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Palladium-Catalyzed Intermolecular Carbene Insertion Prior to Intramolecular Heck Cyclization: Synthesis of 2-Arylidene-3-aryl-1-indanones

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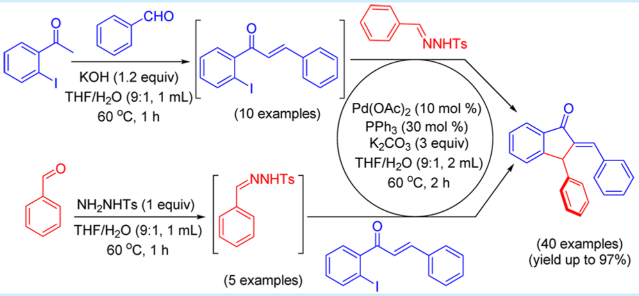
S *Supporting Information*

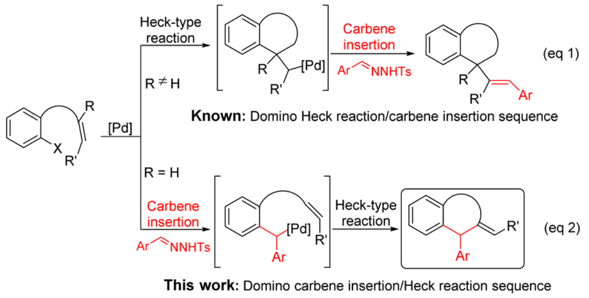
ABSTRACT: A domino process that converges the migratory insertion of carbene with a Heck reaction has been established as a versatile tool for the synthesis of 2-arylidene-3-aryl-1-indanones from very stable and easily accessible *N*-tosylhydrazones and 2′-iodochalcones. The reaction selectively proceeds through 5-*exo-trig* cyclization and delivers the products selectively with the *E* configuration of the double bond in excellent yields. The one-pot synthesis of 2-arylidene-3-aryl-1-indanones involving in situ synthesis of both 2′-iodochalcones and *N*-tosylhydrazones has also been demonstrated.



The transition-metal-catalyzed cross-coupling reaction is an invaluable tool in synthetic chemistry for the construction of C−C bonds.[1] In the current scenario, cross-coupling reactions that involve metal carbene species have emerged as a powerful strategy for the formation of C−C bonds.[2,3] Diazo compounds are widely utilized as a precursor for the generation of metal carbene species.[4] However, the uncertain explosive nature and instability of diazo compounds without electron-withdrawing groups has forced the search for alternative precursors.[5] In recent years, *N*-tosylhydrazones have emerged as convenient precursors for the in situ generation of unstable diazo compounds.[6,7] Palladium has been exploited as a potent catalyst in this field, where the reaction is considered to proceed via migratory insertion of a palladium carbene intermediate.[8,9] In particular, domino C−C bond formations triggered by Pd-catalyzed migratory insertion are very attractive and productive, as structural complexity can be achieved in a single operation.[9]

A few catalytic processes that converge Pd-catalyzed migratory insertion of carbene with other coupling reactions have been reported for the construction of cyclic architectures.[10] In this context, a domino intramolecular Heck reaction followed by migratory insertion of a metal carbene in which the alkylpalladium species originating from the Heck reaction in the absence of *β*-hydride elimination reacts with a diazo compound has been reported (Scheme 1, eq 1).[11] Conversely, a domino process that proceeds through intermolecular carbene insertion followed by a Heck reaction that involves the migratory insertion of alkene would be a novel pathway for construction of different cyclic architectures (Scheme 1, eq 2). This type of domino reaction was attempted using a Pd catalyst and large excess of trimethylsilyl diazomethane as the carbene precursor.[12] However, instead of giving the desired product, the alkylpalladium species generated after the Heck cyclization reacted with another carbene insertion or protodesilylation took place.

Scheme 1. Migratory Insertion of Carbene before or after Heck Reaction



Despite this attempt, the development of such cyclization can be a difficult task, as the intramolecular Heck reaction (migratory insertion of alkene) could be more facile than the intermolecular migratory insertion of carbene. We hypothesized that 2′-iodochalcone could be an appropriate substrate in which an intramolecular Heck reaction is less facile, allowing the intermolecular carbene insertion to occur first, followed by alkene insertion to give five- or six-membered compounds through 5-*exo-trig* or 6-*endo-trig* cyclization in the presence of a Pd catalyst (Scheme 2).

At first, 2′-iodochalcone (**1a**) and *N*-tosylhydrazone **2a** derived from benzaldehyde were chosen as model substrates, and the reaction was carried out with 1.2 equiv of **2a** in the presence of 10 mol % Pd(OAc)$_2$, 30 mol % PPh$_3$, and 3 equiv of K$_2$CO$_3$ in dry

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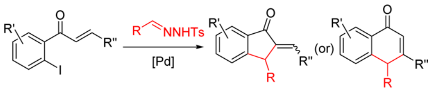
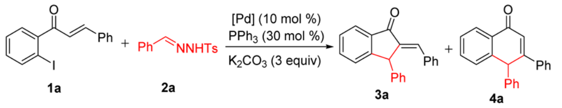
Scheme 2. Proposed Migratory Insertion of Carbene before Heck Reaction



THF at 60 °C. To our delight, the domino reaction proceeded through intermolecular carbene insertion followed by alkene insertion and selectively cyclized in a 5-*exo-trig* manner to give 2-benzylidene-3-phenyl-1-indanone (**3a**) in 36% yield (Table 1, entry 1). The structure and *E*-configured double bond of product **3a** were confirmed by single-crystal X-ray diffraction analysis (Figure 1), and the other product **4a** was not observed. Indanone-containing scaffolds are attractive synthetic targets[13] because they display many biological activities.[14]

Table 1. Optimization of the Reaction Conditions[a]



entry	equiv of **2a**	[Pd]	solvent	*T* (°C)	% yield[b] of **3a** (**4a**)
1	1.2	Pd(OAc)$_2$	THF	60	36 (0)[c]
2	1.5	Pd(OAc)$_2$	THF	60	61 (0)[c]
3	2	Pd(OAc)$_2$	THF	60	82 (0)
4	2	PdCl$_2$	THF	60	71 (0)
5	2	Pd$_2$(dba)$_3$	THF	60	67 (0)
6	2	Pd(OAc)$_2$	THF	60	78 (0)[d]
7	2	Pd(OAc)$_2$	THF/H$_2$O	60	96 (0)[e]
8	2	Pd(OAc)$_2$	THF/H$_2$O	40	76 (0)[e]
9	2	Pd(OAc)$_2$	THF/H$_2$O	60	21 (0)[e,f]
10	2	–	THF/H$_2$O	60	nr (0)[e,g]
11	2	Pd(OAc)$_2$	THF/H$_2$O	60	nr (0)[e,g,h]

[a] Reaction conditions: **1a** (0.25 mmol, 1 equiv), **2a** (1.2–2.0 equiv), K$_2$CO$_3$ (0.75 mmol, 3 equiv), Pd catalyst (10 mol %), PPh$_3$ (30 mol %). [b] Isolated yields. [c] Unreacted 2′-iodochalcone was recovered (53% for entry 1 and 31% for entry 2). [d] TBAC (2 equiv) was used. [e] 9:1 THF/H$_2$O (3 mL) was used. [f] The reaction was conducted without PPh$_3$. [g] nr = no reaction. [h] The reaction was conducted without base.

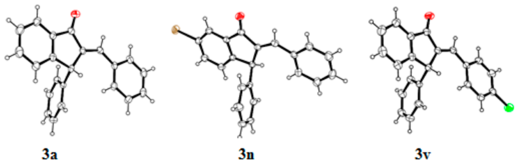
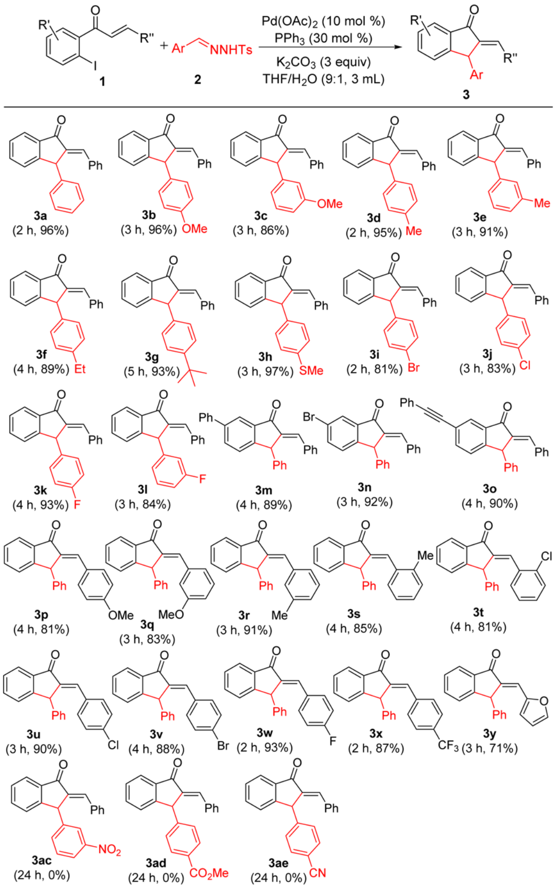


Figure 1. X-ray structures of **3a** (CCDC 1411740), **3n** (CCDC 1411739), and **3v** (CCDC 1411741) with 30% probability ellipsoids.

The yield improved to 82% when 2 equiv of **2a** was used (Table 1, entry 3). Further attempts to improve the efficacy of the reaction with other Pd salts, ligands, bases, and solvents were not beneficial.[15] During the course of the reaction, the reaction medium was not a clear solution, perhaps because of the low solubility of K$_2$CO$_3$ in THF. Since a phase-transfer catalyst can help to bring the inorganic base into the organic medium and accelerate diazo compound formation, TBAC was used as an additive, but no improvement in the yield was observed (entry 6) and the reaction took a longer time for completion (10 h). Then it was presumed that addition of water should improve the reactivity and yield since K$_2$CO$_3$ is soluble in water. As anticipated, the reaction was completed within 2 h and the product was isolated in 96% yield when the reaction was conducted in 9:1 THF/H$_2$O (entry 7). However, the reactivity was drastically reduced when 1:1 THF/H$_2$O was used, and no product formation was observed in only water.[15] Also, the reactivity was reduced when the reaction temperature was lowered to 40 °C (entry 8). The reaction without ligand gave the product in 21% yield (entry 9), and product formation was not observed without the Pd catalyst or base (entries 10 and 11).

The optimized reaction conditions were first explored with *N*-tosylhydrazones derived from different substituted benzaldehydes, and the results are summarized in Scheme 3. It was found that *N*-tosylhydrazones bearing an electron-releasing group reacted smoothly and gave the corresponding products **3b–h** in excellent yields. *N*-Tosylhydrazones with halide substituents, which are beneficial for further functionalization, were well-tolerated under the optimized reaction conditions (**3i** and **3j**).

Scheme 3. Scope of Pd-Catalyzed Insertions of Carbene and Alkene[a,b]



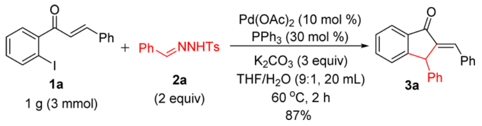
[a] Reaction conditions: **1** (0.25 mmol, 1 equiv), **2** (0.5 mmol, 2 equiv), K$_2$CO$_3$ (0.75 mmol, 3 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (30 mol %), THF (2.7 mL), H$_2$O (0.3 mL), 60 °C. [b] Isolated yields are shown.

Fluoro-substituted *N*-tosylhydrazones were also found to be suitable substrates for this reaction (**3k** and **3l**). However, product formation was not observed when *N*-tosylhydrazones substituted with strong electron-withdrawing groups such as cyano, nitro, and ester were used (**3ac**, **3ad**, and **3ae**). Furthermore, the optimized reaction conditions were examined for a series of substituted 2′-iodochalcones. Phenyl, phenylethynyl, and bromo substituents on the iodide-attached aryl ring of the 2′-iodochalcone afforded the products in admirable yields (**3m**−**o**). The substituent pattern on the other ring of the 2′-iodochalcone had little effect on the reactivity irrespective of electron-withdrawing or -donating nature (**3p**−**y**). Prominently, *ortho* substituents and heterocyclic systems offered the products in good yield (**3s**, **3t**, and **3y**).

The reaction is highly selective, as it delivered a single isomer. The formation of the other isomer was not observed, as confirmed by ^{1}H NMR analysis of the crude reaction mixtures. All of the products isolated were assumed to be *E* isomers, as the X-ray crystallographic analysis of **3a**, **3n**, and **3v** showed the *E* configuration (Figure 1).

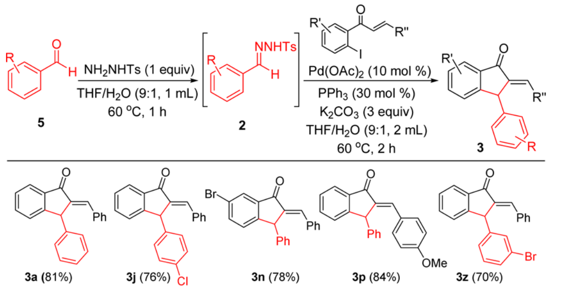
The practical utility of this methodology was established without compromising the reaction conditions. Hence, an 87% yield of **3a** was isolated within 2 h when the reaction was scaled up to 1 g (Scheme 4).

Scheme 4. Gram-Scale Reaction



Next, the execution of this newly developed reaction in one pot was examined by promoting in situ generation of *N*-tosylhydrazones from the corresponding aldehydes **5** and *N*-tosylhydrazides (Scheme 5). Delightfully, an 81% yield of **3a** was obtained in the one-pot reaction where the 2′-iodochalcone and catalyst were added after the reaction of the *N*-tosylhydrazide with benzaldehyde in 9:1 THF/H_2O for 1 h. The efficacy of this one-pot reaction was further extended to other substrates, and comparable yields were obtained in all cases.

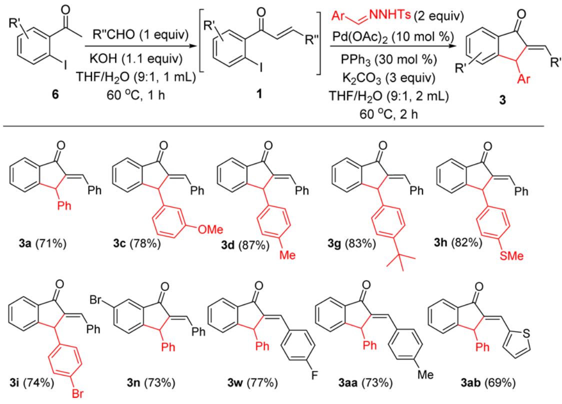
Scheme 5. One-Pot Reaction through in Situ Synthesis of *N*-Tosylhydrazones



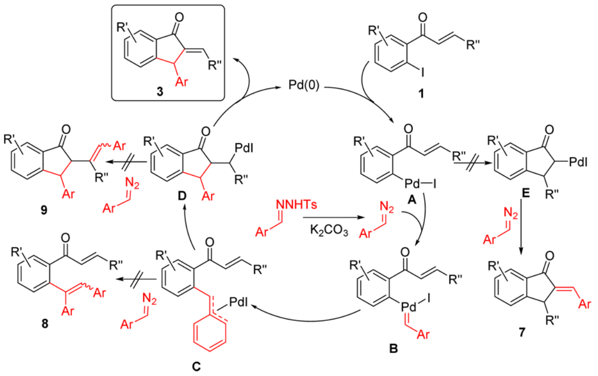
The possibility of developing a one-pot reaction involving in situ generation of the 2′-iodochalcone from 2′-iodoacetophenone (**6**) and the aldehyde was inspected. At the start, **6** was reacted with benzaldehyde in the presence of K_2CO_3 (1.5 equiv) in 9:1 THF/H_2O, but 2′-iodochalcone **1a** was not observed. However, the use of KOH (1.1 equiv) followed by addition of the *N*-tosylhydrazone under the optimized reaction conditions gave product **3a** in 71% yield (Scheme 6). Moreover, the one-pot reaction was applied for the synthesis of other substituted 2-arylidene-3-aryl-1-indanones. All of the reactions proceeded smoothly in spite of the nature of the substituents, and the 2-arylidene-3-aryl-1-indanones were isolated in good yields.

The reaction pathway can be explained as proposed in Scheme 7. Initially, arylpalladium species **A** is generated by oxidative addition of 2′-iodochalcone to Pd(0), and it reacts with the in situ-formed diazo compound to produce intermediate **B**. Then migratory insertion of the palladium carbene leads to benzylpalladium species **C**, which readily undergoes 5-*exo*-*trig* cyclization to give intermediate **D**. Finally, *β*-hydride elimination of intermediate **D** expels the final product **3**.

Scheme 6. One-Pot Reaction through in Situ Synthesis of 2′-Iodochalcones

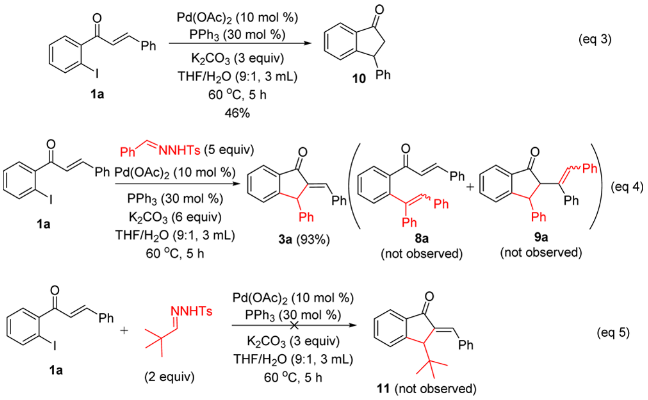


Scheme 7. Proposed Reaction Pathway



Very importantly, when the reaction was conducted in the absence of *N*-tosylhydrazone **2a**, the intramolecular reductive Heck cyclization of 2′-iodochalcone **1a** was observed (Scheme 8, eq 3). The feasibility of intramolecular Heck cyclization suggested that the reaction may produce compound **7** through intermediate **E**. However, the formation of compound **7** was not observed by ^{1}H NMR analysis of the crude reaction mixture. Also, the formation of compounds **8a** and **9a** was not observed even when

Scheme 8. Control Reactions



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the reaction was conducted with 5 equiv of *N*-tosylhydrazone (Scheme 8, eq 4). The reaction of 2′-iodochalcone with the *N*-tosylhydrazone derived from *tert*-butyraldehyde under the optimized reaction conditions did not provide the corresponding product **11**. In this reaction, 2′-iodochalcone remained as such, and decomposition of the *N*-tosylhydrazone to *tert*-butyraldehyde was observed (Scheme 8, eq 5). This result suggests that the reaction may possibly proceed through intermediate **C**. However, detailed mechanistic studies, the development of an overall one-pot synthesis, and the application of this newly developed methodology and its asymmetric version are in progress.

In conclusion, Pd-catalyzed intermolecular carbene insertion followed by an intramolecular Heck reaction has been developed. Very stable and easily accessible *N*-tosylhydrazones and 2′-iodochalcones can be used for the synthesis of 2-arylidene-3-aryl-1-indanones. The reaction is very selective toward 5-*exo-trig* cyclization and *E*-configured double bond formation. The practical utility of this method has been showcased with a gram-scale reaction. Furthermore, the reaction has been successfully demonstrated in one pot with respect to both 2′-iodochalcones and *N*-tosylhydrazones.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02803.

X-ray crystallographic data for **3a** (CIF)
X-ray crystallographic data for **3n** (CIF)
X-ray crystallographic data for **3v** (CIF)
Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. P. Rajakumar on the occasion of his 60th birthday.

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(15) See the Supporting Information for detailed optimization.