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Reductive Coupling of Aryl Halides via C-H Activation of Indene

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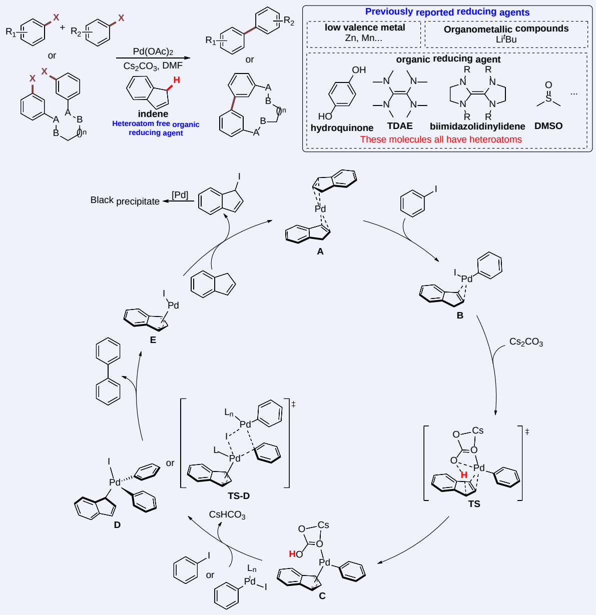
Keywords

Reductive Coupling | Aryl Halides | Indene | Palladium | C-H Activation

Main observation and conclusion

This paper describes the first case of a reductive coupling reaction with indene, a non-heteroatom olefin used as a reducing agent. The scope of the substrate is wide. The homo-coupling, cross-coupling, and synthesis of 12 and 14-membered rings were realized. The control experiment, indene-product curve and density functional theory (DFT) calculations. showed that the *η3*-palladium indene intermediate was formed by C-H activation in the presence of cesium carbonate. We speculate that the final product was obtained through a Pd (IV) intermediate or aryl ligand exchange. In addition, we excluded the formation of palladium anion (Pd(0)$^-$) intermediates.

Comprehensive Graphic Content



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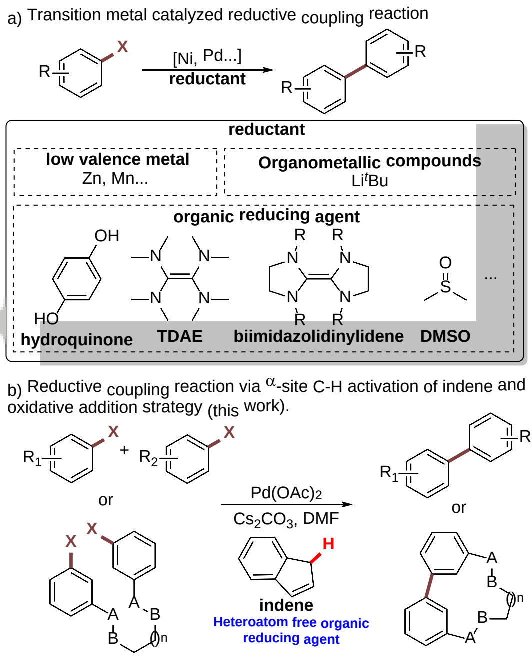
Background and Originality Content

Diaryl structures are very common in catalysts, natural products, pharmaceuticals, polymers and many other important chemicals.[1] Transition metal catalyzed coupling reactions have become the most useful and powerful tool for the synthesis of diaryl structures.[2] Among them, the reductive coupling reaction of halogenated aromatic hydrocarbons is considered to be a more convenient and direct method for the direct synthesis of diaryl compounds.[3] As early as 1971, Smmelhack reported the coupling reaction of halogenated aromatic hydrocarbons using equivalent zero valent nickel as reducing agent.[3a] Then Kumada improved the reaction system by using nickel as the catalyst and zinc as the reducing agent.[3c] At present, low valence metals have become the most common reducers for reductive coupling.[3e, 4] In 2018, Feringa reported the first case of reductive coupling reaction of halogenated benzene with *tert*-butyl lithium used as the reducing agent.[1e] In 1999, Rawal group reported that hydroquinone was used as reducing agent to realize the reductive coupling reaction of halogenated benzene in the presence of cesium carbonate.[5] Heteroatom-containing olefins used as reducing agents, such as TDAE, were first reported by Tanaka in 2002.[3d] Organic reducers are widely used and have different properties than inorganic metal reducers. In addition, the organic reducing agent avoids the danger of flammable and explosive metal reducing agent. (Scheme 1a). Non-heteroatom reducers have not been reported.[6]

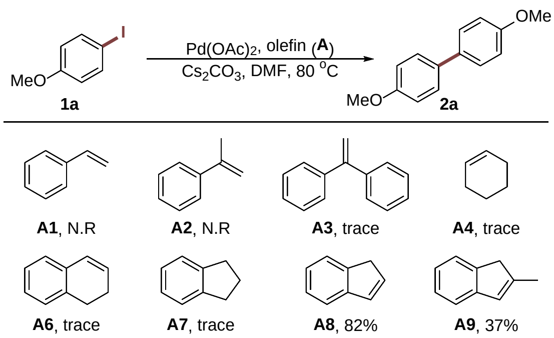
Scheme 1 Reductive coupling of aryl halides via the C-H activation of indene



Olefins are widely used as active functional groups in transition metal catalysis.[7] Some olefins, such as norbornene, have unique catalytic properties.[8] Catellani discovered the *o*-C-H alkylation and arylation of iodobenzene based on the properties of norbornene. The ligand of the reaction system was further modified by Lautens, and Catelani-Lautens reaction system was established.[9] In recent years, Dong, Zhou, Liang and Gu further introduced C-H amination, acylation and sulfhydrylation into the reaction, which greatly improved the application value of Catellani reaction.[10] Therefore, it is very important to find and summarize the unique properties and reaction mechanism of olefins for the research and development of new transition metal catalytic reactions.

Results and Discussion

Table 1 Screening of olefins^a



^{a} Reaction conditions: substrate **1a** (0.4 mmol, 2 equiv.), Pd(OAc)₂ (10 mol%, 0.02 mmol, 4.5 mg), olefin (**A1**-**A9**, 0.8 mmol), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), DMF (3.0 mL), 80 ℃, 7h. Isolated yields.

Initially, we used palladium acetate as a catalyst to systematically investigate the addition of various olefins. It is expected that products other than Heck reaction products participated by olefins can be obtained. We tried styrene, α-methylstyrene, diphenyl ethylene, cyclohexene, dihydronaphthalene and indane, but no other products were obtained. Fortunately, we used indene as an additive and obtained the reductive coupling product in 82% yield (Table 1). Then, we investigated the derivatives of indene, and when 2-methylindene was used, the reaction was inhibited. This may be due to the steric hindrance of the methyl group, which inhibits the coordination between olefins and palladium. To better understand the reaction mechanism, we added catalytic amount of ligands to the reaction system and equivalent indene. Except for 2-methyltriphenyl-phosphine, which has a weak coordination ability and high steric hindrance, the reaction was completely inhibited. Note that dipyridine has little effect on the reaction (Table S1, see Supporting Information, SI).

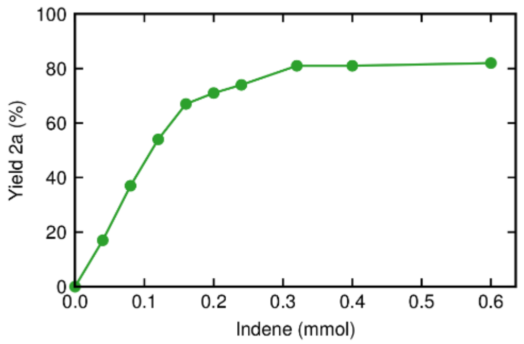
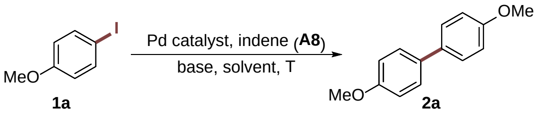


Figure 1. The Indene-Product Curve.

To explore whether indene is used as a ligand or a reducing agent, we generated data curves for the amount of indene and biphenyl product (**2a**). The results showed that when the amount of indene was less than 0.2 mmol, the reaction yield was linearly related to the amount of indene. However, when the amount of indene was more than 0.2 mmol, the increase in yield was not obvious. This proves that the formation of one molecule of **2a** requires a molecule of indene using as a reducing agent (Figure 1).

Table 2 Optimization of reaction conditions and control experiment[a]

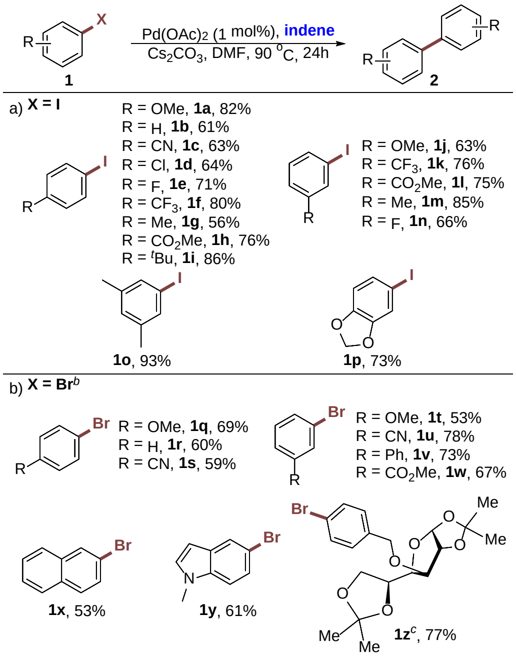


entry	catalyst	solvent	base	T/℃	Yield (%)
1	$Pd(OAc)_2$	DMF	Cs_2CO_3	80	82
2	$PdCl_2$	DMF	Cs_2CO_3	80	81
3	$Pd(dba)_2$	DMF	Cs_2CO_3	80	76
4	$Pd(OAc)_2$	DMF	K_2CO_3	80	55
5	$Pd(OAc)_2$	DMF	Na_2CO_3	80	trace
6	$Pd(OAc)_2$	DMF	K_3PO_4	80	61
7	$Pd(OAc)_2$	DMF	-	80	trace
8	$Pd(OAc)_2$	EtOAc	Cs_2CO_3	80	81
9	$Pd(OAc)_2$	THF	Cs_2CO_3	80	69
10	$Pd(OAc)_2$	toluene	Cs_2CO_3	80	<5
11	$Pd(OAc)_2$[b]	DMF	Cs_2CO_3	80	81
12	$Pd(OAc)_2$[b]	DMF	Cs_2CO_3	90	**82**

[a] Reaction conditions: substrate **1a** (0.4 mmol, 2 equiv.), $Pd(OAc)_2$ (10 mol%, 0.02 mmol, 4.5 mg), indene (**A8**, 0.4 mmol), base (0.8 mmol, 4.0 equiv.), solvent (3.0 mL), 7h. Isolated yields. [b] $Pd(OAc)_2$ (1 mol%, 0.5 mg), Cs_2CO_3 (0.4 mmol, 2.0 equiv.), 24h.

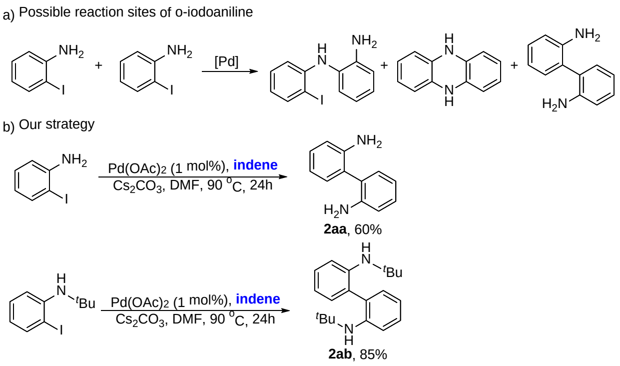
We further optimized the reaction conditions. First, we screened the palladium catalyst, and the results showed that the anions of the Pd catalyst had little effect on the reaction results (Table 2, entries 1-3). Subsequently, we investigated the inorganic base, and the cation of the base had a great influence on the reaction (entries 4-6). Note that the reaction does not take place without adding base to the reaction system (entries 7). Therefore, we speculate that cesium carbonate, as a key substance, participates in the C-H activation of indene. The reaction solvent was further screened, and the results showed that the target products can be obtained in ester and ether solvent (entries 8-9). In weakly polar solvents, such as toluene, the reaction yield was low (entry 10). Finally, the amount of palladium catalyst reduced to 2 mol% had little effect on the reaction results.

Table 3 Investigation of the substrate scope for reductive homo-coupling[a]



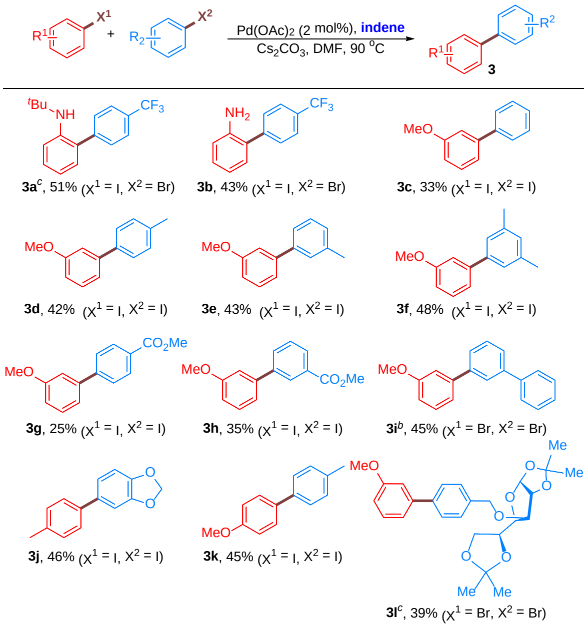
[a] Reaction conditions: substrate **1a** (0.4 mmol, 2 equiv.), $Pd(OAc)_2$ (1 mol%, 0.5 mg), indene (**A8**, 0.4 mmol), Cs_2CO_3 (0.4 mmol, 2.0 equiv.), DMF (3.0 mL), 90 ℃, 24h. Isolated yields. [b] $Pd(OAc)_2$ (2 mol%, 0.9 mg). [c] 120 ℃.

Scheme 2 Reductive Coupling Reaction of *o*-Iodoaniline.



Subsequently, we began to investigate the scope of the substrate. The substrate scope of this reaction is very wide. Both electron-donating and electron-withdrawing iodobenzenes can be applied to the reaction to obtain corresponding biphenyl products. Noted that halogen-substituted (-Cl, -F) iodobenzenes and polysubstituted iodobenzene can also be compatible. Unfortunately, when *o*-substituted (-Me, -OMe) iodobenzenes were used as substrates, the target products could not be obtained successfully (see Supporting Information, SI). All kinds of bromobenzenes can also be used in this reaction, including fused naphthalene and heterocyclic indole. In particular, for acid-base unstable glucofuranose, the target product was obtained successfully in this reaction system, which indicated that the reaction system was mild (Table 3).

Table 4 Investigation of the substrate scope for the reductive cross-coupling[a]



[a] Reaction conditions: substrate **1** (0.2 mmol, 1 equiv.), **1’** (0.4 mmol, 2 equiv.), $Pd(OAc)_2$ (2 mol%, 0.9 mg), indene (**A8**, 0.6 mmol, 3 equiv.), Cs_2CO_3 (0.8 mmol, 4.0 equiv.), DMF (3.0 mL), 90 ℃, 24h. Isolated yields. [b] $Pd(OAc)_2$ (4 mol%, 1.8 mg). [c] $Pd(OAc)_2$ (4 mol%, 1.8 mg), 120 ℃.

In order to further verify the applicability of the reaction. We found that *o*-iodomethoxybenzene and *o*-methyliodobenzene are not suitable for this reaction, but *o*-iodoaniline substrates can be

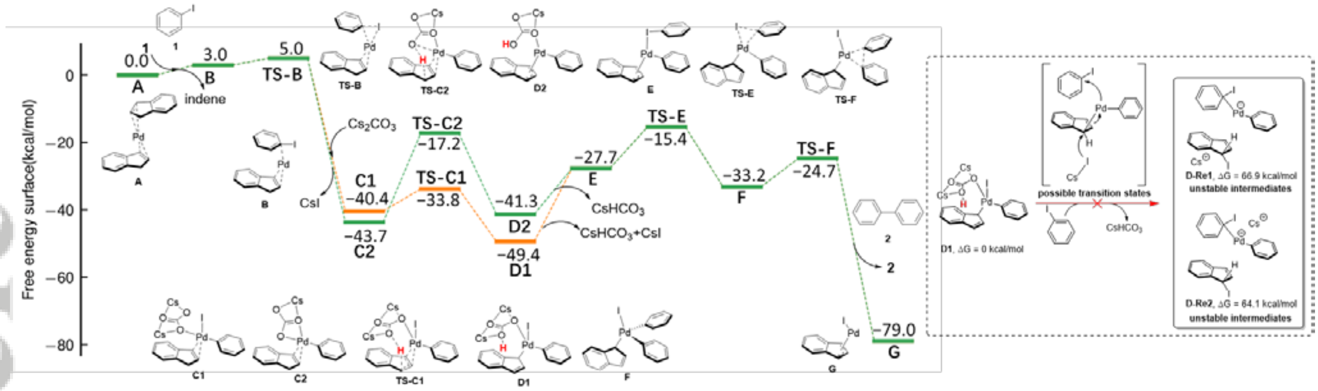
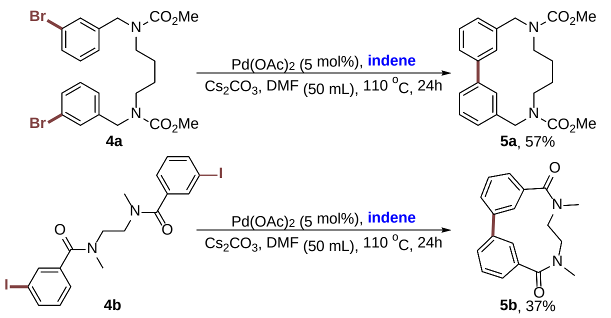


Figure 2 Density Functional Theory (DFT) Calculations Showing the Mechanism of Reductive Coupling

well applied to the reaction, and the products are single and the selectivity is good. The target product [1,1'-biphenyl]-2,2'-diamine can be obtained from *o*-iodoaniline in 60% yield. It is an important class of compounds and widely used in ligands and drugs. When o-iodoaniline **1ab** has a protective group, the yield is higher (Scheme 2).

Table 5 The Synthesis of 12 and 14-Membered Rings^a



^{a} Reaction conditions: substrate **4** (0.2 mmol, 1 equiv.), Pd(OAc)$_2$ (5 mol%, 2.3 mg), indene (**A8**, 0.4 mmol), Cs$_2$CO$_3$ (0.6 mmol, 3.0 equiv.), DMF (50.0 mL), 110 ℃, 24h.

Then we tried to apply this reaction to cross coupling. The reaction yield of N-^{t}Bu-*o*-aminoiodobenzene with trifluoromethyl bromobenzene was high. *o*-Iodoaniline reacted directly with bromobenzene, and corresponding target prefins are widuct was obtained. Other *o*-substituted iodobenzenes were not suitable for this reaction, which may be related to the unique structure of the palladium-indene intermediate. Subsequently, we reacted o-iodomethoxybenzene with electron-withdrawing (-CO$_2$Me) and electron-donating (-Me) iodobenzene, and the corresponding target products were obtained. Among them, the yield of *m*-methyl or *m*-ester substituted iodobenzene is relatively high. In addition, p-methyliodobenzene, 1,2-methylenedioxybenzene, *p*-methoxyiodobenzene and bromobenzene can also be used in this reaction (Table 4). It is worth mentioning that the cross-coupling reaction of sugar-containing substrate was successfully realized. In addition, the cross coupling has no chemical selectivity and a large number of homo-coupling by-products are produced (see Supporting Information, SI).

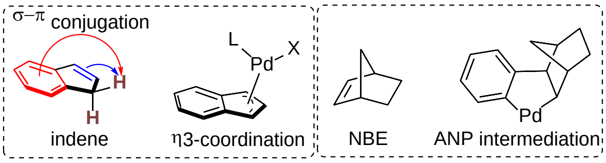


Figure 3 Chemical properties of indene and norbornene (NBE).

Finally, we successfully applied this reaction to the synthesis of 12-membered ring and 14-membered ring by a diluting solvent strategy. Diaryl macrocycles are important in organic natural products and drugs. Due to the instability of phenylboronic acid derivatives, our method is more convenient for substrate preparation than the Suzuki Miyaura coupling strategy (Table 5).

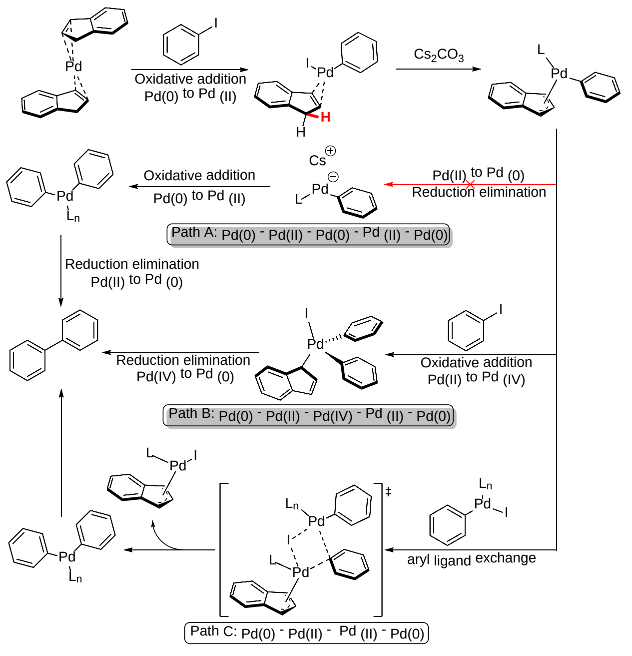


Figure 4 Three possible mechanisms of reductive coupling.

According to the screening of olefins, the reaction properties of indene are different from those of other olefins in palladium catalysis. This may be due to the σ-π conjugation of methylene (-CH$_2$-) with the benzene ring and olefin. Compared with the C-H bond of other methylene groups, it should be easier to break the C-H bond. There are few studies on indene related metal complexes. *η3*-Coordination complexes of indene and palladium were reported in 2000.[11]

To prove this assumption, the reaction mechanism was studied by density functional theory (DFT) (Figure 2). First, iodobenzene reacts with the η2-palladium indene complex by the oxidative addition process. The energy barrier of this process is very low, only 5.0 kcal/mol. Then, cesium carbonate is coordinated with palladium to form intermediate **C1**, and intermediate **C2** of cesium iodide (CsI) removal. The energy of **C2** is 3.3 kcal/mol lower than that of **C1**, so the **C2** intermediate is more stable than **C1**. Subsequently, the 1,3-migration of olefins takes place in intermediate **C1** to obtain η1-palladium indene intermediate **D1**. However, **C2** obtained the η3-palladium indene intermediate **D2** by a direct C-H activation reaction, which is the concerned metallization deprotection (CMD) process. Palladium anions, such as acetate (AcO^-) chloride (Cl^-), have little effect on the reaction, while cesium carbonate plays a key role in the reaction, which is consistent with the experimental results (Figure 5).

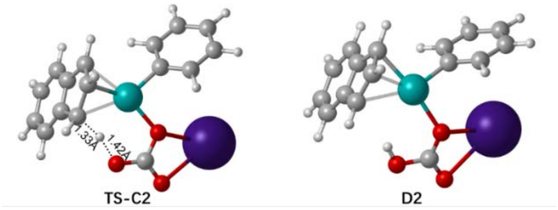


Figure 5 The structure of **TS-C2** and **D2**

In the past, some literatures suggested that the palladium catalyzed reductive coupling reaction was formed by the formation of negative electron palladium ($Pd(0)^-$), followed by the oxidative addition of another molecule of halogenated aromatic hydrocarbon (Figure 4, Path A). This path has been proposed in previous reports, but has never been verified by experiments or theoretical methods.[3d, 4f, [11]] Then we first verify the mechanism of path A, and we found that the Gibbs free energy of palladium anion intermediate (Pd(0)-, **D-Re2**, see SI)) is very high (ΔG =64.1 kcal/mol). Therefore, path A is unlikely to be a reliable mechanism (Figure 2). Based on our experience in the field of Pd/NBE chemistry, we speculate that the palladium (II) intermediate of indene can be further oxidized and added along with halobenzene to form a palladium (IV) intermediate (Figure 3). Therefore, we considered that there is a mechanism of tetravalent palladium, like Catellani reaction (Path B).

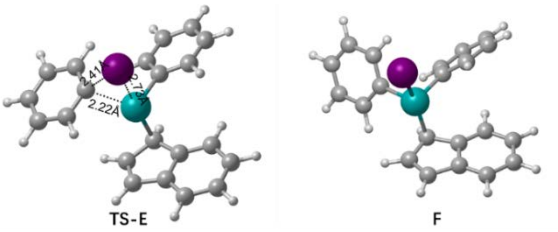


Figure 6 The structure of **TS-E** and **F**

In path B, intermediate **D1** removed cesium iodide (CsI) and cesium bicarbonate ($CsHCO_3$), and intermediate **F** was obtained by oxidative addition with iodobenzene. The energy barrier of this process is 34 kcal/mol, which is difficult to occur. Intermediate **D2** only needs to remove cesium bicarbonate, and the energy barrier for subsequent oxidative addition is only 25.9 kcal/mol. Intermediate **F** can be obtained successfully (Figure 6). Target product **2** and intermediate **G** were obtained by the reduction and elimination process of intermediate **F**. Intermediate **G** is further combined with indene, and intermediate **A** is formed by reduction and elimination reaction. Thus, the catalytic cycle has been achieved.

In addition, the mechanism of aryl ligand exchange was proposed. In Path C, the coordination mode of palladium intermediates is very complex. Unfortunately, we failed to give the detailed mechanism by DFT calculation.

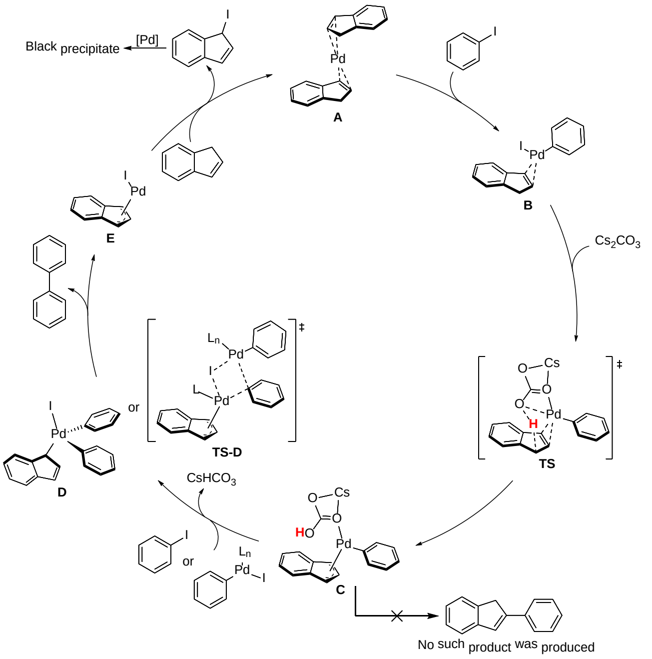


Figure 7 Possible Mechanism of Reductive Coupling Reaction.

To sum up, we give the possible mechanism. Firstly, indene palladium compound **A** reacts with iodobenzene by oxidation addition, and then C-H activation reaction takes place under the promotion of cesium carbonate to form η3-palladium indene complex **C**. It is worth noting that the coupling product of indene and iodobenzene can not be produced by the reduction elimination reaction of the intermediate **C**. Subsequently, the intermediate **D** was synthesized by oxidative addition with another molecule of iodobenzene. In addition, the reaction may go through the process of aryl ligand exchange (**TS-D**). Finally, the target product is obtained by reduction elimination. The coupling reaction of every two molecules consumes one molecule of indene. It is consistent with the experimental results. In addition, we speculate that a large number of insoluble black solids were formed by the catalysis of palladium (Figure 7).

Conclusions

In conclusion, we reported the first palladium-catalyzed reductive coupling reaction using indene as a reducing agent. The homo-coupling, cross-coupling, and synthesis of 12 and 14-membered rings were realized. Compared with low valence metal, indene is not easy to spontaneous combustion and has potential industrial application value. In terms of economic benefits, it is cheaper and easier to obtain than common organic reducers. In the aspect of mechanism research, we excluded the formation of palladium anion ($Pd(0)^-$) intermediates, and proposed two possible mechanisms of Pd (IV) and aryl ligand exchange. The mechanism will be further studied in the future.

Experimental

(1) General Procedure for the Reductive homo-Coupling

In a 20 mL tube, **1** (0.4 mmol, 2 equiv.), $Pd(OAc)_2$ (1 mol%, 0.5 mg) and Cs_2CO_3 (0.4 mmol, 2.0 equiv.) were added and charged with argon more than three times (The tube was sealed with tipping plug). Indene (**A8**, 0.4 mmol, 2 equiv.) and DMF (3 mL) was injected into the tube via syringes. The mixture was stirred at room temperature for 15 minutes, and then placed in a pre-heated oil bath at 90 °C stirring at 900 rpm for 24 h. After the reaction was completed, ethyl acetate and water were added and extracted in a separatory funnel. The extracted organic phase was combined and dried with Na_2SO_4. The solvent was removed by rotary evaporator. The crude product was purified with chromatography column on silica gel.

(2) General Procedure for the Reductive Cross-Coupling

In a 20 mL tube, **1** (0.2 mmol, 1 equiv.), **1'** (0.4 mmol, 2 equiv.), $Pd(OAc)_2$ (2 mol%, 0.9 mg) and Cs_2CO_3 (0.8 mmol, 4.0 equiv.) were added and charged with argon more than three times (The tube was sealed with tipping plug). Indene (**A8**, 0.6 mmol, 3 equiv.) and DMF (3 mL) was injected into the tube via syringes. The mixture was stirred at room temperature for 15 minutes, and then placed in a pre-heated oil bath at 90 °C stirring at 900 rpm for 24 h. After the reaction was completed, ethyl acetate and water were added and extracted in a separatory funnel. The extracted organic phase was combined and dried with Na_2SO_4. The solvent was removed by rotary evaporator. The crude product was purified with chromatography column on silica gel or preparative TLC (PTLC).

(3) General Procedure for the Synthesis of 12 and 14-Membered Rings

In a 100 mL round-bottom flask, **4** (0.2 mmol, 1 equiv.), $Pd(OAc)_2$ (5 mol%, 2.2 mg) and Cs_2CO_3 (0.6 mmol, 3.0 equiv.) were added and charged with argon more than three times (The tube was sealed with tipping plug). Indene (**A8**, 0.4 mmol, 2 equiv.) and DMF (50 mL) was injected into the tube via syringes. The mixture was stirred at room temperature for 15 minutes, and then placed in a pre-heated oil bath at 110 °C stirring at 900 rpm for 24 h. After the reaction was completed, DMF was removed by vacuum distillation. Then, ethyl acetate and water were added and extracted in a separatory funnel. The extracted organic phase was combined and dried with Na_2SO_4. The solvent was removed by rotary evaporator. The crude product was purified with chromatography column on silica gel or preparative TLC (PTLC).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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Reductive Coupling of Aryl Halides via C-H Activation of Indene

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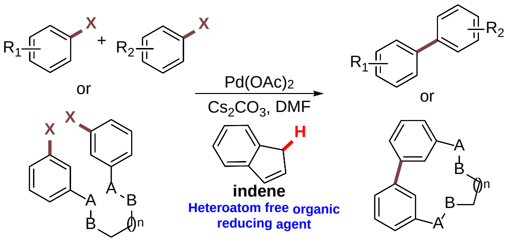

This paper describes the first case of a reductive coupling reaction with indene, a non-heteroatom olefin used as a reducing agent. The scope of the substrate is wide. The homo-coupling, cross-coupling, and synthesis of 12 and 14-membered rings were realized. The control experiment, indene-product curve and density functional theory (DFT) calculations. showed that the *η3*-palladium indene intermediate was formed by C-H activation in the presence of cesium carbonate. We speculate that the final product was obtained through a Pd (IV) intermediate or aryl ligand exchange. In addition, we excluded the formation of palladium anion ($Pd(0)^-$) intermediates.