-difunctionalization, and the bicycle[2.2.1]heptane skeleton is indispensable. **c**, In this work hybrid cycloolefin ligand has been developed as a covalent catalytic module, which enables a general Pd/olefin cooperative catalysis.

This idea was inspired by the palladium/norbornene (Pd/NBE) cooperative catalysis (Fig. 1b)[12-18], which was originally discovered by Catellani and co-workers[19], and further

implemented into a general synthetic methodology by the Lautens group[20,21] and many other research groups. In this chemistry, NBE reacts with an arylpalladium species to form an arylnorborylpalladacycle (ANP) intermediate, which then allows for sequential introduction of an electrophile (E^+) and a termination group (TG) at the *ipso*- and *ortho*-positions of the aryl ring, and finally regenerates NBE. On a catalytic viewpoint, NBE represents a unique olefin-type covalent co-catalyst that bonds to the substrate, enables new reactivity, and recovers its original structure while releasing the product. While in most cases this co-catalyst should be used in sub- or even super-stoichiometric amounts to ensure reactivity, this process has been regarded as an efficient protocol for vicinal difunctionalization of arene substrates. However, the Pd/NBE cooperative catalysis is constrained to NBE and its structurally modified derivatives in which the bicyclo[2.2.1]heptene skeleton remains[22-28], and to date people have to admit that the NBE structure is indispensable due to its unique structural feature[17]. It has been a long-standing question that whether or not an unstrained olefin without the NBE skeleton could be used in the covalent cooperative catalysis[29]. This question, together with the question before, represent the quest for a new type of cooperative olefin ligand. We intended to address these questions, not only for sake of curiosity, but also for exploiting the potential of metal-olefin cooperative catalysis. Here, we report that hybrid cycloolefin ligands could function as a covalent catalytic module in combination with Pd to achieve a Pd/olefin cooperative catalysis, and a detailed mechanistic study clearly revealed the non-innocent nature of the ligand.

Results and Discussion

Ligand Design

We envisioned to design a molecule consisting of a cycloolefin moiety and a coordination site as the proposed hybrid cycloolefin ligand (Fig. 1c). In this ligand, the coordination site is tethered to the α-position of the cycloolefin, aiming to facilitate alkene insertion into an arylpalladium species by coordination. This directed insertion could exclude the existence of a hydrogen atom *syn* to palladium, avoiding undesired *β*-hydride elimination. The cycloolefin framework keeps the aryl group and the palladium center suprafacial after the insertion step, enabling arylcycloalkylpalladacycle (ACP) formation under basic conditions. We hypothesized that, this ACP intermediate may behave similarly to the ANP intermediate[12], allowing a reaction sequence involving the introduction of an electrophile at the *ortho* position, regeneration the cycloolefin motif by *β*-carbon elimination, and the attachment of a termination group at the *ipso* position.

The first ligand designed for this propose (**L1**) features a cyclopentenyl group as the cycloolefin unit, a diarylphosphine group as the coordination unit, and a flexible ethylene bridge uniting both units. To test its performance on cooperative catalysis, the *ortho*-alkylation/*ipso*-Heck reaction[19] of aryl iodide **1a** with alkyl iodide **2a** and acrylate **3a** was chosen as the model reaction (Fig. 2a). To our excitement, the desired difunctionalization product **4a** was obtained in a moderate yield, together with the Heck-type byproduct **5a**. Not surprisingly, a phosphine oxide derivative of this ligand, **L1-O**, exhibited complete loss of activity for promoting the formation of **4a**, while the byproduct **5a** was still produced. The success of ligand **L1** was a proof-of-concept that showcased the competence of the phosphine-cycloolefin hybrid ligand in Pd/olefin cooperative catalysis, though improvements on both activity and selectivity were still demanded.

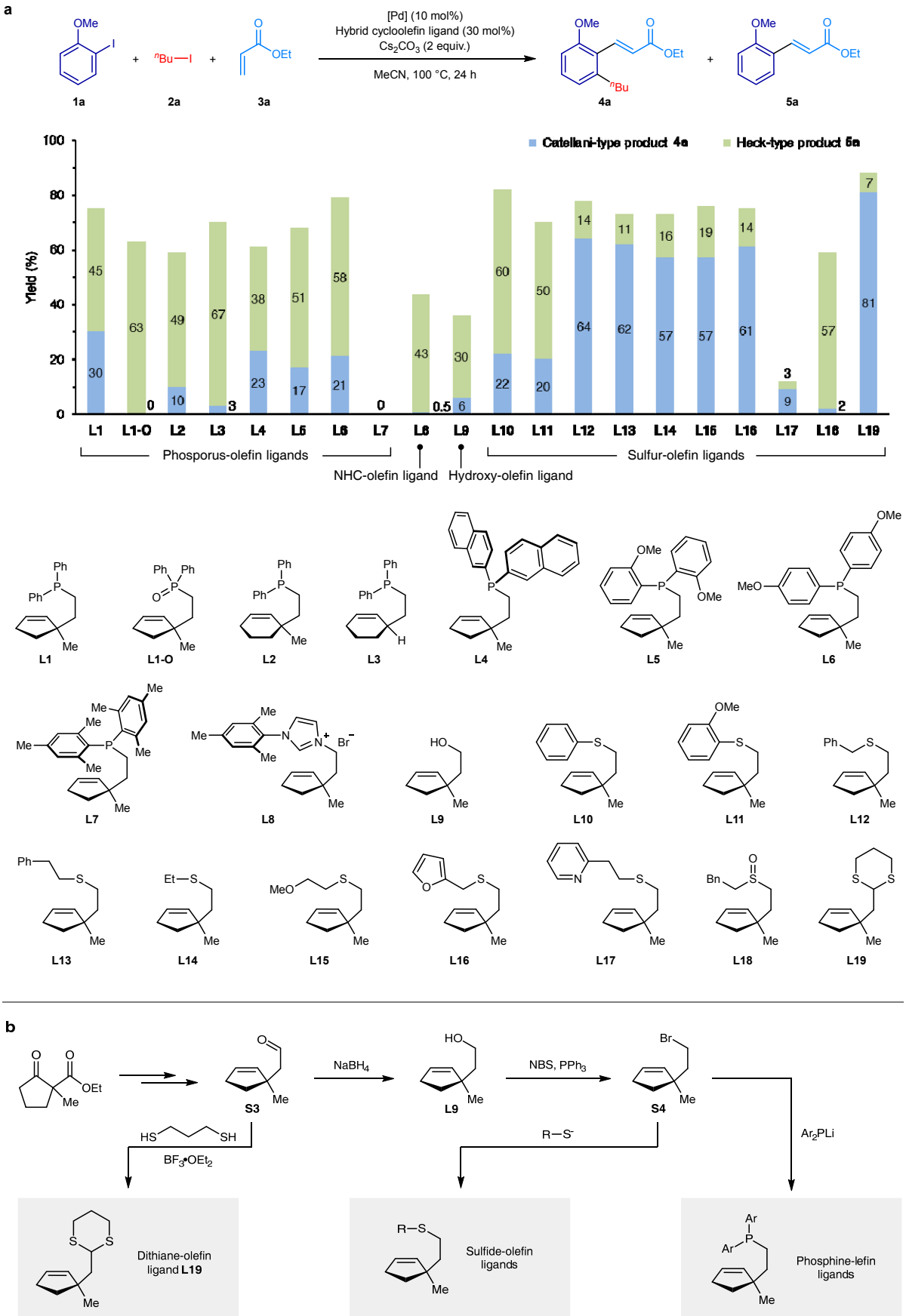


Fig. 2. Hybrid olefin ligands for Pd/olefin cooperative catalysis. a, Structure-activity relationship. Reaction conditions: iodoarene **1a** (0.2 mmol), iodide **2a** (0.4 mmol), acrylate **3a**

(0.4 mmol), the palladium source [0.02 mmol, for ligands **L1-L8**, $Pd(OAc)_2$ was employed; for ligands **L9-L19**, $Pd(dba)_2$ was employed (dba = dibenzylideneacetone)], ligand (0.06 mmol), Cs_2CO_3 (0.4 mmol for **L1-L7**, 0.8 mmol for **L8** and **L9**, 0.6 mmol for **L10-L19**), acetonitrile (2 mL) as the solvent, 100 °C, sealed tube, 24 h. **b**, Representative synthetic routes of phosphine-, sulfide-, and dithiane-olefin ligands.

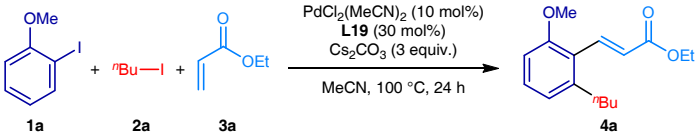
Ligand Structure-Activity Relationship (SAR)

We then focused on improving the performance of the hybrid cycloolefin ligand (Fig. 2a). Switching the cycloolefin ring system from cyclopentene to cyclohexene (**L2**) resulted a decreased reactivity. The α-methyl group on the cycloolefin seemed to be beneficial, as removal of it (**L3**) led to significantly decreased activity in the cooperative catalysis. We then turned back to the cyclopentenyl unit and investigated the effect of the aryl substituents of the phosphine unit. However, to our disappointment, varying the aryl group between naphtha-2-yl (**L4**), 2-methoxyphenyl (**L5**), 4-methoxyphenyl (**L6**), and 2,4,6-mestyl (**L7**) groups did not improve the performance of the ligand. Given that the nature of the coordination site may dramatically alter the reactivity of the metal center, we attempted to use an *N*-heterocyclic carbene (NHC) motif (**L8**) or a hydroxyl group (**L9**) as the coordination unit in place of phosphine. However, both ligands were found unsatisfactory, though tiny amounts of the desired product **4** were still produced.

Interestingly, sulfide ligands, which are not prevalently used in palladium catalysis[30-33], were found to be superior. Aryl sulfide ligands **L10** and **L11** exhibited comparable activity to that of phosphine ligands, while alkyl sulfide ligands **L12-16** performed much better. It was found that, the substituent on the alkyl group exerts a minor effect on ligand activity, except that a coordinating pyrid-2-yl group (**L17**) suppresses the activity remarkably. A sulfoxide-cycloolefin ligand **L18** (as a 1:1 diastereomeric mixture) also exhibited a low reactivity. Quite interestingly, dithioacetal-cyclopentene ligand **L19** exhibited the best activity amongst all ligands tested, which minimized the formation of the Heck product **5a** and afforded the difunctionalization product **4a** in an excellent yield. Overall, the SAR study identified hybrid cycloolefin ligand as a generic design for Pd/olefin cooperative catalysis, and revealed the performance of the hybrid cycloolefin ligand as a function of the coordination site. Most of these ligands are easily accessible from common precursors (Fig. 2b).

A series of control experiments were performed with the optimal ligand **L19** to understand the role of each reaction component (Table 1). Not surprisingly, it was found that both palladium and the hybrid cycloolefin ligand **L19** were indispensable for the catalysis (entries 1-3). $Pd(dba)_2$ as the source of palladium instead of $PdCl_2(MeCN)_2$ exerted a minor influence on the efficiency of the reaction (entry 4). Potassium carbonate was found to be incompetent as the base compared with cesium carbonate (entry 5). *N*,*N*-dimethylformamide (DMF) is also a compatible solvent, albeit somewhat inferior to acetonitrile (entry 6). Performing the reaction at 80 ºC resulted in a decreased yield (entry 7). Finally, we were delighted to find that only 5 mol% Pd and 10 mol% of **L19** were sufficient to promote the desired difunctionalization reaction efficiently (entry 8). Lowering the loading of **L19** from 10 mol% to 6 mol% still resulted in satisfactory activity of the catalytic system, albeit minor decrease in yield and selectivity was observed (entries 9 and 10). For comparison, the reaction using 30 mol% NBE instead of **L19** was far less efficient (entry 11), demonstrating the advantage of the new ligand in Pd/olefin cooperative catalysis.

Table 1. Control experiments[a]



1a **2a** **3a** **4a**

Entry	Variation of reaction conditions	Yield of **4a** (%)[b]	Yield of **5a** (%)[b]
1	None	86	4
2	No Pd	0	0
3	No **L19**	0	78
4	$Pd(dba)_2$ instead of $PdCl_2(MeCN)_2$	81	7
5	K_2CO_3 instead of Cs_2CO_3	8	5
6	DMF instead of MeCN	56	9
7	80 °C instead of 100 °C	66	5
8	5 mol% [Pd], 10 mol% **L19**, 1.2 equiv. **3**	84	7
9	5 mol% $Pd(dba)_2$, 10 mol% **L19**, 1.2 equiv. **3**	79	4
10	5 mol% $Pd(dba)_2$, 6 mol% **L19**, 1.2 equiv. **3**	72	16
11	30 mol% NBE instead of **L19**	12	33

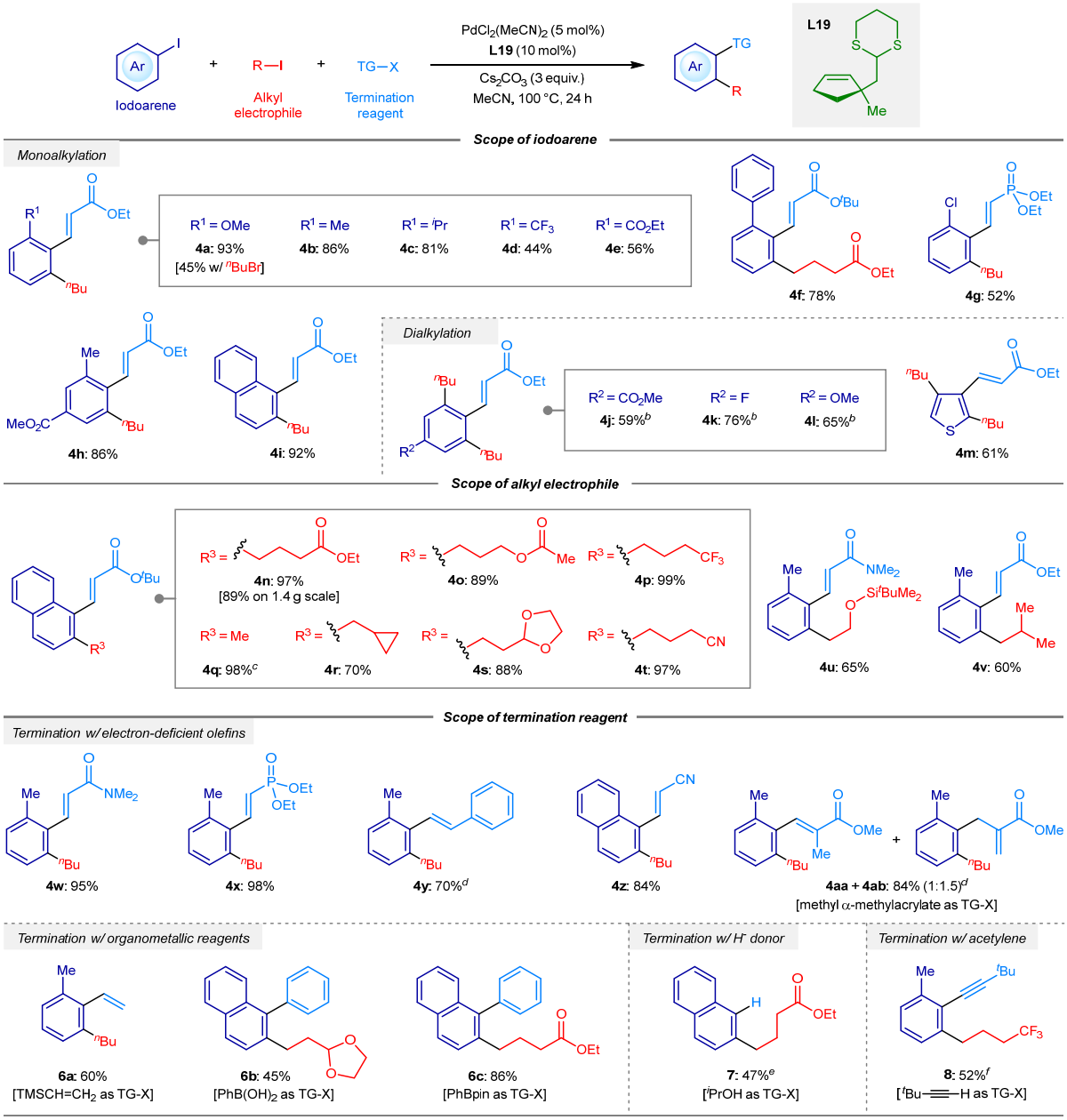
[a]Reaction conditions: iodoarene **1a** (0.2 mmol), alkyl iodide **2a** (0.4 mmol), acrylate **3a** (0.4 mmol), $PdCl_2(MeCN)_2$ (0.02 mmol), **L19** (0.06 mmol), Cs_2CO_3 (0.6 mmol), acetonitrile (2 mL) as the solvent, 100 °C, sealed tube, 24 h. [b]Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Substrate Scope

With the optimal reaction conditions in hand, the substrate scope of this Pd/olefin cooperative catalysis was explored (Table 2). In the *ortho*-alkylation/*ipso*-Heck reaction, a series of iodoarene substrates with different 2-substituents, including methoxy (**4a**), methyl (**4b**), isopropyl (**4c**), trifluoromethyl (**4d**), carboxylic ester (**4e**), phenyl (**4f**), and chloro (**4g**), were found to be compatible. 2,4-Disubstituted iodobenzene **4h** and α-iodonaphthalene (**4i**) were also suitable substrates, affording the difunctionalization products in excellent yields. When iodoarenes without an *ortho* substituent were employed, both *ortho* positions were alkylated in good yields (**4j-m**), and the selective mono *ortho*-alkylation was not achieved even if only one equivalent of the alkyl electrophile was employed.

The scope of the alkyl electrophile was also tested in the *ortho*-alkylation/*ipso*-Heck reaction. It was found that, primary alkyl iodides bearing a variety of functional groups served as suitable electrophiles for the cooperative catalysis (**4n-u**), while a tertiary carbon center at the *β*-position slightly diminished the reactivity (**4v**). It was noteworthy that, methyl triflate (MeOTf) was a perfect electrophile[34] that allowed for efficient *ortho*-methylation/*ipso*-Heck reaction (**4q**), while *n*-butyl bromide exhibited decreased reactivity compared with *n*-butyl iodide (**4a**).

Table 2. *ipso,ortho*-Difunctionalization of iodoarenes catalyzed by Pd/**L19**[a]



[a]Reaction conditions: iodoarene **1** (0.4 mmol), alkyl iodide **2** (0.8 mmol), termination reagent **3** (0.48 mmol), $PdCl_2(MeCN)_2$ (0.02 mmol), **L19** (0.04 mmol), Cs_2CO_3 (1.2 mmol), acetonitrile (4 mL) as the solvent, 100 °C, sealed tube, 24 h. Yields of isolated products were reported. [b]1.2 mmol (3 equiv.) of the alkyl iodide and 1.6 mmol (4 equiv.) of Cs_2CO_3 was used. [c]α-Iodonaphthalene (0.8 mmol), methyl triflate (0.8 mmol), *tert*-butyl acrylate (0.4 mmol), $Pd(dba)_2$ (0.04 mmol), **L19** (0.06 mmol), and Cs_2CO_3 (1.0 mmol) were used. [d]1.0 mmol (2.5 equiv.) of the electron-deficient olefin was used. [e]0.2 mmol (0.5 equiv.) of isopropanol was used as the termination reagent. [f]1.2 mmol (3 equiv.) of the alkyl iodide was used.

A variety of termination pathways were found viable in this catalytic system. Electron-deficient alkenes, including acrylamide (**4w**), vinylphosphonate (**4g** and **4x**), styrene (**4y**), acrynitrile (**4z**), and α-methylacrylate (**4aa** + **4ab**), served as appropriate termination reagents

to afford the products in good to excellent yields. Organometallic reagents, including vinylsilane (**6a**)[35], phenylbronic acid (**6b**)[36], and phenylbronic ester (**6c**)[37], were employed to produce the *ortho*-alkylation/*ipso*-coupling products in satisfactory yields. The use of isopropanol as a hydride donor[38] resulted in the *ortho*-alkylation/*ipso*-hydrogenation product **7** in a moderate yield. Terminal alkyne as the termination reagent led to a decent yield of the *ortho*-alkylation/*ipso*-Sonogoshira coupling product **8**[39].

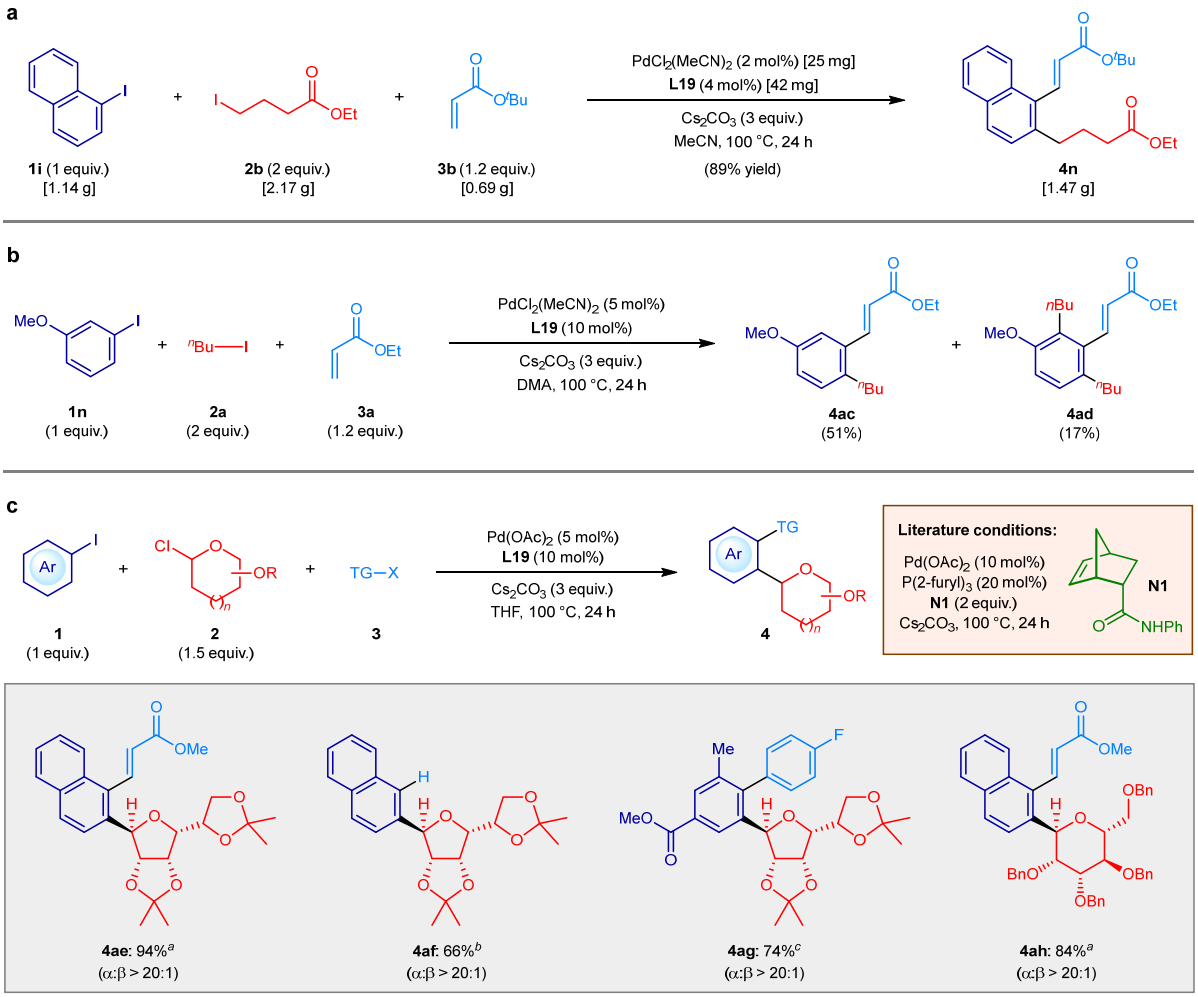


Fig. 3. Synthetic utility of the Pd/L19 catalytic system. a, Gram-scale synthesis of product **4n** with a lower catalyst loading. **b**, Mono *ortho*-alkylation/*ipso*-Heck reaction of a *meta*-substituted iodoarene. **c**, Application in the *ipso*-functionalization-*ortho*-glycosylation reactions of aryl iodides. [a]1.2 equiv. of methyl acrylate was used as the terminating reagent. [b]2 equiv. of isopropanol was used as the terminating reagent. [c]2 equiv. of 4-fluorophenylbronic acid pinacol ester was used as the terminating reagent and toluene was used as the solvent.

This highly efficient catalytic system enabled some synthetic tasks challenging for Pd/NBE cooperative catalysis. First, difunctionalization of iodoarene **1i** at a gram-scale could be performed with only 2 mol% of Pd and 4 mol% of **L19** to afford a good yield of product **4n**, which was not possible in the Pd/NBE cooperative catalysis with such low catalyst loading (Fig. 3a)[17]. Second, for an *ortho*-unsubstituted iodoarene (e.g., *meta*-substituted iodoarene), the Pd/NBE catalytic system usually faces an "*ortho*-constraint" and fails to produce the

difunctionalization product with selective installation of one *ortho* group. The Dong group developed a set of structurally-modified NBE catalysts to tackle this problem and achieved selective mono *ortho*-amination, -acylation and -arylation, while selective mono *ortho*-alkylation remained underexplored[40]. Interestingly, we found that the Pd/**L19** system could promote mono *ortho*-butylation/*ipso*-Heck reaction of *meta*-substituted iodobenzene **1n** to produce the product **4ac** in a reasonable yield, showcasing the potential of the designed olefin ligand to address the "*ortho*-constraint" in alkylative difunctionalization (Fig. 3b). Third, glycosyl chloride was recently found to be a new type of alkyl electrophile for the Pd/NBE cooperative catalysis, but a superstoichiometric of structurally-modified NBE together with a phosphine ligand were found essential for catalytic activity[41]. Gratifyingly, the present Pd/**L19** catalytic system was able to promote the *ortho*-glycosylative difunctionalization of iodoarenes in a highly efficient and selective manner without using any additional ligand, and the yields were even superior as compared with the previous method (Fig. 3c).

Overall, the above experimental findings identify the dithiane-cyclopentene ligand **L19** as a unique and versatile molecule, and its performance in Pd/olefin cooperative catalysis is even superior to that of NBE given that it lacks a highly strained ring system. This ligand exhibits perfect activity for promoting *ortho*-alkylation, while attempts to achieve other *ortho*-functionalization variants (e.g., amination and acylation)[42,43] were unsuccessful at this stage. We hypothesized that this is probably due to the lack of a second vacant coordinate site on the ACP intermediate as a result of side-arm coordination.

Reaction Mechanism

The most significant aspect regarding the present cooperative catalysis is the reaction mechanism, in which the evidence for covalent catalytic behavior of the cycloolefin ligand is the key point. To our disappointment, attempts to isolate possible intermediates in the reaction catalyzed by Pd/**L19** were fruitless, which was probably due to their lability. Then we focused again on the less reactive phosphine-cycloolefin ligands (Fig. 4a). Gratifyingly, when iodoarene substrate **1a**, Pd(II), and ligand **L4** were heated in the presence of cesium carbonate, complex **9** was obtained in a reasonable yield. A more efficient procedure to prepare this complex employed trimethylamine to facilitate Pd(II) reduction, which avoided the use of excess phosphine-cycloolefin ligand **L19** and remarkably increased the yield of complex **9**. Single crystal X-ray diffraction (XRD) analysis unambiguously confirmed the structure of this complex, in which the ligand cyclopentyl unit bonds to both the substrate arene ring and the palladium center. The phosphine unit on the side-arm coordinates to Pd, which evidences the directed insertion of the cycloolefin moiety into the aryl-palladium bond.

With this complex in hand, the organometallic transformations in the cooperative catalysis were studied in a greater detail. Treatment of complex **9** with sodium methoxide or silver carbonate at room temperature led to *ortho*-C-H palladation, which resulted in the clean formation of the ACP complex **10** (Fig. 4a). Nuclear magnetic resonance (NMR) analysis indicated that three neighboring protons remain on the methoxy-substituted aryl ring in complex **10**, two of which exhibit descending ^{31}P-^{1}H coupling constants ($J_{P\text{-}H}$). This is in agreement with the proposed palladacycle structure, in which the palladium forms a covalent bond with the aryl ring at the *ortho*-position. The identity of this complex was also supported by deuterium labeling experiments, in which the *in-situ* generated complex **10** was treated with excess deuterated acetic acid (CH_3COOD) in methanol-d_4 (CD_3OD) to afford complex **9**-*d* with

85% *ortho*-deuterium incorporation on the aryl ring (Fig. 4b). Currently we are not aware of the identity of the ligand L binding to the vacant site of the ACP complex, which is probably a solvent molecule (acetonitrile).

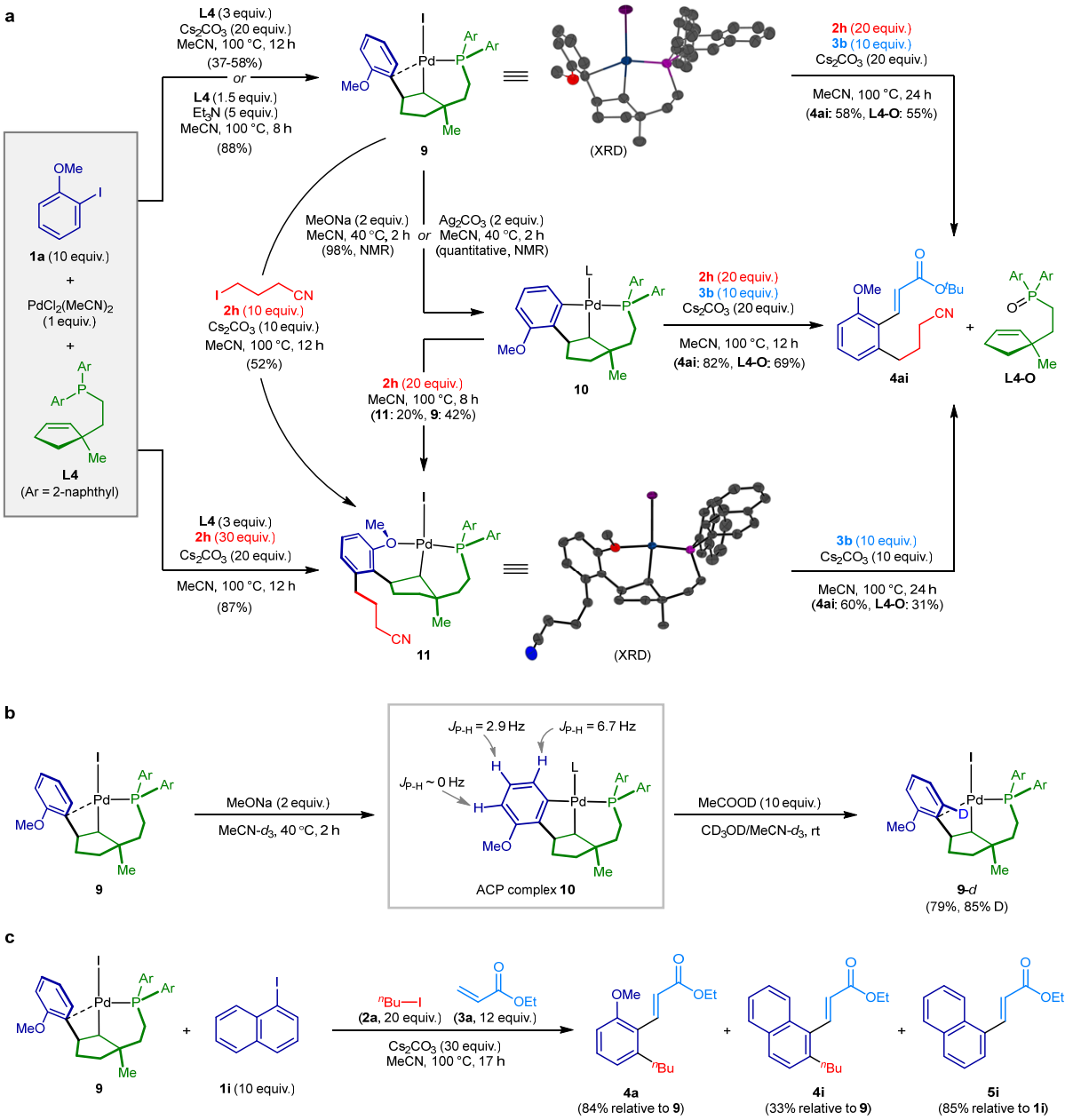


Fig. 4. Mechanism of the Pd/olefin cooperative catalysis with L4. a, The transformation network involving complexes **9**, **10**, and **11** demonstrated the non-innocent nature of the hybrid cycloolefin ligand. **b**, NMR analysis of ACP complex **10**, together with the deuterium labeling experiment with deuterated acetic acid, verified the identity of this palladacycle intermediate. **c**, Crossover experiment employing complex **9** and aryl iodide **1i** afforded two difunctionalizaiton products, which confirmed the regeneration of catalytically active species in the Pd/olefin cooperative catalysis after product release.

The activity of ACP complex **10** towards alkyl electrophile was then studied (Fig. 4a). After heating a solution of **10** (prepared by deprotonation of complex **9** by Ag_2CO_3) and alkyl iodide **2h** at 100 °C, a new aryl-Pd-ligand complex **11**, in which the *ortho*-position of the aryl ring was alkylated, was produced in 20% yield. XRD analysis confirmed its structure and disclosed a coordination mode different from complex **9**, in which the oxygen atom in the *ortho*-methoxy group coordinates to Pd instead of the *ipso*-carbon, probably due to the steric bulkiness introduced after *ortho*-alkylation. It was found that, the *ortho*-alkylated complex **11** could be synthesized more efficiently under synthetically relevant conditions. By reacting complex **9** with excess alkyl iodide **2h** and Cs_2CO_3, or by directly running the reaction between iodoarene **1a**, Pd(II), and **L2** in the presence of Cs_2CO_3, complex **11** was obtained in good yields.

All three aryl-Pd-ligand-type complexes were found to converge at the final difunctionalization product **4ai** (Fig. 4a). Complexes **9** and **10** afforded product **4ai** after treatment with excess **2a** and **3b** in the presence of Cs_2CO_3. When complex **11** was treated with excess acrylate **3b**, product **4ai** was also produced in a reasonable yield. In particular, in all reactions the oxidized ligand **L4-O** was isolated in significant amounts, which is the evidence for the retro-insertion step in the cooperative catalysis.

The final step that closes the catalytic cycle of the Pd/olefin cooperative catalysis was supported by a crossover experiment (Fig. 4c). When complex **9** was reacted under synthetically relevant conditions with iodoarene **1i**, alkyl iodide **2a**, and acrylate **3a**, the formation of both difunctionalization products **4a** and **4i** was observed in addition to the Heck-type product **5i**. Despite a low yield of the cross-product **4i**, its formation definitely demonstrates that the alkylated organopalladium complex was able to release the final product while regenerating the reactive species for the next catalytic cycle. The above results clearly illustrate a transformation network for the Pd/olefin cooperative catalysis (Fig. 1c), in which the cycloolefin unit actively participates in the bond-forming and bond-breaking events.

Conclusion

In summary, in this work we show that hybrid cycloolefin ligand functions as a novel non-innocent ligand in palladium catalysis, which enables efficient *ipso*,*ortho*-difunctionalization of iodoarenes. The mode of action of this ligand has been elucidated by detailed mechanistic study, which provided direct evidences for reversible covalent bonding between the substrate and the cycloolefin unit that leads to the key organopalladium intermediates. The present work demonstrates a new concept in olefin ligand design, and opens an avenue to a more general Pd/olefin cooperative catalysis without the NBE constraint. We anticipate this ligand design to be a starting point for the development of olefin-based non-innocent ligands, which may lead to the discovery of more unprecedented reaction modes and catalytic systems that advance synthetic chemistry.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information. Metrical parameters for the structure of complex **9** and **11** (see Supplementary Information) are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference numbers CCDC 2060007, CCDC 2060009, respectively.

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