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ABSTRACT

A mild, efficient, and practical catalytic system for the synthesis of highly privileged stilbene pharmacophores is reported. This system uses N-heterocyclic carbene palladium (II) Pyridine (NHC-Pd (II)-Py) complex to catalyze the formation of carbon-carbon bonds between olefin derivatives and various bromide. This simple, gentle and user-friendly method can offer a variety of stilbene products in excellent yields under solvent-free condition. And its scale-up reaction has excellent yield and this system can be applied to industrial fields. The utility of this method is highlighted by its universality and modular synthesis of a series of bioactive molecules or important medical intermediates.

GRAPHICAL ABSTRACT



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KEYWARDS

NHC-Pd (II)-Py; aromatic bromides; olefins; stilbene; synthesis

Introduction

The stilbene scaffold is a key pharmacophore in sunscreen,^[1] natural products^[2,3] and pharmaceuticals^[4,5] that accomplish a wide range of important functions (a small sampling of which are provided in Scheme 1). Due to the importance of stilbene scaffold in the synthesis of leading molecules,^[6] a variety of preparative methodologies have been developed. Particularly, the Heck reaction was used as one of the important methods for the synthesis of stilbene and its analogues.^[7]

The Heck reaction was discovered by Mizoroki^[8] and Richard F Heck^[9] in the early 1970s, which has been proven to be one of the most important methods for carbon-carbon formation between organic halides and olefins in organic chemistry. In the past 40 years, the Heck reaction has been widely used in many organic synthesis which includes the synthesis of biologically active molecules,^[6,10] natural products,^[11] fine

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Scheme 1. Biologically active stilbene derivatives.

chemicals,^[1] active pharmaceutical ingredients (APIs).^[12] It now belongs to an essential section of palladium-catalyzed cross-coupling reactions.^[13]

The traditional Heck reaction usually couples aryl halide (C-halogen bond) with olefin in the presence of a palladium catalyst.^[14] Later, it was reported that different ligands, metal sources, or metal sources substrates were used in the Heck reaction system. In the past ten years, scientists have discovered many highly efficient homogeneous palladium-containing catalystic systems. According to the difference of organic ligands coordinated with metal palladium, the reaction can be divided into a variety of catalytic systems, which contain electron-rich, sterically hindered phosphorus ligands,^[15] nitrogen ligands^[16,17] sulfur ligand^[18] and N-heterocyclic carbene (NHC)^[19] ligand. The Heck reaction is a powerful catalytic method for carbon-carbon (C-C) bond formation in synthetic organic chemistry. Currently, various aryl substitution reagents that operate under palladium catalysis instead of aryl halides have been developed, such as diazonium salts,^[20] aniline,^[21] nitrobenzene,^[22] phenylboronic acid^[23] have been used for the Heck reaction. The wide application of Heck reaction in organic synthesis urges many scientists to find more effective, cheaper and readily available catalytic systems. Subsequently, the catalytic system of iron,^[24,25] nickel,^[26] indium,^[27] cobalt,^[28] selenium^[29] metal complexes have been reported in the literature for Heck reaction (Scheme 2).

Transition metal carbene complexes are one of the frontiers in the research of metal organic chemistry. Since Fischer^[30] introduced carbene into inorganic and metal-organic chemistry in 1964, carbene derivatives have been widely used in organic reactions and synthesis. Soon after, Ofele^[31] and Wanzlick^[32] reported the metal complexes containing N-heterocycles for the first time. Unlike other metal complexes, it has an electronic effect and a steric hindrance effect on a pair of lone electrons on NHC nitrogen and carbon atoms, which make the dissociation energy of the metal-carbon bond between the metal and the N-heterocyclic carbene complex high, so the properties of NHC are very stable. Since free N-heterocyclic carbene was successfully separated by Arduengo^[33] in 1991, the N-heterocyclic carbene palladium complex has attracted the interest of many scientists and been researched extensively and deeply. In 1995, Herrmann^[34] reported for the first time the application of N-heterocyclic carbene and its palladium complex in the Heck reaction, which greatly promoted the application of N-heterocyclic carbene and its metal complex in the catalytic reaction.^[35,36]

The use of N-heterocyclic carbenes (NHCs) as ligands has led to an array of exciting developments in Pd-catalyzed cross-coupling reactions.^[37,38] The high sensitivity of isolated NHCs necessitates handling under rigorously anhydrous conditions.^[37,39–41] In situ preparation of active Pd–NHC catalysts has been the dominant strategy to (a)previous work



Scheme 2. Heck coupling reactions.

circumvent this problem.^[42] Subsequently, the groups of Herrmann,^[43,44] Nolan,^[45–47] Beller,^[48] and Sigman^[49] have published an array of monoligated Pd–NHC complexes that show high levels of activity in Pd-catalyzed reactions. However, these catalysts were all prepared under rigorous anhydrous conditions even when the isolated carbene was not used. In 2006, Organ^[50] developed a process for the preparation of Pd–NHC precatalysts in air, using readily available starting materials on a large scale in order to overcome the strict synthesis conditions of Pd–NHC catalysts and the disadvantages of low acceptance rate. Here, their group first reported the use of pyridine as a non-carbene auxiliary ligand. Not only the good coordination ability of pyridine is used to stabilize the Pd (II) complex, but also the advantage that pyridine is easy to leave and form an empty coordination site to bind to the substrate is fully utilized.^[51]

Influenced by the work of Organ^[50] and coworkers, we also use pyridine as a noncarbene ligand to synthesize NHC-Pd (II)-Py. At the same time, NHC's good δ -electron donating properties and high basicity greatly enhance the catalytic activity of Pd (II) complexes.^[52] Inspired by these results, we report a method to synthesize a series of stilbenes in high yields by forming carbon-carbon bonds between organic halides and olefins under the condition of (0.01 eq) NHC-Pd (II)-Py. In addition, the reaction system is so simple in operation, and various stilbene can be quickly and efficiently obtained by large-scale experiments.

Results and discussion

The optimization procedure was carried out with Bromobenzene **1a** and Styrene **2a** as model substrates for the NHC-Pd (II)-Py-catalyzed carbon-carbon cross-coupling. Some representative results are shown in Table 1.

In our initial experiments, the Heck reaction of bromobenzene and styrene was carried out with (0.15 eq) NHC-Pd(II)-Py, (0.5 eq) Cs_2CO_3 and (1.0 mL) 1,4-dioxane at 100 °C for 12 h. Gratifyingly, the reaction went smoothly and the expected product was obtained in good yield under these conditions, (Table 1, entry 1). When KOtBu, KOH or K₂CO₃ was used as the base with other conditions unchanged (Table 1, entries 2, 3 and 4), the reaction can achieve a moderate to good yield; When Et₃N or 2,6-Lutidine was used as





Entry	Cat (eq)	Base (eq)	Solvent	Temp (°C)	Yield (%) ^b
1	NHC-Pd (II)-Py (0.15)	Cs_2CO_3 (0.5)	1,4-Dioxane	100	85
2	NHC-Pd (II)-Py (0.15)	KOtBu (0.5)	1,4-Dioxane	100	65
3	NHC-Pd (II)-Py (0.15)	KOH (0.5)	1,4-Dioxane	100	70
4	NHC-Pd (II)-Py (0.15)	K_2CO_3 (0.5)	1,4-Dioxane	100	60
5	NHC-Pd (II)-Py (0.15)	Et ₃ N (0.5)	1,4-Dioxane	100	31
6	NHC-Pd (II)-Py (0.15)	2,6-Lutidine (0.5)	1,4-Dioxane	100	50
7	NHC-Pd (II)-Py (0.01)	-	1,4-Dioxane	100	NR ^c
8	NHC-Pd (II)-Py (0.15)	Cs_2CO_3 (0.5)	DMF	100	80
9	NHC-Pd (II)-Py (0.15)	Cs_2CO_3 (0.5)	THF	80	82
10	NHC-Pd (II)-Py (0.15)	Cs_2CO_3 (0.5)	CH₃CN	80	40
11	NHC-Pd (II)-Py (0.15)	Cs_2CO_3 (0.5)	toluene	100	18
12	NHC-Pd (II)-Py (0.15)	Cs_2CO_3 (0.5)	-	100	92
13	NHC-Pd (II)-Py (0.05)	Cs_2CO_3 (0.5)	-	100	90
14	NHC-Pd (II)-Py (0.01)	Cs_2CO_3 (0.5)	-	100	90
15	NHC-Pd (II)-Py (0.01)	Cs_2CO_3 (1.0)	-	100	91
16	NHC-Pd (II)-Py (0.01)	Cs ₂ CO ₃ (3.0)	-	100	89
17	NHC-Pd (II)-Py (0.01)	Cs_2CO_3 (0.3)	-	100	93
18	NHC-Pd (II)-Py (0.01)	Cs_2CO_3 (0.1)	-	100	30
19	NHC-Pd (II)-Py (0.01)	Cs_2CO_3 (0.3)	-	130	82
20	NHC-Pd (II)-Py (0.01)	Cs_2CO_3 (0.3)	-	70	65
21	PdCl ₂ (0.15)	Cs ₂ CO ₃ (0.3)	1,4–Dioxane	100	NR ^c
22	-	Cs_2CO_3 (0.3)	-	100	NR ^c

^aAll reactions were carried out with **1a** (1 mmol), **2a**(1.2 eq), cat (1.0–15 mol %), base (0.3–3 eq), solvent (1.0 mL) at 100 °C for 12 h. ^bIsolated yields. ^cNo reaction.

the base, the yield of product 3a is low at 31% and 50%, respectively (Table 1, entries 5 and 6). Meanwhile, reaction was proved not to occur without base, which indicated that anionic bases played a vital role in this system (Table 1, entry 7). Based on the results of the previous screening, the influence of the solvent was then investigated. The reaction of equivalent bromobenzene and styrene was conducted in solvent DMF, THF, toluene, CH₃CN respectively, and can get low to moderate yields (Table 1, entries 8-11). However, the desired product can be obtained in good yield under solvent-free conditions (Table 1, entry 12). Further investigation evidenced that the amount of NHC-Pd (II)-Py was reduced from 0.15 eq to 0.1 eq, while the yield did not change (Table 1, entries 12–14). Next, increasing the amounts of Cs_2CO_3 from 0.5 eq to 3 eq, we found no significant increase in yield (Table 1, entry 14-16). While decreasing the amounts of Cs_2CO_3 to 0.1 eq, the yield of product **3a** was significantly reduced (Table 1, entry 17 and 18). Interestingly, 0.3 eq Cs₂CO₃ was proved to be sufficient to provide excellent yield of product 3a. Reducing the reaction temperature would extend the reaction time (Table 1, entry 20) and cause the styrene to slowly polymerize, while using a higher temperature was accelerated the polymerization of styrene, thereby reducing the yield (Table 1, entry 19). Thus, 100 °C was chosen as most suitable temperature for the reaction system. Meanwhile, reaction was proved not to occur when PdCl₂ was used as catalyst (Table 1, entry 21). Finally, the optimal condition of the reaction system was



Table 2. NHC-Pd (II)-Py complex catalyzed reactions of aromatic bromides and olefins.

determined: 0.01 eq NHC-Pd (II)-Py and 0.3 eq Cs_2CO_3 were used for solvent-free reaction at 100 °C for 12 hours, and the yield exceeded 90%.

Having established the optimized reaction conditions, we tested a variety of substituted aromatic bromine and olefin derivatives to probe the versatility of our catalytic system, and the results are summarized in Table 2. Both bromobenzene and styrene derivatives containing electron-donating groups and electron-withdrawing groups have good tolerance in this reaction, and the corresponding stilbene is obtained in high yield (>90%). To our delight, the reaction of different aromatic brominated derivatives with styrene and its derivatives in the catalytic system also provides good yields. We found that the reaction of 2-bromonaphthalene with 4-methylstyrene and styrene also proceeded very well, with very good yields of 97% and 98%, respectively (Table 2, 3j and 3k). Heterocyclic aromatic bromines are considered to be challenging substrates for



Scheme 3. Reaction scale-up.

heck carbon-carbon cross-coupling.^[53,54] However, the heteroaromatic substrate is also compatible with the catalystic system, and reacts with styrene derivatives to produce the corresponding products 3g, 3p, 3q with yields of 96%, 90% and 93%. In addition, the corresponding product obtained from the reaction of 9-vinylanthracene and bromobenzene can also reach a yield of 96%. After proving the universality of aromatic bromides and styrene in this method, the Heck reaction of aryl halide and tert-butyl acrylate can also provide good yields in the same catalytic reaction system (Table 2, 3r, 3s, 3t and 3u).

To demonstrate the utility of this method, resveratrol, which exerts anti-cancer,^[55] anti-bacterial,^[56] and anti-fatigue effects,^[56] was synthesized from 5-bromoresorcinol and 4-hydrozystyrene in one step, and the yield is as high as 93% (Table 2).

In order to further prove the potential application of this NHC-Pd (II)-Py catalyzed carbon-carbon coupling, we further illustrated its scalability. Under the conditions of this catalytic system, the reaction of 1-bromo-4-nitrobenzene and styrene was used as a scale-up reaction model. To our delight, under the conditions of this catalytic system, when the reaction was scaled up to 49.5 mmol (1i, 10g scale), the desired product 3i was isolated in 88% yield (Scheme 3).

3. Conclusion

In summary, we have developed an efficient method for the Heck coupling of olefins with various substituted aryl bromides by NHC-Pd (II)-Py under solvent-free conditions. The presented synthetic methodology reveals excellent reactivity and good functional group tolerance with moderate to excellent yields. The reaction system is so simple and in operation that various stilbene can be obtained quickly and efficiently and applied to the industry. Further extension of the application of the system to synthesis of other bioactive molecules or important medical intermediates based on this method is in progress in our laboratory.

4. Materials and methods

4.1. Chemicals and materials

Most of chemicals were purchased from Sigma-Aldrich, Strem, Acros, TCI or Alfa Aesar and used as such unless stated otherwise. ¹H and ¹³C NMR data were recorded with Bruker Advance III (600 MHz) spectrometers with tetramethylsilane as an internal standard. All chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. All chemical shifts were reported relative tetramethylsilane (0 ppm for ¹H), CDCl₃ (77.0 ppm for ¹³C) and DMSO- d_6 (2.50 ppm for ¹H, 39.50 ppm for ¹³C), respectively.



Scheme 4. Synthesis of complexes NHC-Pd (II)-Py.

TLC plates were visualized by exposing UV light or by iodine. Purification of crude compounds and separation of reaction mixtures were carried out by column chromatog-raphy using silica gel (200–300 mesh, Shanghai, China). All substrates are known compounds according to the literature.

4.2. General procedure for Heck Cross-Coupling reactions

To a single-necked flask (15 mL) equipped with a stir bar charge with 1 (1 eq, 1 mmol), 2 (1 eq, 1.2 mmol), NHC-Pd (II)-Py (0.01 eq, 0.06 g) and Cs_2CO_3 (0.3 eq, 0.1 g). Then the reaction flask was stirred at 100 °C for 12 h, and then the reaction mixture was cooled to room temperature. After removing the solvent under reduced pressure, the pure product was obtained by silica gel column chromatography (eluent: petroleum ether/ethyl acetate).

The experimental operation of the amplification reaction is the same as the general operation, but the work-up of the scale-up reaction is relatively convenient and simple. After the reaction was completed, the reaction solution was filtered while hot, and the filtrate was collected. The filtrate was frozen to -8 °C until yellow crystals precipitated out, and then filtered. After the filter cake is dried, the desired stilbene product is obtained.

4.3. Preparation of the catalyst

- i. A mixture of 2,6-diisopropylaniline (33.9 mmol) and HOAc (1.18 mmol) and 15 mL MeOH was stirred in at 50 °C, then slowly dropwise added 15 mL of a MeOH solution of glyoxal (40% aqueous solution, 16.7 mmol) in 15 minutes. After the addition, the mixture continuing to stir at 50 °C for 30 minutes and then at room temperature for 10 hours. The reaction mixture was filtered dried to obtain 5.6 g of yellow compound $\mathbf{a}^{[57]}$ (87% yield).
- ii. **a** (8.5 mmol) and paraformaldehyde (8.5 mmol) were added into 30 mL EtOAc and stirred vigorously to dissolve at 70 °C. Then, 20 mL of TMSCl (0.85 mmol) in EtOAc was slowly added dropwise to the reaction flask within 20 minutes. After reacting for 2 h, the reaction mixture is cooled to 10 °C and filtered. The filter cake was washed with EtOAc and dried to obtain 3.2 g of compound $\mathbf{b}^{[57]}$ as a white solid (89% yield).
- iii. A mixture of b (2.84 mmol), PdCl₂ (2.84 mmol), pyridine (2.84 mmol), K₂CO₃ (2.84 mmol) and THF (20 mL) were refluxed in a nitrogen atmosphere for about 24 hours. The product was purified by flash column chromatography to obtain 1.1 g yellow product c (NHC-Pd (II)-Py) (61% yield) (Scheme 4).^[58]



Figure 1. The X-ray crystal structure of c (NHC-Pd (II)-Py).

The structure of c (NHC-Pd (II)-Py) was established by the ¹H and ¹³C NMR spectroscopic data (Supporting Information) and X-ray analysis. The X-ray crystal structure of c is shown in Figure 1.

Supporting information

Full experimental detail, ¹H and ¹³C NMR spectra, X-ray data. This material can be found via the "Supplementary Content" section of this article's webpage.

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