

Palladium mediated C_{Phenyl}-H bond activation of 2-furylimines versus *tert*-2-furylbenzylamines



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ABSTRACT

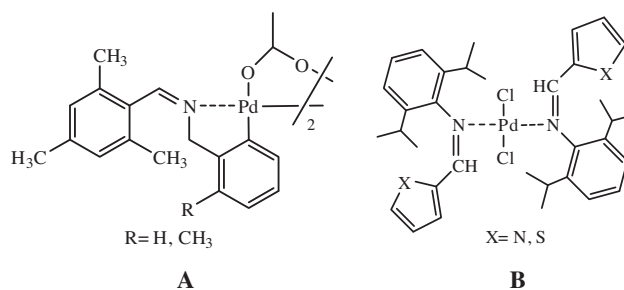
The reactions of 2-furylimines **2a–f** and Na₂PdCl₄ in the presence of NaOAc at 8–10 °C result in nitrogen–palladium coordinated complexes **3a–f**. Reduction of **2d–f** with NaBH₄ followed by *N*-methylation leads to the corresponding *tert*-2-furylbenzylamines **5a–c**. Treatment of **5a–c** with Na₂PdCl₄ at the same reaction condition as mentioned above affords palladacycles **6a–c** where the Pd atoms connect to the phenyl ring rather than the furyl ring. The fact that **5a–c** are more active than **2d–f** in C_{Phenyl}-H bond activation implies that the electron density of C10 or C8 atom in former is higher than those in latter. Compounds **3a–f**, **5a–c**, **6a–c** were identified by elemental analysis, IR and NMR. In addition, the structures of **3b**, **3f** and **6c** were also confirmed by their single crystal X-ray diffractions.

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1. Introduction

Donating group assisted C–H bond activation, e.g. cyclopalladation has emerged as a powerful tool in a variety of transformations including C–C, C–X (X = F, Cl, Br, I, N, O, S) bond formations [1]. With the rapid development of drug chemical industry, chemists are eager to obtain some pharmaceutically active compounds which cannot be synthesized by convention methods. However, regioselective cyclopalladation reaction provides such an opportunity. Regioselective cyclopalladation has been investigated extensively so far for many kinds of ligands [2] particular for benzylideneamines [3]. For an example, Martínez and co-workers reported that when benzylbenzylideneamines were treated with palladium(II) acetate, the formation of five-membered *endo* palladacycles was dominated [3b] and the major reason was attributed to the pseudo-aromatic character of the *endo* palladacycles (also called *endo* effect) [4]. The authors [3b] also found that the formation of five-membered *exo* palladacycles only took place (**A**) when *endo* cyclometalation required the formation of a six-membered compound via aliphatic C–H bond activation or when the steric hindrance affected the planarity of the imines in an important way. Chang and co-workers [5] observed that the reactions of

bulky 2-furylimines or 2-thienylimines and Na₂PdCl₄ produced the palladium coordinated complexes (**B**), the *endo* and *exo* palladacycles requiring C_{Furyl}-H and C_{Aliphatic}-H bond activations, respectively were not isolated. Our previous studies on the cyclometalations of *tert*-ferrocenylamines revealed that the C–H bond activation by platinum(II) always occurred at the ferrocenyl ring rather than phenyl ring [6]. Since a lot of cyclometalations are in electrophilic substitution process, how the electron densities of the aromatic or aliphatic carbons affect the regioselective C–H bond activation will become an interesting topic. In this paper, we will present here the comparative studies on the cyclopalladation of *N*-(2-furylmethylene)benzylamines and *tert*-*N*-(2-furylmethyl)benzylamines. In order to better elucidate the regioselectivity, the reactions of three furylimines, *N*-(2-furylmethylene)anilines (R = 4-CH₃, H, 2-Cl) and Na₂PdCl₄ will be also added.



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2. Results and discussion

2.1. Synthesis of complexes **3a–f** and palladacycles **6a–c**

The reactions of furan-2-carbaldehyde **1** with anilines and benzylamines resulted in aldimines **2a–f** in good yields (Scheme 1). Treatment of **2a–f** with Na_2PdCl_4 at 8–10 °C in the presence of NaOAc in methanol afforded the coordinated complexes **3a–f** as yellow or orange solids. But the *endo* palladacycles from **2a–f** and *exo* palladacycles from **2d–f** (Chart 1) were not isolated. Later, we realized that the reaction temperature might affect the formation of palladacycles, so we increased the reaction temperature to 25 °C and even to 50 °C. However, the results were same as described previously.

Frustrated by the results of **2** particular for **2d–f**, we turn our attention to the cyclopalladation of **5a–c** (also Scheme 1). As illustrated in Scheme 1, Ligands **5a–c** were prepared from **2d–f** after reduction with NaBH_4 followed by *N*-methylation with formaldehyde and NaBH_3CN . Furylamines **5a–c** were allowed to react with Na_2PdCl_4 at 8–10 °C in the presence of NaOAc. After the reactions completed (monitored by TLC), the solvent was evaporated and the residues were dissolved in acetone followed by addition of acetone solution of PPh_3 . Removal of acetone afforded the crude products. After purification with chromatography, yellow solids were isolated in moderate yields and were finally characterized as palladacycles **6a–c**.

2.2. Characterization of **3a–f**, **5a–c**, and **6a–c**

The structures of **3a–f**, **4a–c**, **5a–c** and **6a–c** were identified by elemental analysis, IR and NMR. In IR spectra, the C=N stretch vibration absorption of **2** appears at $\nu \sim 1624 \text{ cm}^{-1}$ whereas the absorption of **3** shifts to $\nu \sim 1613 \text{ cm}^{-1}$ indicating that the $\text{CH}=\text{N} \cdots \text{Pd}$ coordination pattern in **3** is present. The ^1H NMR spectra of **3** clearly demonstrate that both the chemical shifts of H4 in **3a–f** and H5 in **3d–f** locate at the downfield, and they are $\delta \sim 8.50 \text{ ppm}$ and $\delta \sim 4.60 \text{ ppm}$, respectively. However, the IR absorption of **6** does not show significant changes compared to the IR spectra of **5** due to the characteristics of saturated nitrogen atoms. In **5a–c**, the satellites of H5 are singlet ($\delta \sim 3.70 \text{ ppm}$). But, they are split into a typical AB coupling system in **6a–c** and shift to downfield ($\delta \sim 4.35 \text{ ppm}$). The H4 give out a similar splitting pattern as H5 demonstrated. A better explanation for this phenomenon is

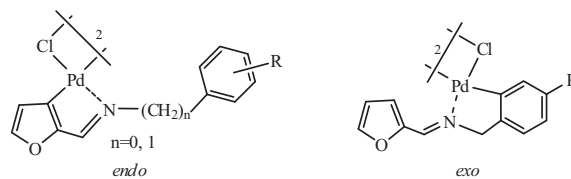


Chart 1. The forms of palladacycles (left, from **2a–f**, right, from **2d–f**).

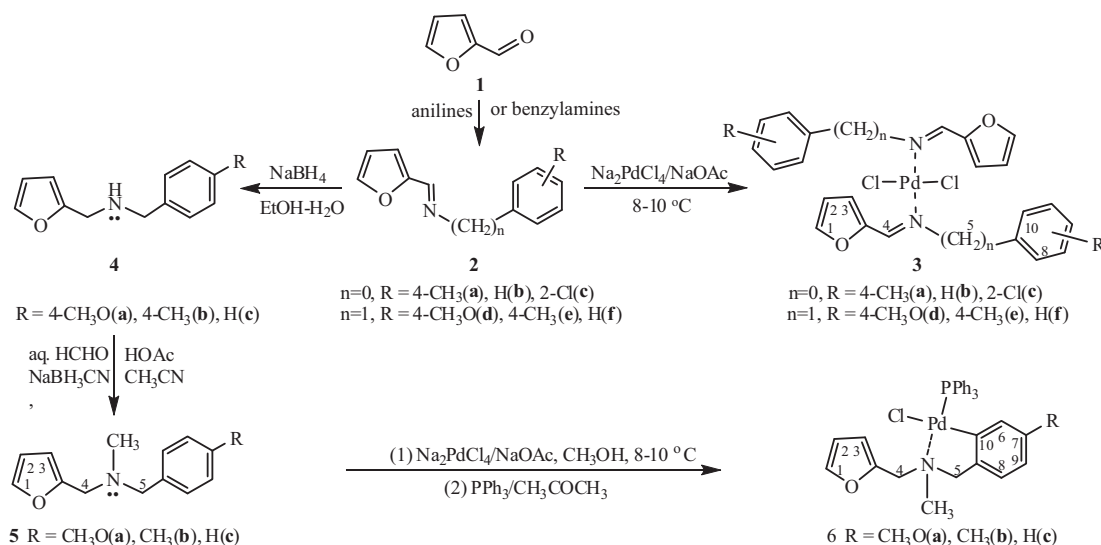
that H4, H5 are diastereotopic because the nitrogen atom in compound **6** is a chiral centre. Additionally, the chemical shifts of $\text{N}-\text{CH}_3$ in **6** move to the lower magnetic field with $\delta \sim 2.90 \text{ ppm}$.

2.3. Crystal structures of **3b**, **3f** and **6c**

The structures of complexes **3b**, **3f** and palladacycle **6c** were confirmed further by their single crystal X-ray diffractions (Figs. 1–3). The crystallographic data and refined parameters for **3b**, **3f** and **6c** are tabulated in Table 1, and their selected bond lengths and angles are listed in Table 2. X-ray diffraction studies demonstrates that two molecules of **3b** or **3f** (Figs. 1 and 2) coordinate to palladium(II) atom in a *trans* orientation. A similar *trans* coordination pattern between N atom and PPh_3 (Fig. 3) is also observed in **6c**. The average N–Pd bond lengths in **3b** (2.012 Å) and **3f** (2.011 Å) are slight shorter than that of palladium(II) coordinated bulky furylimines (2.050 Å) [5]. However, the N–Pd bond length in **6c** (2.154 Å) is longer than those of **3b**, **3f** probably because of the formation of five-membered rigid palladacycle. The C–Pd bond length (2.013 Å) is longer than that of the reported cyclopalladated amines (2.000 Å) [2a]. The $\text{N1}-\text{Pd}-\text{N2}$ bond angle in **3b** (178.59°) is very close to the ideal 180° angle. However, the $\text{N1}-\text{Pd}-\text{N2}$ bond angle in **3f** (173.50°) and the N–Pd–P angle in **6c** (173.75°) are smaller than ideal 180°. In **6c**, palladium(II) atom is in a slight distorted square-planar environment, bonded to Cl, P, N and C_{phenyl} atoms. The deviations of the atoms from the mean plane defined by the former five atoms are Pd -0.0482 , Cl 0.1725 , P -0.1503 , N -0.1852 and C_{phenyl} 0.2111 Å, respectively.

2.4. Regioselective cyclopalladation

As we know, the electrophilic and nucleophilic substitutions easily take place at the α - and β -positions of the furyl ring,



Scheme 1. Synthesis of complexes **3** and palladacycles **6**.

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