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Palladacycle-Catalyzed Tandem Allylic Amination/Allylation Protocol for One-Pot Synthesis of 2-Allylanilines from Allylic Alcohols

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Abstract: An efficient methodology involving the predominant formation of C–C bonds is described for the first direct synthesis of 2-allylanilines from allylic alcohols *via* a one-pot tandem allylic amination/allylation protocol catalyzed by a palladacycle under mild conditions without the requirement for additional activators.

Keywords: 2-allylanilines; allylation; allylic amination; C–C bond formation; palladacycles

A "green" direct catalytic substitution of allylic alcohols with the inherent dual advantages of avoiding the formation of stoichiometric amounts of unwanted chemical waste (in the synthesis of activated substrates and during amination) as well as the formation of water as the sole co-product has recently attracted much attention from both environmental and economical points of view.[1,2] However, due to the inertness of the hydroxy moiety in such scenarios, direct substitutions of allylic alcohols typically require high temperatures,[3] neat conditions,[4] or considerable amounts of activators.[5–14] To date, there are several reports on the transition metal-catalyzed allylic amination of allylic alcohols or allylic alcohol derivatives with arylamines leading to the predominant generation of *N*-allylanilines *via* C–N bond formation.[1c,10b,15–17] Subsequent conversion of the *N*-allylanilines themselves into 2-allylanilines is attractive since the products obtained are starting materials for the preperation of bicyclic nitrogen-containing heterocycles through the cyclization of the nitrogen onto the double bond.[18] However, the synthesis of 2-allylanilines *via* thermal, protic acid-promoted and charge-accelerated rearrangments reported to date all have drawbacks of harsh reaction conditions, low yield or limited substrate scope.[19] A few recent reports have also appeared of microwave-assisted and heteropoly acid (HPA)-catalyzed processes but these have demonstrated limited substrate scope or low yields.[20] A one-pot procedure which combines the efficient allylic amination of allylic alcohols and the subsequent allylation of the *N*-allylaniline products which can be conducted under mild conditions to provide a direct access to 2-allylanilines with good regioselectivity and high yield is therefore desirable. This attractive synthetic methodology will avoid the formation of chemical waste in multistep synthesis and is atom economical.

Palladacycles have attracted much attention in the homogeneous catalysis of reactions such as cross-coupling,[21] allylic amination,[22] allylic rearrangement[23] and so on. We have previously explored the use of palladacycles for the asymmetric Claisen rearrangement reaction[24] and also investigated their potential in C–N bond formation scenarios such as hydroamination.[25] We have also recently reported their efficacy in C–P bond formation reactions.[26] We report here the catalytic properties of a simple cationic palladacycle (Figure 1) which is readily derived from the well known dimeric complex $\{[Pd[Me_2NCH_2C_6H_4](\mu\text{-}Cl)\}_2$.[27] This cationic complex is chemically stable and is soluble in most organic solvents. Furthermore,

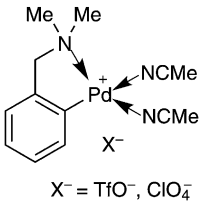
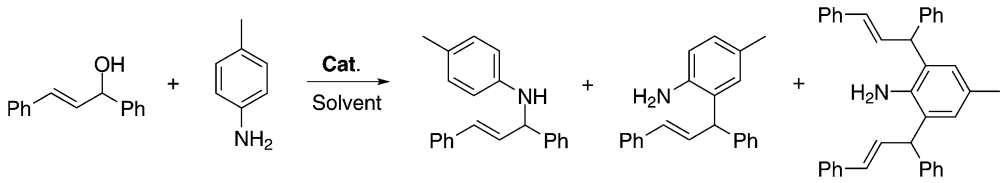


Figure 1. Structure of the palladacycle.

Table 1. Optimization of the reaction conditions.



1a **2a** **3aa** **4aa** **5aa**

Entry[a]	Solvent	Temperature [°C]	Time [h]	Yield[b] [%]	Product ratio[c]
1	DCE	70	12	94	0:91:9
2	tolueue	70	12	–	–
3	dioxane	70	12	–	–
4	DMF	70	12	–	–
5	CH_3CN	70	12	16	100:0:0
6	DCE	40	12	17	100:0:0
7	DCE	50	12	45	80:20:0
8	DCE	60	12	50	70:30:0
9	DCE	70	6	85	15:80:5

[a] Unless otherwise indicated, all reactions were performed using substrate (0.5 mmol), amine (0.75 mmol), catalyst (5 mol%).
[b] Isolated yield of **3aa**+**4aa**+**5aa**.
[c] Product ratio of **3aa**:**4aa**:**5aa**.

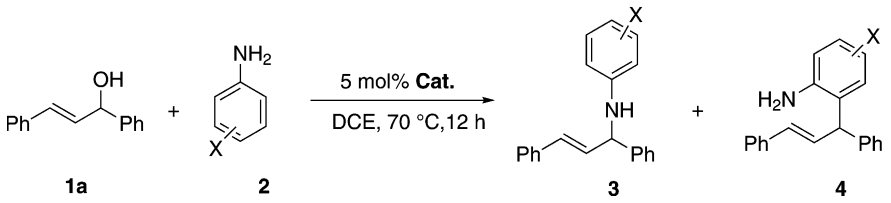
the distinct electronic directing influence originating from the strong π-accepting aromatic carbon and the σ-donating nitrogen donor are well established.[28] Such electronic properties would allow electronically different substrates to interact simultaneously with the palladium centre for coupling or addition reactions. We herein present the application of this palladacycle as an efficient catalyst for the one-pot tandem allylic amination/allylation protocol for the synthesis of 2-allylanilines from allylic alcohols.

Initially the catalyst was evaluated using 1,3-diphenyl-2-propen-1-ol (**1a**) and toluidine (**2a**) (Table 1, entry 1) and 2-allylaniline was found to be the major product of the reaction contrary to the usual predominance of the *N*-allylated product in similar catalytic scenarios. It needs to be noted that the allylic amination occurs without the need for any external activator and even more significantly the subsequent allylation can occur at the relatively low temperature of 70 °C. Encouraged by these results, we proceeded to optimize the conditions and an evaluation of solvents showed that the non-coordinating solvent DCE provided the best results (Table 1, entry 1). It was also established that 70 °C was indeed the optimum temperature with lower temperatures giving poor yields (Table 1, entries 6–8). It is noteworthy that similar reactivity and product selectivity were observed when TfO^- and ClO_4^- were used as counterions.

With the optimum conditions established, we proceeded to screen various arylamines and good to high yields were achieved in all cases (Table 2). A key point in the catalyst design is that it allows the simultaneous interaction of the allylic alcohol and the amine substrate on the palladium centre. The electronic character of the arylamines seems to greatly influence the regioselectivity, while the reactivity towards allylic amination seems relatively unaffected. As shown in Table 2 , electron-donating groups at the *para* position of anilines enhanced both reactivity and selectivity in favour of the *C*-allylated products (Table 2, entries 1–3), while the presence of a electron-withdrawing group such as nitro or carboxylate favoured the *N*-allylated products (Table 2, entries 12–14) and no *C*-allylated product was observed in such instances. This trend however seems to be disrupted when a very strong electron-withdrawing group like trifluoromethyl (Table 2, entry 6) is involved. This observation can be attributed to the fact that the lone pair of the amino group in this aniline substrates is not able to interact with the Pd centre as compared to aniline substrates with weaker electron-withdrawing groups. The trend reversal also occurs in the presence of a potentially coordinating group such as cyano (Table 2, entry 7) which competes with the amino group for coordination on the palladium.

When halogens (F, Cl) were introduced (with their electron-donation ability by conjugation and electron-withdrawing potential by induction) at the *para* position of aniline, the *C*-allylation products were still preferred (Table 2, entries 4, 5, 10, 11). For *para* mono-substituted arylamines, monoallylation products in which allylation occurred at the *ortho* position were observed as the major product and the diallylation products in which substitution occurred simultaneously at both the *ortho* positions were the minor ones. To avoid such an undesired diallylation, 2,4-di-

Table 2. Palladacycle-catalyzed tandem allylic amination/allylation reaction.



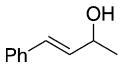
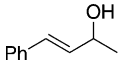
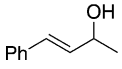
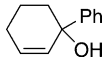
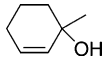
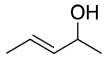
1a 2 3 4

Entry[a]	Anilines	Yield[b] of **3** [%]	Yield[b] of **4** [%]
1	4-Me, **2a**	–	85
2	4-OMe, **2b**	–	86
3	4-OPh, **2c**	–	89
4	4-F, **2d**	–	85
5	4-Cl, **2e**	–	88
6	4-CF_3, **2f**	–	83
7	4-CN, **2g**	–	90
8	2,4-di-Me, **2h**	–	95
9	2,4-di-OMe, **2i**	–	93
10	2,4-di-F, **2j**	–	90
11	2,4-di-Cl, **2k**	–	88
12	4-NO_2, **2l**	96	–
13	4-CO_2Me, **2m**	95	–
14	4-CO_2H, **2n**	85	–

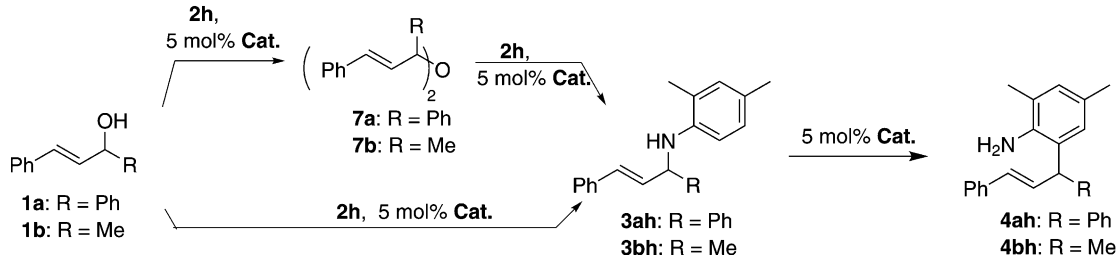
[a] Unless otherwise indicated, all reactions were performed at 70 °C using allylic alcohol (0.5 mmol), amine (0.75 mmol), catalyst (5 mol%) in 1,2-dichloroethane (3 mL) for 12 h.
[b] Isolated yield.

Table 3. Palladacycle-catalyzed tandem allylic amination/allylation reaction of various alcohols.

1 2 4 6

Entry[a]	Alcohol		Anilines	Yield[b] of **4** [%]	Yield[b] of **6** [%]
1[c]		**1b**	**2a**	80	–
2[c]		**1b**	**2b**	75	–
3[c]		**1b**	**2h**	92	–
4		**1c**	**2h**		78
5		**1d**	**2h**		75
6		**1e**	**2h**		72
7[c,d]		**1f**	**2h**	70	–

[a] Unless otherwise indicated, all reactions were performed at 70 °C using allylic alcohol (0.5 mmol), amine (0.75 mmol), catalyst (5 mol%) in 1,2-dichloroethane (3 mL) for 12 h.
[b] Isolated yield.
[c] Reactions were performed at 90 °C.
[d] For 24 h.



Scheme 1. Proposed reaction pathway for the palladium-catalyzed tandem allylic amination/allylation reaction.

substituted arylamines were also screened as reactants and the results showed that only the corresponding monoallylation products were formed and higher yields were obtained as expected (Table 2, entries 8–11).

Various aromatic amines were employed under optimized conditions providing the 2-allylanilines in good to high yields (70–95%) (Table 2). Reactions involving relatively less activated allylic alcohol substrates **1b**, **1d** and **1f** needed higher temperature (90 °C) in order to obtain good yields. Excellent regioselectivities were observed when substituted anilines were employed in the tandem one-pot allylic amination/allylation of other allylic alcohols **1b–f** (Table 3) with **4** or **6** being formed as the major products. This reaction favours the less sterically hindered products.

To obtain insights into the reaction mechanism, a closely monitored experiment was conducted with **1a**/**1b** in the presence of catalyst (5 mol%) (Scheme 1). The results indicated the gradual formation of the *N*-allylated product **3ah**/**3bh** along with the formation of an intermediate di(1,3-diphenyl-2-propenyl) ether **7a**/di(1-methyl-3-phenyl-2-propenyl) ether **7b** at the early stage of the reaction. These results revealed that the formation of **3ah**/**3bh** may proceed *via* two pathways as shown in Scheme 1: namely, a direct allylic amination with **1a**/**1b** and an allylation *via* the intermediate **7a**/**7b**. Subsequently, **3ah**/**3bh** underwent the allylation reaction to give the 2-allylaniline **4ah**/**4bh**.

In summary, we have developed a one-pot palladacycle-catalyzed tandem allylic amination/allylation of allylic alcohols that provides direct access to hithero unaccessible 2-allylanilines in high yields and under mild conditions with water being the only by-product and without any activator. We have also proposed a reaction pathway for this catalyzed tandem reaction protocol.

Experimental Section

Typical Procedure for Palladacycle-Catalyzed Preparation of Substituted 2-Allylanilines (1a and 2a as Examples)

To a 25-mL sealed tube were successively added **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (0.025 mmol) and 1,2-dichloroethene (3 mL). The resultant reaction mixture was stirred at 70 °C for 12 h. On completion, the reaction mixture was concentrated under reduced pressure and the resultant residue was directly purified by flash column chromatography on silica gel (EtOAc/*n*-hexane: 1/50→1/15) to give 2-allylaniline **4aa** in 85% yield.

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