

Palladium catalyzed N–H bond insertion and intramolecular cyclization cascade: the divergent synthesis of heterocyclics†

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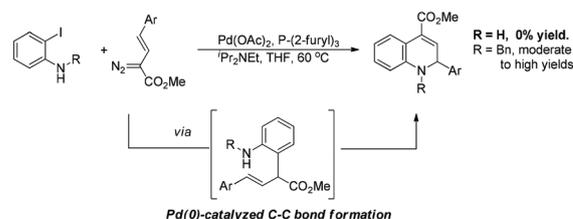
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The palladium catalyzed carbenoid based N–H insertion and electronic effect controlled 5-*exo-trig* or 6-*endo-trig* mode Heck cyclization in one-pot has been realized for *ortho*-iodoanilines, in which PdCl₂ was used as the single palladium resource. The corresponding indoles and quinolines were obtained respectively. However, for *ortho*-triflateanilines, base promoted cyclization is preferred and the lactones were obtained.

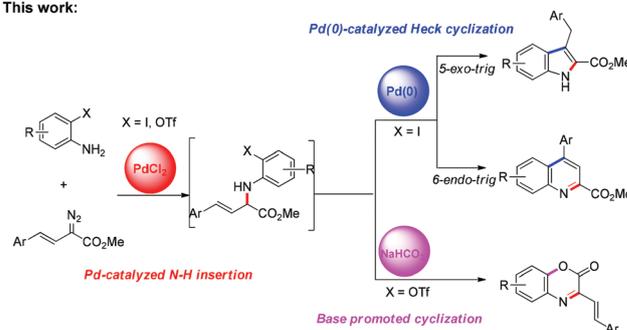
Increased focus has been placed on the development of different types of organic transformations in one pot, which allows rapid construction of highly functionalized molecules with a multiple catalytic system.¹ Undoubtedly, this atom economic approach is time and cost saving. In view of the ability to be converted easily between different oxidation states, palladium complexes could be selected as good candidates to catalyze different reactions in one pot.² Inspired by this strategy and our own investigations on carbenoid chemistry of diazo compounds,³ we envisioned that the combination of palladium catalyzed N–H insertion and Heck cyclization in one pot would facilitate the development of novel methodologies.

In another part, palladium catalyzed C–C bond formations from diazo compounds have received considerable attention during the past decade;⁴ in contrast to rhodium, copper and other metal complexes,⁵ the application of palladium catalysts in N–H insertion remains relatively unexplored.⁶ Recently, we reported the first palladium-catalyzed stereoselective N–H insertion from diazo substrates to prepare chiral α -amino esters.^{3a} Just recently, Feng and co-workers described the highly enantioselective N–H insertion catalyzed by a palladium and chiral guanidine catalytic system.⁷ In early 2013, Liang

Previous report (by Liang *et al*):



This work:



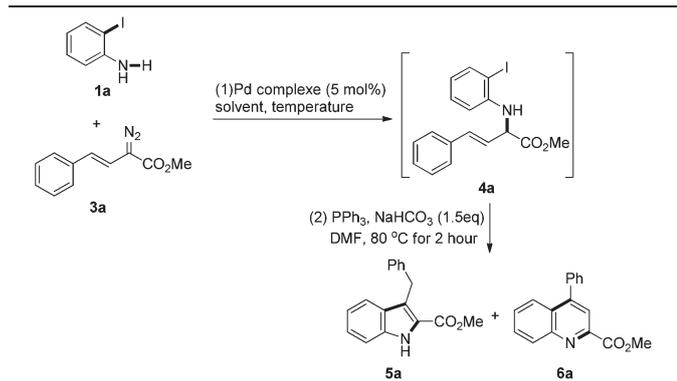
Scheme 1 Pd-catalyzed one-pot synthesis of heterocyclics.

and co-workers reported a palladium catalyzed reaction between vinyldiazoacetates and *N*-substituted-*ortho*-iodoanilines, in which Pd(0)-catalyzed C–C bond formation was postulated as the first step (Scheme 1).⁸ During our investigation on the utilization of similar substrates to Liang's report, we imagined that the C–N bond could have formed firstly rather than the C–C bond in the presence of Pd(II) complexes under specific reaction conditions. Moreover, the insertion products are potential substrates for Heck cyclization. So, followed by Pd(0)-catalyzed intramolecular Heck cyclization, ring-closing would take place logically. In view of the fact that these two independent reactions could be catalyzed by different palladium species, it is reasonable to postulate that the two different transformations could be completed in one pot just by controlling the oxidation of palladium (Scheme 1). In this communication, we wish to present the utilization of arylvinyl

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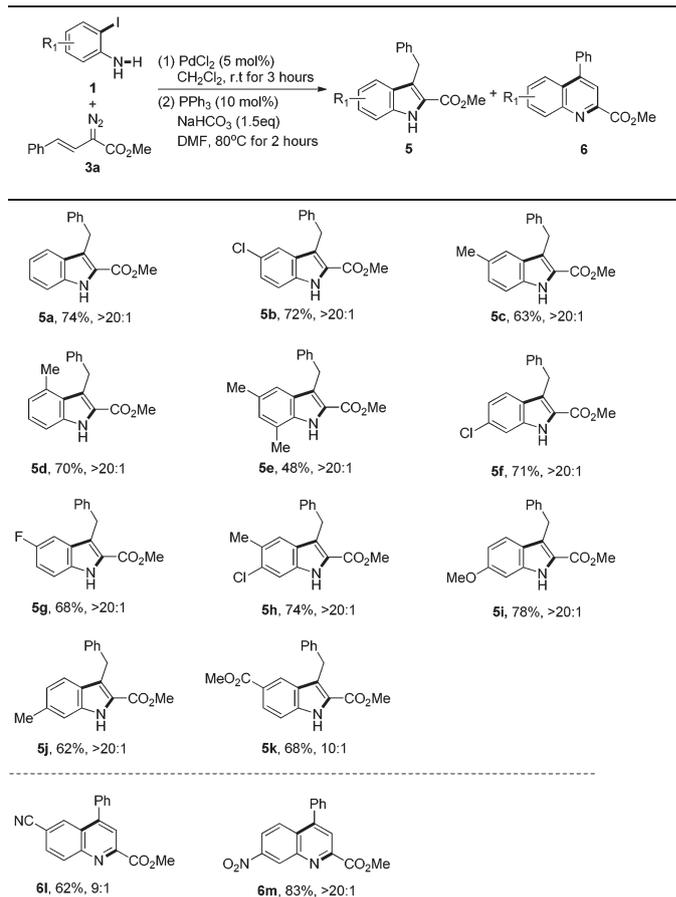
Table 1 Optimization of the reaction conditions^a

Entry	Pd complexes	Solvent ^b	5a ^c (yield%)	6a ^c (yield%)
1	PdCl ₂	CH ₂ Cl ₂	74	0
2	Pd(PPh ₃) ₄	CH ₂ Cl ₂	—	—
3	Pd(OAc) ₂	CH ₂ Cl ₂	32	0
4	Pd ₂ (dba) ₃	CH ₂ Cl ₂	45	0
5	Pd(TFA) ₂	CH ₂ Cl ₂	12	0
6	Pd(dppf)Cl ₂	CH ₂ Cl ₂	—	—
7	PdCl ₂	DMSO	13	0
8	PdCl ₂	DCE	54	0
9	PdCl ₂	DMF	16	<5%
10 ^d	PdCl ₂	CH ₂ Cl ₂	40	0

^a All reactions were carried out with **1a** (0.52 mmol), **3a** (0.5 mmol), PdCl₂ (5 mol%), and solvent (2 mL) at r.t. for 3 hours unless otherwise noted; then PPh₃ (0.05 mmol, 10 mol%), NaHCO₃ (0.75 mmol) and DMF (2 mL) were added and the mixture was continued to be stirred at 80 °C for 2 hours. ^b Solvents were examined for the N–H insertion step. ^c Isolated yields. ^d The reaction temperature is 40 °C; DCE = 1,2-dichloroethane, DMF = *N,N*-dimethylformamide, DMSO = dimethyl sulfoxide.

diazoacetates and *ortho*-iodo/triflate-anilines to construct three different types of heterocyclics. It is noteworthy that different from Liang's procedure, our investigation featured the Pd-catalyzed C–N bond rather than C–C bond formation as the first step. Moreover, the *N*-nonsubstituted iodoanilines work well in our approach but are totally inert in Liang's procedure.⁸

Our investigation started from the reaction of aniline (**1a**) with phenylvinyl diazoacetate (**3a**) in the presence of different palladium complexes. Upon optimizing the reaction parameters aiming at getting high selectivity, the best result was obtained when the reaction was performed with PdCl₂ (5 mol%) in dichloromethane at room temperature for 3 hours followed by Heck reaction (PPh₃ and NaHCO₃ in DMF). The indole (**5a**) was obtained in 74% isolated yield in two steps (Table 1, entry 1). For the palladium complexes examined, Pd(PPh₃)₄ and Pd(dppf)Cl₂ were totally inert to the process, which meant that these two catalysts cannot initiate the first insertion step (Table 1, entries 2 and 6). This phenomenon was consistent with our former report that the presence of phosphorus ligands was detrimental to the palladium-catalyzed N–H insertion.^{3a} Other palladium complexes gave low yields in the one-pot procedure too. High temperature resulted in a decreased yield (Table 1, entry 10). Generally, for the

Table 2 Substrate scope^{a,b,c}

^a All reactions were carried out with **1** (0.52 mmol), **3a** (0.5 mmol), PdCl₂ (5 mol%), and CH₂Cl₂ (2 mL) at r.t. for 3 hours; then PPh₃ (0.05 mmol, 10 mol%), NaHCO₃ (0.75 mmol) and DMF (2 mL) were added and the mixture was continued to be stirred at 80 °C for 2 hours. ^b The ratios were determined by ¹H-NMR analysis of crude products. ^c Isolated yields of the major products.

following Heck cyclization step, the 5-*exo-trig* and 6-*endo-trig* modes of annulations are both favored to afford the corresponding five or six member ring-closing products (Scheme 1).⁹ However, for the reaction of **1a** and **3a**, the 6-*endo-trig* ring-closing product (**6a**) was not observed and the indole (**5a**) was isolated as the single isomer.

With the optimized reaction conditions in hand, we next investigated the reaction of different substituted anilines with **3a** (Table 2). As observed, for the electron-donating and weak electron-withdrawing substituted *ortho*-iodoanilines, the 5-*exo-trig* annulation was preferred and the indoles were obtained as the major products (Table 2, from **5a** to **5j**). However, the anilines bearing strong electron-withdrawing groups (such as NO₂ and CN) afforded quinolines as the major isomers (Table 2, **6l** and **6m**) in which the 6-*endo-trig* annulation was the prior ring-closing mode. However, the carboxylate substituted aniline rendered the indole as the major product (Table 2, **5k**), probably owing to the relatively weaker electron-

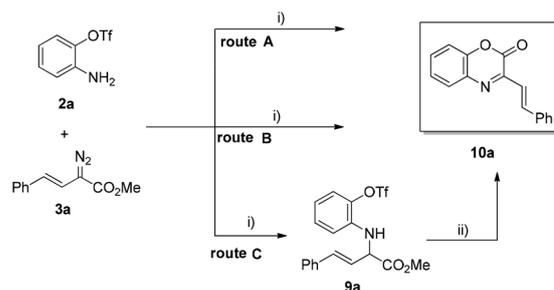
Table 3 Substrate scope^{a,b,c}

Reaction Scheme	
	<p>(1) PdCl₂ (5 mol%), CH₂Cl₂, r.t. for 3 hours (2) PPh₃ (10 mol%), NaHCO₃ (1.5 eq), DMF, 80°C, 2 hours</p>
	<p>7a, Ar = <i>p</i>-MeC₆H₄, 80%, >20:1 7b, Ar = <i>p</i>-ClC₆H₄, 71%, >20:1</p> <p>7c, Ar = <i>p</i>-MeC₆H₄, 64%, >20:1 7d, Ar = <i>p</i>-ClC₆H₄, 80%, >20:1 7e, Ar = <i>o</i>-MeOC₆H₄, 67%, >20:1 7f, Ar = <i>m</i>-ClC₆H₄, 82%, >20:1</p> <p>7i, 76%, >20:1 7j, 46%, >20:1 7k, Ar = <i>p</i>-MeC₆H₄, 73%, >20:1 7l, Ar = <i>p</i>-ClC₆H₄, 74%, >20:1 7m, Ar = <i>o</i>-MeOC₆H₄, 72%, >20:1</p> <p>7n, Ar = <i>p</i>-MeC₆H₄, 66%, 10:1 7o, Ar = <i>m</i>-ClC₆H₄, 33%, 1:1 (7o:8a)</p> <p>7p, Ar = <i>p</i>-MeC₆H₄, 32%, 1:1 (7p:18b)</p> <p>8a, Ar = <i>m</i>-ClC₆H₄, 31%, 1:1 (7o:8a)</p> <p>8b, Ar = <i>p</i>-MeC₆H₄, 33%, 1:1 (7p:8b) 8c, Ar = <i>p</i>-CNC₆H₄, 70%, >20:1 8d, Ar = <i>m</i>-ClC₆H₄, 73%, >20:1</p> <p>8e, Ar = <i>p</i>-MeOC₆H₄, 81%, >20:1 8f, Ar = <i>p</i>-MeC₆H₄, 78%, >20:1 8g, Ar = <i>m</i>-ClC₆H₄, 73%, >20:1</p>

^a Same reaction conditions with Table 2. ^b The ratios were the major isomer to the minor one, which were determined by ¹H-NMR analysis of crude products. ^c Isolated yields of the major products.

withdrawing ability of the carboxylate group compared with nitro and cyano groups.

Next, the substrate scope of the one-pot reaction has been further investigated (Table 3). Similar to the above observations, for iodoanilines bearing the electron-donating or weak electron-withdrawing substitutes, the indoles were obtained as the major products (Table 3, **7a** to **7m**). For the strong electron-withdrawing nitro-substituted anilines, the quinolines were isolated as the major isomers in high yields (Table 3, **8e** to **8g**). However, the carboxylate substituted iodoaniline afforded the indole and quinoline nearly in a 1:1 ratio when reacted with *meta*-chloro-phenyldiazoacetate (Table 3, **7o**/**8a**), which indicated that the 5-*exo-trig* and 6-*endo-trig* annulations had equal opportunity in the ring-closing process. The same phenomenon was observed for the reaction between *para*-cyano-iodoaniline and *para*-methyl-phenyldiazoacetate (Table 3, **7p**/**8b**). The above experiments disclosed the fact that the 5-*exo-trig* and 6-*endo-trig* annulations were affected by both the diazo compounds and the anilines.



Scheme 2 Control experiments. Reaction conditions: route A: (i) PdCl₂ (5 mol%), CH₂Cl₂, r.t. for 3 hours and then PPh₃ (10 mol%), NaHCO₃ (1.5 eq.), DMF, 80 °C, 2 hours. Route B: (i) PdCl₂ (5 mol%), and CH₂Cl₂, r.t. for 3 hours and then NaHCO₃ (1.5 eq.), DMF, 80 °C, 2 hours. Route C: (i) PdCl₂ (5 mol%), and CH₂Cl₂, r.t. for 3 hours. (ii) NaHCO₃ (1.5 eq.), DMF, 80 °C, 2 hours.

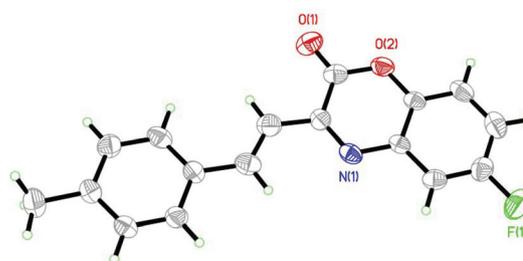
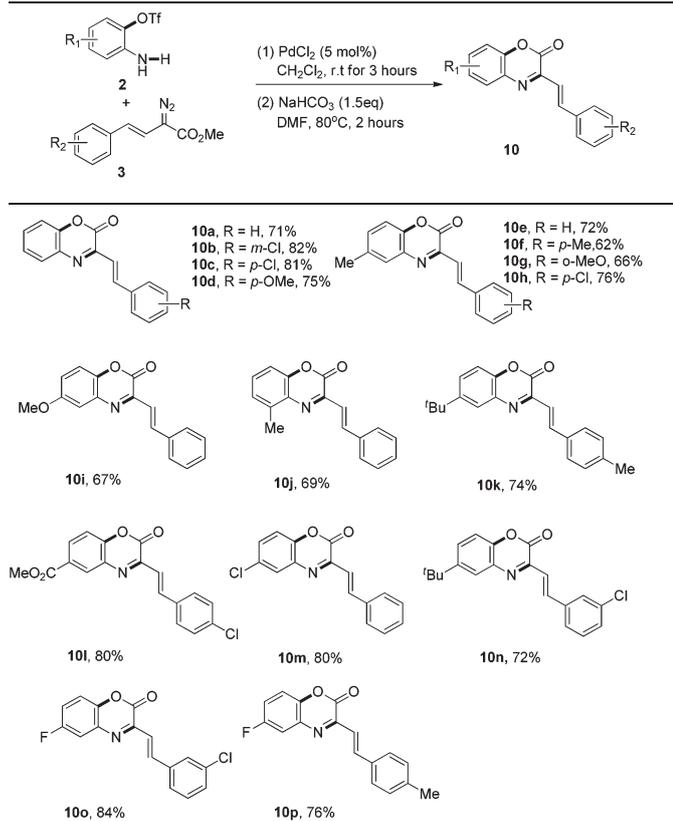


Fig. 1 X-ray crystal structure of **10p**.

Further investigation on the use of *ortho*-triflateanilines in this reaction revealed a different ring-closing mode with *ortho*-iodoanilines. Surprisingly, the annulations did not proceed *via* the Heck cyclization. The NMR analysis of the final product of the reaction between **2a** and **3a** gave different spectra to indole and quinoline. In contrast, the lactone (**10a**) was isolated as a unique product in 71% yield (Scheme 2, route A). Moreover, the structure of the lactone was further confirmed by X-ray crystallographic analysis of **10p** (Fig. 1).

The formation of the lactone rather than indole or quinoline for the triflateaniline (**2a**) indicated that the annulation did not proceed *via* Pd-catalyzed Heck reaction. To further understand this reaction process, we only added NaHCO₃ to the reaction mixture during the second step in the absence of triphenylphosphine (Scheme 2, route B). As expected, only the lactone was obtained. Furthermore, the N-H insertion intermediate **9a** has been separated in pure form and treated with NaHCO₃ directly (Scheme 2, route C), and **10a** was obtained cleanly. The controlled experiments disclosed that the base-promoted annulation was superior to the Heck cyclization even under the Heck reaction conditions when triflateanilines were utilized in the one-pot procedure.

With the standard reaction conditions in hand, the influence of substitutes of the two substrates had been investigated (Table 4). Generally, the reaction proceeded smoothly to deliver the lactones in moderate to high yields. The electron-

Table 4 One-pot reaction of 2 and 3^{a,b}

^a All reactions were carried out with 2 (0.52 mmol), 3 (0.5 mmol), PdCl₂ (5 mol%), and CH₂Cl₂ (2 mL) at r.t. for 3 hours; then NaHCO₃ (0.75 mmol) and DMF (2 mL) were added and the reaction mixture was continued to be stirred at 80 °C for 2 hours. ^b Isolated yields.

withdrawing substituted triflateanilines afforded the corresponding lactones in higher yields than the electron-donating substituted anilines (Table 4).

In summary, the palladium-catalyzed one-pot process of N–H insertion followed by electronic effect controlled Heck cyclization between *ortho*-iodoanilines and vinyl diazoacetates has been realized. For the iodoanilines, the corresponding indoles and quinolines were obtained respectively through 5-*exo-trig* or 6-*endo-trig* ring-closing mode. For the triflateanilines, the lactones were obtained, which proceeded through base promoted annulation rather than Heck cyclization. As a result, three different heterocyclics were obtained respectively. Currently, the studies on palladium catalyzed carbenoid insertion into other X–H bonds are ongoing, as well as further investigation into the reaction mechanism and synthetic applications.

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