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ARTICLE TYPE

Palladium-Catalyzed Three-Component Reaction of *N*-Tosylhydrazone, Norbornene and Aryl Halide

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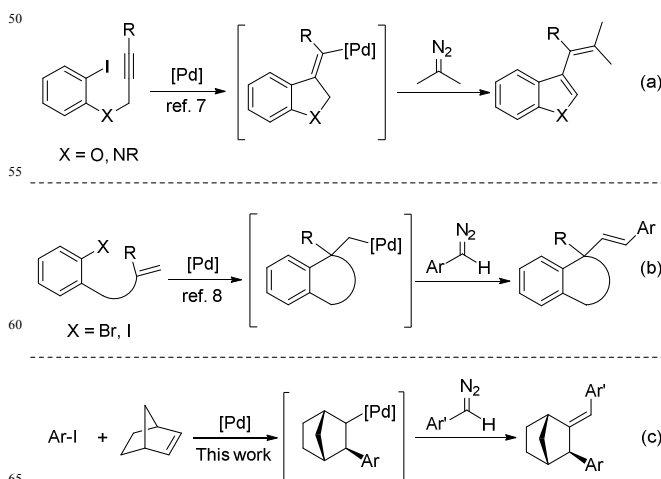
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A palladium-catalyzed three-component reaction of *N*-tosylhydrazone, norbornene and aryl halide has been demonstrated. In this reaction, an intermolecular Heck-type reaction occurs, which is followed by alkyl palladium carbene migratory insertion process. This transformation provides an efficient and convenient methodology for the double functionalization of norbornene with good to excellent yields.

In the past few years, a novel type of cross coupling reactions involving metal carbene migratory insertion has emerged as a powerful method for the construction of C-C bonds.¹ Diazo compounds, either directly used or generated *in situ* from *N*-tosylhydrazones, are the carbene precursors in these transformations.^{2,3} Notably, the diazo compounds can be introduced into various transition-metal-catalyzed transformations, making it possible to develop cascade reactions that involve metal carbene migratory insertion process.^{4,5} These cascade reactions provide useful methodologies for the construction of complex molecules.

Palladium complex has been regarded as an outstanding catalyst in this type of cascade reactions. The palladium species generated in a catalytic system may be trapped by diazo substrate to form a Pd carbene species, which is then followed by migratory insertion. A number of cascade transformations have been recently developed based on this strategy.^{4,6-8} For example, we have developed a palladium-catalyzed cyclization and carbene migratory insertion tandem reaction for the synthesis of 3-vinylindoles and 3-vinylbenzofurans.⁷ As illustrated in Scheme 1a, the vinyl Pd species, generated through intramolecular alkyne insertion, is trapped by a diazo substrate that is generated *in situ* from the corresponding *N*-tosylhydrazone. Gu and co-workers reported a palladium-catalyzed intramolecular olefin insertion/alkyl palladium carbene migratory insertion cascade reaction (Scheme 1b).⁸



Scheme 1 Palladium species in cross coupling reactions involving carbene migratory insertion.

Notably, in these two cases the palladium intermediates were formed *via intramolecular* insertion of unsaturated systems. Meanwhile, the *intermolecular* insertion of unsaturated systems to organopalladium species, in combination with similar carbene migratory insertions, provides opportunity to develop multi-component cascade reactions. In this context, we have demonstrated acyl migratory insertion in a palladium-catalyzed multi-component reaction of aryl iodide, CO, diazo compounds and triethylsilane.⁹ Very recently, allenes were successfully employed as the unsaturated systems to react with aryl halides and diazo compounds under the catalysis of palladium complex, providing an alternative method for the synthesis of 1,3-dienes.¹⁰

Although significant progress has been achieved in this type of cascade reaction, to the best of our knowledge, olefin as one of the most common unsaturated systems has not been applied in this type of intermolecular cascade reactions. There are two major challenges for this reaction: 1) the direct Heck reaction between aryl halides and olefins; 2) the cyclopropanation reaction between carbene precursors and olefins. We conceived that norbornene could be used as the unsaturated system to avoid such problems, thus achieving the desired intermolecular cascade reaction. The strained double bond of norbornene is highly inclined to insert into the Pd-C bond of the aryl palladium species. Since the

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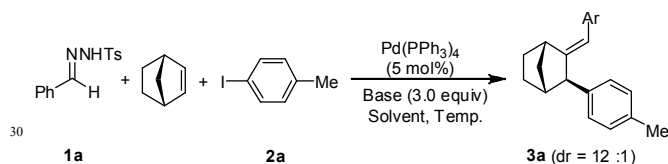
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generated alkyl palladium species has no *cis*- β -hydride,¹¹ the designed cascade reaction is expected to proceed preferentially (Scheme 1c). Herein, we report the study on the three-component reaction between aryl iodides, norbornene and *N*-tosylhydrazones.

At the initial studies, Pd(PPh₃)₄ was selected as the catalyst and *N*-tosylhydrazone (**1a**), norbornene and aryl iodide (**2a**) were used as the substrates to optimize the reaction conditions. To our delight, the desired product was obtained as a mixture of diastereomers (12 : 1) in 75% yields with K₂CO₃ as the base. The structure of the major isomer was confirmed by X-ray crystallographic analysis as **3g**.¹² Other bases, such as Cs₂CO₃, LiOtBu, NaOMe, gave poor results (entries 2-4). Switching the solvent from toluene to dioxane or 1,2-dichloroethane gave the product **3a** in 35% and 52% yields, respectively (entries 5 and 6), while with acetonitrile as the solvent, only trace amount of product could be obtained (entry 7). The yield could be significantly improved when the amount of *N*-tosylhydrazone (**1a**) was increased from 1.0 to 1.2 equivalents (entries 8-10). Besides, the concentration seems to have no obvious impact on the reaction (entries 8-10). Finally, the temperature effect was examined. The reaction at 80 °C and 90 °C afforded similar results, while the reaction at 100 °C gave inferior result (entry 11).

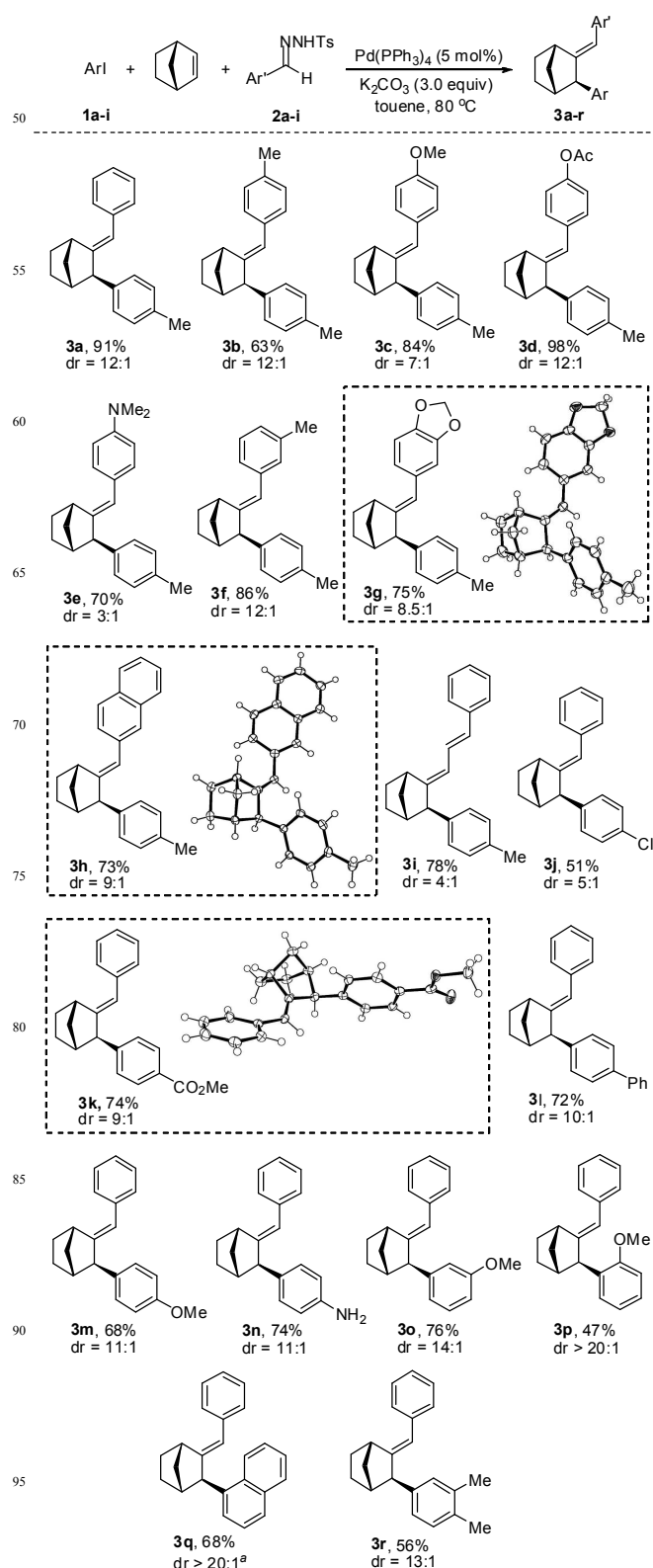
Table 1 Optimization of the reaction conditions^a



Entry	Base	Solvent	Temp (°C)	Yield (%) ^b
1	K ₂ CO ₃	toluene	90	75
2	Cs ₂ CO ₃	toluene	90	trace
3	LiOtBu	toluene	90	10
4	NaOMe	toluene	90	23
5	K ₂ CO ₃	dioxane	90	35
6	K ₂ CO ₃	DCE	90	52
7	K ₂ CO ₃	MeCN	90	trace
8 ^{c,d}	K ₂ CO ₃	toluene	90	90
9 ^{c,e}	K ₂ CO ₃	toluene	90	87
10 ^{c,d}	K₂CO₃	toluene	80	91
11 ^c	K ₂ CO ₃	toluene	100	73

^a If not otherwise noted, reaction conditions are as following: **1a** (0.30 mmol), norbornene (0.60 mmol), **2a** (0.30 mmol), [Pd] (5 mol%), and base (3.0 equiv) in solvent (3 mL) at 90 °C for 5 h. ^b Isolated yields. ^c The reaction was conducted with 0.36 mmol **1a** for 10 h. ^d Toluene (2 mL) was used. ^e Toluene (4 mL) was used.

With the optimized reaction conditions, we then proceeded to examine the substrates scope for various *N*-tosylhydrazones (Scheme 2). The aromatic aldehyde *N*-tosylhydrazones with the *para* and *meta* substituents worked smoothly for this three-component reaction and gave the desired products in good to excellent yields (**3b-f**). The *multi*-substituted and polycyclic aromatic substrates were also suitable for this transformation,



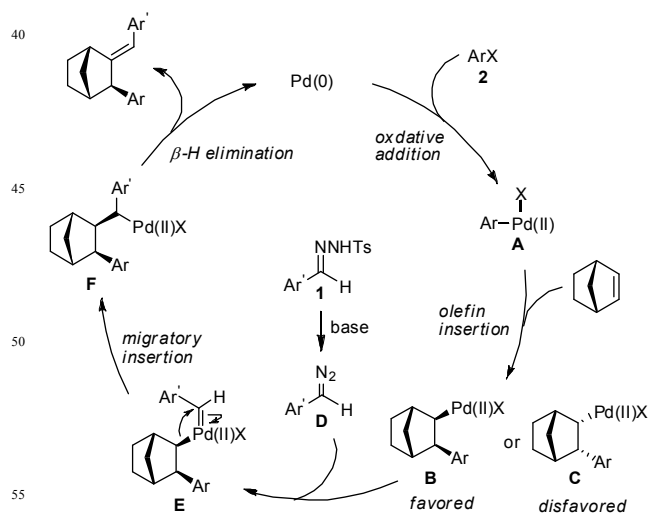
Scheme 2 Scope of *N*-tosylhydrazone and aryl iodide. Reaction conditions: **1a-i** (0.36 mmol), norbornene (0.60 mmol), **2a-i** (0.30 mmol), Pd(PPh₃)₄ (5 mol%) and base (3.0 equiv) in toluene (2 mL) at 80 °C for 10 h. The diastereoisomeric ratio was determined by ¹H NMR and the yields all refer to isolated yields.

affording the corresponding products **3g** and **3h** in 75% and 73% yields, respectively. Notably, the reaction with cinnamaldehyde *N*-tosylhydrazone could also give the desired product **3i** in 78% yield under the standard conditions.

Next, the scope of aryl iodides was examined. To our delight, the expected products could be obtained in good to excellent yields for both electron-rich and electron-deficient substrates (**3j-p**). In the case when the aromatic iodide bears an *ortho* substituent, the reaction only afforded moderate yield of the coupling product (**3p**), presumably due to the effect of steric hindrance. As expected, the naphthalene and multiply aromatic iodides were also tolerated in this reaction under the same reaction conditions.

It is worth mentioning that in all the cases only two of the four possible stereoisomers (*E*, *Z* of double bond; *exo*, *endo* of Ar) could be identified, with the stereomeric ratio ranging from 3:1 to >20:1. When the two stereomeric mixture of the product **3e** was subjected to Pd/C-catalyzed hydrogenation, four hydrogenated products were formed according to GC-MS analysis.¹³ This may indicate that the stereoisomerism of the product is due to *exo* and *endo* of the Ar group, rather than the *E*, *Z* of the double bond. The structures of **3g**, **h** and **k** were unambiguously established by X-ray crystallographic analysis.¹² Therefore, we can conclude that the *exo* isomers with *E* double bond configuration as shown in Scheme 2 are the major stereoisomers in this three-component coupling reaction.

As illustrated in Scheme 3, a plausible reaction mechanism has been proposed for this reaction. The first step is the oxidative addition of aryl halides to the Pd(0), affording the arylpalladium species **A**. Subsequent norbornene insertion to carbon-palladium bond leads to intermediates **B** and **C**. In the diastereomer **B**, the aromatic group and palladium were in the *exo*-position, whereas in the intermediate **C**, the aromatic group and palladium situated in the *endo*-position. The intermediate **B** is favoured over **C** due to the less steric hindrance in the former. Subsequently, the intermediate **E** is generated by dediazonation of the *in situ* generated diazo compounds by the alkylpalladium species **B**.



Scheme 3 Proposed mechanism.

From the intermediate **E** the migratory insertion of an alkyl group to the palladium carbene produces complex **F**.^{8,14} Finally, the β -hydride elimination of intermediate **F** gives the final product and regenerated the Pd(0) catalyst in the presence of base.

In conclusion, we have developed a palladium-catalyzed cascade reaction of *N*-tosylhydrazone, norbornene and aryl halide, in which the intermolecular insertion of alkene into aryl palladium species has been followed by palladium carbene formation and subsequent migratory insertion. This reaction provides an efficient method for double functionalization of norbornene. Further efforts are directed to the development of other cascade reactions that involve metal carbene migratory insertion process.

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