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Graphical Abstract

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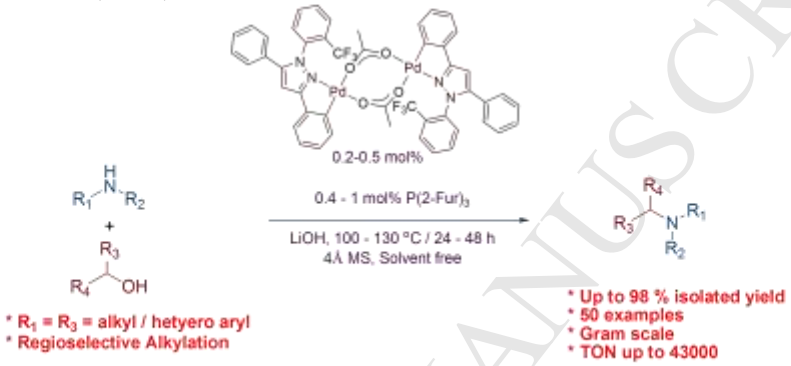

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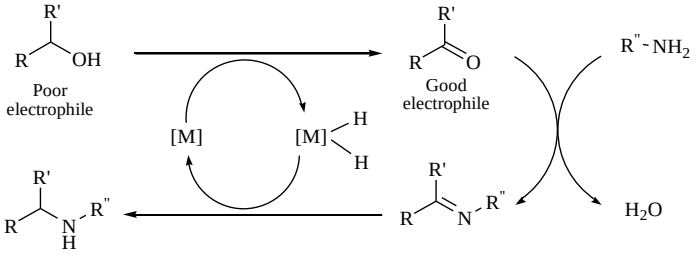
ABSTRACT

Simple pyrazole based palladacycle-phosphine with a high turnover has been developed and applied for the N-alkylation of amines and sulfanilamide using alcohols as substrates by hydrogen borrowing strategy. N-alkylation of primary and secondary amines resulted in high isolated yields at 100-130 °C, under solvent free conditions. More challenging secondary aliphatic as well as aromatic alcohols were also successfully utilized as alkylating agents under similar reaction conditions. The turn over number reached up to 43000 for N-benzylation of aniline using benzyl alcohol. Notably, regioselective N-alkylation of 2-aminobenzothiazole and 4-aminobenzenesulfonamide to the corresponding 2-N-(alkylamino)azoles and 4-amino-(N-alkyl)benzenesulfonamides using alcohols as alkylating agents have been achieved using our new pre-catalyst-phosphine system.

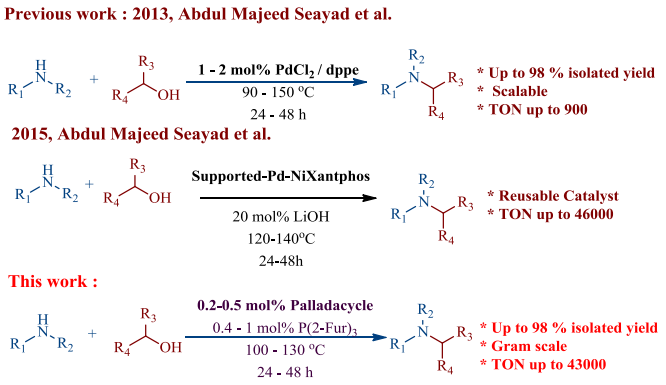
1. Introduction

Metal catalyzed carbon-carbon and carbon-heteroatom reactions are powerful tools that are widely utilized by the synthetic chemist in a great number of syntheses.[1] Key to the success of such catalytic reactions is the development of new methodologies, ligands and (or) pre-catalysts. N-alkylation of amines is an important class of reactions[2] applied in the synthesis of pharmaceuticals, pesticides and functional materials. Traditionally, reactive alkyl halides have been used for the production of N-alkylated amines which often produces over-alkylated products. This method not only reduces the overall yield of the product but also produces stoichiometric amounts of waste. On the other hand use of alcohols as alkylating reagents has emerged as an interesting greener approach, owing to the fact that it produces only water as a byproduct by using "*hydrogen borrowing*" methodology [2]. As alluded in the literature,[2,5c] the poor electrophilic alcohols are activated to more active carbonyl intermediates by temporary removal of hydrogen from the alcohols. In the presence of amine the insitu formed carbonyl is converted into imine, which upon hydrogenation forms the final alkylated amine by transferring the borrowed hydrogen (Scheme 1).

Various catalytic systems using different metals have been developed and used for the N-alkylation of amines using alcohols.[2-7] However in comparison with the Ru[3] and Ir[4] based catalysts, there are limited studies on the development of Pd-based[5] catalysts or pre-catalysts, especially homogeneous[5c,5e] pre-catalysts for N-alkylation of amines using alcohols. Recently Ramón and co-workers[5e] reported $Pd(OAc)_2$ (1 mol %) in the presence of 100 mol % of CsOH at temperatures of 130−150 °C in toluene as the solvent. Using benzylic alcohols as the alkylating agent, up to 99% yield of the alkylated amine was reported. However, this system was not active under the optimized conditions when aliphatic or secondary alcohols were used as the alkylating agents. In 2013, Seayad and co-workers[5c] reported (Scheme 2) $PdCl_2$ as a catalyst in the presence of dppe or Xantphos(*t*-Bu) as the ligand for the N-alkylation of primary and cyclic secondary amines, with TON up to 900 using neat reagents (no solvent) at temperatures of 90-150 °C. It is noteworthy to mention that an improved TON of about 46000 was reported using supported-palladium NiXantphos complex.[5b] Keeping these reported results in mind we focused our efforts in developing more active homogenous catalysts for the N-alkylation of amines using alcohols.



Scheme 1. C-N bond formation by *hydrogen borrowing*



Scheme 2. Palladium mediated N-alkylation of amines using alcohols, a comparison

Palladacycles[8] are the most promising and versatile catalysts (or) pre-catalyst in carbon-carbon and carbon-heteroatom bond forming reactions. Owing to their facile synthesis, easy handling and possibility of tuning electronic and steric properties many research groups have devoted their efforts in synthesizing new palladacycles and studying their applications in catalysis, organic synthesis, materials and medicinal chemistry. Among the different types of palladacycles, pyrazole-based palladacycles are scarcely studied[8d] for their applications towards catalysis. Grigg and co-workers showed that pyrazole-based palladacycles could effectively be used for C-C bond formation. In a recent study we[8e] showed the synthesis of 1,3,5-triphenylpyrazole palladium dimer and its catalytic activity towards Mizoroki-Heck and Suzuki-Miyaura cross-coupling reactions. Although ample reports exist for the dehydrogenation of alcohols,[8c] C-N and C-C bond formations using alkyl or aryl halides as reagents and palladacycles as catalyst or pre-catalyst,[9] surprisingly to the best of our knowledge none of the palladacycle based pre-catalysts have been tested for the N-alkylation of amines and sulfanilamide using alcohols as reagent. Herein, we report a new palladacycle which is stable in air- and moisture and highly active towards N-alkylation of amines and sulfanilamide.

2. Experimental

2.1 General

All reagents and solvents were obtained from commercial sources. Solvents were purified according to standard procedures. ^{1}H, ^{13}C, and ^{19}F spectra were recorded using Bruker 400 MHz instrument. All ^{1}H and ^{13}C NMR spectra were referenced internally to solvent signals and ^{19}F NMR spectra, to α,α,α-trifluorotoluene (0.05% in $CDCl_3$; δ = -63.73). High resolution mass spectra (HRMS) were recorded with micro TOF-QII mass spectrometer. Elemental analyses was carried out with a VarioMICRO CHNS analyzer (IIT-Bhubaneswar). Single-crystal X-ray diffraction data were collected at 296 K using, Mo-Kα radiation (0.71073 Å). Crystallographic data for the palladacycle-**1** and compound **49** and details of X-ray diffraction experiments and crystal structure refinements are given in Table S1. SADABS absorption corrections were applied in both cases. The structures were solved and refined with SHELX suite of programs. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms. Crystallographic data for the structure of palladacycle-**1** and compound **49** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC- 1446359, 1526743. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; email: deposit@ccdc.cam.ac.uk).

2.2 General procedure for N-alkylation of amines using benzyl alcohol

An oven dried Schlenk tube was charged with amine (3.0 mmol), alcohol (3.6 mmol),LiOH (1.5 mmol), palladacycle (6.0 x10^{-3}mmol, 0.20 mol %), P(2-Fur)$_3$ (12.0 x10^{-3}mmol, 0.40 mol %) and activated 4 Å MS (100 mg) in argon atmosphere. The reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and washed with water followed by brine solution. The organic phase was dried over anhydrous sodium sulphate. After removal of the solvent, the crude was subjected to column chromatography on silica gel using ethyl acetate and *n*-hexane mixtures to afford the N-alkylated product.

2.3 General procedure for N-alkylation of amines using primary and secondary alcohols

A similar protocol as mentioned for N-alkylation of amines using benzyl alcohol was used. The quantities involved are as follows: Amine (3.0 mmol), alcohol (6.0 mmol), LiOH (1.5 mmol), pre-catalyst (1.5 X 10^{-2} mmol 0.50 mol %), P(2-Fur)$_3$ (1.5 X 10^{-2} mmol, 1.00 mol%) and activated 4 Å MS (100 mg). The reaction mixture was stirred at 120 – 130 °C for 24 - 48 h.

2.4 Procedure for N-alkylation of 2-aminobenzothiazole using aryl alcohols

An oven dried Schlenk tube was charged with LiOH (1.5 mmol), pre-catalyst (6 x 10^{-3} mmol, 0.20 mol %), P(2-Fur)$_3$ (12 x 10^{-3} mmol, 0.40 mol%) and activated 4 Å MS (100 mg). The tube was connected to a vacuum line under argon and purged three times. To the reaction mixture, 2-aminobenzothiazole (3.0 mmol) and alcohol (6.0 mmol) were added. The Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 100 °C for 24 h. At the end of the reaction time, the reaction mixture was cooled to room temperature, diluted with methanol (5 mL), and the tube was washed with methanol three more times (3x2 mL). The methanol solution was concentrated under vacuum and the crude was subjected to column chromatography on silica gel using ethyl acetate and *n*-hexane mixtures to afford the N-alkylated product.

2.5 Procedure for N-alkylation of sulfanilamide using aryl alcohols

An oven dried Schlenk tube was charged with LiOH (1.5 mmol), pre-catalyst (1.5 x 10^{-2} mmol), P(2-Fur)$_3$ (3 x 10^{-2} mmol) and activated 4 Å MS (100 mg). The tube was connected to a vacuum line under argon and purged three times. To the reaction mixture, sulfanilamide (3.0 mmol) and aryl alcohol (6.0 mmol) were added. The Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 120 °C for 24 h. At the end of the reaction time, the reaction mixture was cooled to room temperature, diluted with methanol (5 mL), and the tube was washed with methanol three more times (3x 2 mL). The methanol solution was concentrated under vacuum and the crude was

subjected to flash column chromatography on silica gel using ethyl acetate and *n*-hexane mixtures to afford the N-alkylated product.

2.6 Procedure for gram scale reaction for N-benzylation of aniline using benzyl alcohol

A similar protocol as mentioned for N-alkylation of amines using benzyl alcohol was used. The quantities involved are as follows: Amine (1.0 g, 10.7 mmol), alcohol (12.8 mmol), LiOH (5.3 mmol), palladacycle (1.1 x 10^{-7}mmol, 0.001 mol %), P(2-Fur)$_3$ (2.2 x 10^{-7}mmol, 0.002 mol %) and activated 4 Å MS (300 mg). The reaction mixture was stirred at 130 ^{o}C for 48 h. Yield =1.75 g (89%).

2.7 Synthesis of 3, 5-diphenyl-1-(2-(trifluoromethyl) phenyl)-1H-pyrazole[10]

1,3-Diphenylpropane-1,3-dione (2.54 g, 11.30 mmol) and (2-(trifluoromethyl)phenyl) hydrazine (2.00 g, 11.30 mmol) were taken in 100 mL round bottom flask. Then 15 mL of methanol and 15 mL of acetic acid were added to the flask and the reaction mixture was refluxed for 12 h. To the reaction mixture, saturated sodium carbonate solution was added and the compound was extracted using dichloromethane. The solvent was removed under vacuum and the residue was purified by column chromatography (*n*-hexane-ethyl acetate as eluent) to afford the product, 3,5-diphenyl-1-(2-(trifluoromethyl) phenyl)-1H-pyrazole.Yield: 3.14g (8.6 mmol, 76%). m.p: 109-110 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8 Hz, ArH, 2H), 7.82 (t, *J* = 4 Hz, ArH, 1H), 7.55 (t, *J* = 4 Hz, ArH, 2H), 7.44 (t, *J* = 8 Hz, ArH, 2H), 7.35 (t, *J* = 8 Hz, ArH, 2H), 7.28-7.24 (m, ArH, 5H), 6.89 (s, 4Pz-H, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 146.3, 138.3, 133.0, 132.6, 130.7, 129.9, 129.3, 128.8, 128.6, 128.4, 128.3, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 126.1, 104.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -60.81 (s) ppm. HRMS (ESI): calcd. for $C_{22}H_{15}F_3N_2$ ([M+H]$^+$) : 365.1260, found : 365.1273. Elemental analysis calcd (%) for $C_{22}H_{15}F_3N_2$: C 72.52, H 4.15, N 7.69; found: C 72.60, H 4.22, N 7.58. ; found: . IR (KBr) : ν (cm^{-1}) = 3064 (m), 1501 (m), 1485 (m), 1465 (m), 1315 (s), 1154 (m), 1137 (s), 1113 (m), 761 (s), 596 (s).

2.8 Cyclopalladation of 3, 5-diphenyl-1-(2-(trifluoromethyl) phenyl)-1H-pyrazole

Palladium acetate (1.23 g, 5.50 mmol) and 3, 5-diphenyl-1-(2-(trifluoromethyl) phenyl)-1H-pyrazole (2.00 g, 5.50 mmol) were suspended in glacial acetic acid (20 mL) and the mixture was heated in an oil bath (100 °C, 2 h). The reaction mixture (in hot condition) was filtered through celite to remove palladium black and the solution was concentrated. The residue was re-dissolved in dichloromethane, layered with *n*-hexane and stored at 5 °C for 24 h and filtered through celite (1cm height) and silica gel (100-200 mesh, 1cm height) to remove remaining palladium black traces. The solvents were removed under vacuum and the yellow product was recrystallized from a mixture of dichloromethane and *n*-hexane. Yield : 2.57 g (4.8 mmol, 88%). mp: 218-219 ^{o}C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* =8 Hz, ArH, 2H), 7.50 (t, *J* = 8 Hz, ArH, 2H), 7.41 (t, *J* = 8 Hz, ArH, 2H), 7.28-7.21 (m, ArH, 6H), 7.17-7.15 (m, ArH, 2H), 7.04 ((t, *J* = 8 Hz, ArH, 2H), 6.95 (d, *J* =8 Hz, ArH, 6H), 6.88-6.82 (m, ArH, 4H), 6.30 (s, 4Pz-H, 2H), 1.42 (s, OAc) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 159.6, 146.6, 137.8, 134.6, 132.3, 131.7, 131.2, 130.1, 129.5, 129.1, 128.9, 128.8, 128.4, 128.0, 127.9, 127.9, 127.8, 125.1, 124.1, 122.2, 101.4, 24.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -60.2 ppm. HRMS (ESI): calcd. for $C_{46}H_{31}F_6N_4O_2Pd_2$ {[M-OAc]$^+$} : 998.0535, found : 998.0497. Elemental analysis calcd (%) for $C_{48}H_{36}F_6N_4O_4Pd_2$: C 54.41, H 3.42, N 5.29; found: C 54.30, H 3.29, N 5.22. IR (KBr):ν (cm^{-1}) = 3055 (m), 1593 (s), 1576 (s), 1505 (m), 1419 (m), 1316 (s), 1140 (s), 765 (s), 697 (m).

3. Results and discussion

3.1 Synthesis and characterization of palladacycle

The palladium pre-catalyst (palladacycle (1)) was synthesized in two steps from commercially available starting materials according to literature reported method.[8d,e] The formation of the pre-catalyst was confirmed by standard techniques like ^{1}H, ^{13}C &^{19}F NMR spectroscopy, HRMS and elemental analysis as well as single crystal X-ray analysis (Figure 1, Table S1). It is noteworthy to mention that the palladacycle (1) reported in this study shows C-H bond activation on the 3-phenyl of the pyrazole and not on the N-phenyl of the pyrazole as observed in our previous studies.[8d,11]

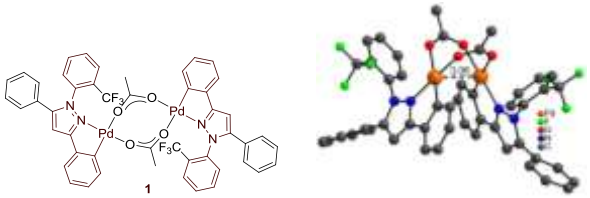


Fig. 1. (left) Chemdraw representation of palladacyle (1) (right) Molecular structure of palladacycle (1) used in this study (hydrogen atoms are omitted for clarity).

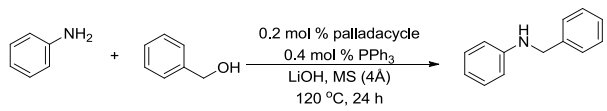
3.2 Optimization and study of catalyst efficiency towards N-alkylation of aniline with benzyl alcohol

Initially, we studied the reaction of benzyl alcohol with aniline as a model reaction using different bases/solvents, 4 Å molecular sieves for 24 h by using 0.2 mol % of pre-catalyst and 0.4 mol % of PPh_3(1:1 ratio metal to ligand) as a ligand at 120 °C. After screening various solvents and bases, we found that LiOH (50 mol%) was the best choice under solvent free conditions (Table 1). The use of carbine as a ligand resulted a low yield of only 19 %. When we lowered the temperature from 120 °C to 100 °C using PPh_3 as a ligand the yield got reduced from 91 % to 26 %.

To determine the best suited phosphine for a particular reaction, in many instances it is necessary to rely on a trial and error type screening process.[12] Keeping this in mind we examined the effect of different phosphines at 100 °C. The combination of the pre-catalyst with P(2-Fur)$_3$ gave an almost quantitative yield (98 %) of the N-alkylated product. Next, the amount of P(2-Fur)$_3$ loading with respect to pre-catalyst was evaluated. It was found that 2:1 ratio of the P(2-Fur)$_3$ to pre-catalyst is optimum to get maximum yield of the desired product (see table 2, entries 8,9,10 and 11). In the absence of P(2-Fur)$_3$, the combination of the pre-catalyst with the base gave a low yield of 12 % (Table 2, entry 14). Under similar conditions, in the absence of the pre-catalyst no product formation was observed (Table 2, entry 13), however palladium precursors such as $Pd(OAc)_2$, $PdCl_2$ or $Pd_2(dba)_3$ gave lower

yields of 26 %, 46% and 37% respectively (Table 2, entry 16, 17 & 18). It is noteworthy that the N-phenyl ring of pyrazole ligand with electron withdrawing group (-CF_3) gave high yields of the N-alkylated product. However, our previously reported palladacycle[8d] did not yield any product under the reaction conditions mentioned above. The observed results are consistent with pyrazole-based palladacycles reported by Grigg and co-workers, where fluorinated pyrazoles show superior activity for the Heck reaction. We believe that fluorination on pyrazoles plays a very important role for the observed catalytic activity of our palladacycle reported in this study over the non-fluorinated pyrazole.

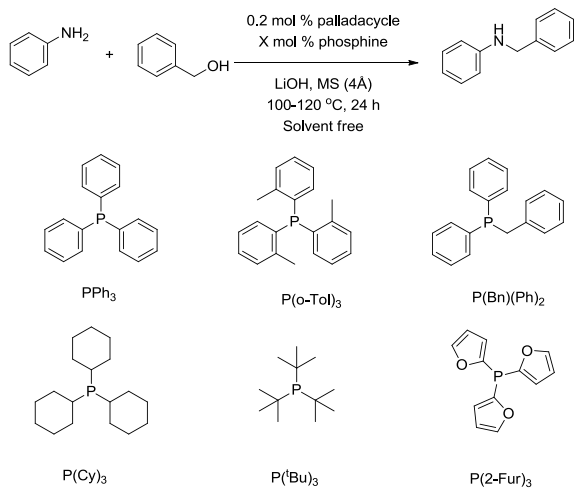
Table 1. Optimization of N-alkylation of aniline with benzyl alcohol using palladacycle[a]



Entry	Base	Solvent	Yield[b] (%)
1	LiOH	Benzene	Trace
2	LiOH	Toluene	19
3	LiOH	*o*-Xylene	27
4	LiOH	TBB	76
5	LiOH	-	91
6	LiOH.H_2O	-	82
7	KO^{t}Bu	-	76
8	Cs_2CO_3	-	Trace
9	K_3PO_4	-	Trace
10	KOH	-	Trace
11	NaOH	-	Trace
12[c]	LiOH	-	90
13[d]	LiOH	-	73

[a]Reaction condition: aniline (3.0 mmol), benzyl alcohol (3.6 mmol), LiOH (1.5 mmol), precatalyst (6.0 x 10^{-3} mmol), PPh_3 (12.0 x 10^{-3} mmol), TBB =*tert*-butyl benzene. [b]Isolated yield after column chromatography. [c]50 mol% LiOH was used, [d]25 mol% LiOH was used

Table 2. Palladacycle catalysed N-alkylation of aniline using benzyl alcohol: Screening of phosphines[a]



Entry	Phosphine	X	Phosphine/ palladacycle	T (°C)	Yield[b] (%)
1	PPh_3	0.4	2	120	91
2	PPh_3	0.4	2	110	54
3	PPh_3	0.4	2	100	26
4	$P(2\text{-Tol})_3$	0.4	2	100	19
5	$P(Bn)(Ph)_2$	0.4	2	100	24
6	$P(Cy)_3$	0.4	2	100	6
7	$P(^tBu)_3$	0.4	2	100	Trace
8	$P(2\text{-Fur})_3$	0.4	2	100	98
9	$P(2\text{-Fur})_3$	0.2	1	100	91
10	$P(2\text{-Fur})_3$	0.6	3	100	64
11	$P(2\text{-Fur})_3$	0.1	0.5	100	81
12	$P(2\text{-Fur})_3$	0.4	2	100	28[c]
13	$P(2\text{-Fur})_3$	0.4	-	100	0[d]
14	-	-	-	100	12[e]
15	$P(2\text{-Fur})_3$	0.4	2	100	56[f]
16	$P(2\text{-Fur})_3$	0.4	-	100	26[g]
17	$P(2\text{-Fur})_3$	0.4	-	100	46[h]
18	$P(2\text{-Fur})_3$	0.4	-	100	37[i]

[a]Reaction condition: aniline (3 mmol), benzyl alcohol (3.2 mmol), LiOH (1.5 mmol), [b]Isolated yield after column chromatography, [c]LiOH was not used, [d]Palladacycle was not used, [e]$P(2\text{-Fur})_3$ was not used, [f]Molecular sieves were not used, [g]Instead of precatalyst 1, 0.4 mol% $Pd(OAc)_2$ was used, [h]Instead of precatalyst 1, 0.4 mol% $PdCl_2$ was used, [i]Instead of precatalyst 1, 0.2 mol% $Pd_2(dba)_3$ was used

The efficiency of the catalyst for the N-alkylation of aniline using benzyl alcohol as an alkylating agent was studied by gradually decreasing the pre-catalyst loading from 0.2 mol% to 0.001 mol% and by increasing the temperature from 100 °C to 130 °C (Table 3). With 0.01 mol % of pre-catalyst at 100 °C, 93 % (TON = 4600) of the N-alkylated product was observed. When the catalyst loading was lowered to 0.001 mol %, the pre-catalyst exhibited higher turnover number (43000) at 130 °C, which is among the highest TON's (Table 3, entry 11) reported for any homogeneous Pd-based catalytic system till date for N-alkylation of amines using aniline and benzyl alcohol.

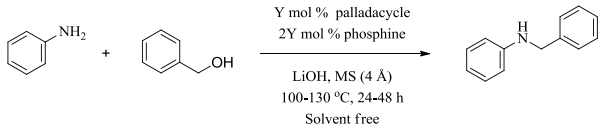
3.3 Substrate scope of the reaction for N-alkylation of various amines using primary and secondary alcohols

With these optimized conditions, we examined the substrate scope of the reaction using various substituted anilines, secondary amines and heterocyclic amines with benzyl alcohol at 100 °C using 0.2 mol % of pre-catalyst (Table 4). As presented in Table 4, most of the amines underwent the coupling reactions with benzyl alcohol to yield the desired product in good to excellent yields. Aromatic amines such as aniline, *o,p*-methoxy aniline, *o,m,p*-methyl aniline, *o,p*-fluoroaniline and benzylamine

were alkylated to give the corresponding N-benzyl amines in isolated yields of 74 to 98 % (Table 4, compounds 1-9). Cyclic secondary amines were also readily alkylated to the corresponding tertiary amines in good yields (Table 4, compounds 11 and 12). Aromatic primary alcohols such as *p*-methyl benzyl alcohol, *p*-methoxy benzyl alcohol were also used as alkylating agents (Table 4, compounds 14, 15). Sterically hindered *o*-methyl benzyl alcohol, *o*-methoxy benzyl alcohol and 2-biphenyl methanol were also efficiently utilized as alkylating agents at 120 °C (Table 4, compounds 15, 16 and 17). *o*-Toluidine was also successfully alkylated with 3,4-methylenedioxy benzyl alcohol (Table 4, compound 18). However, 4-chloroaniline and 4-bromoaniline were failed to give the desired products.

The least reactive and more challenging alcohols such as aliphatic alcohols and secondary alcohols were also tested for N-alkylation using our pre-catalyst (Table 5). The reaction between aliphatic alcohols such as 1-octanol, 1-hexanol, *n*-butanol with *p*-methoxy aniline or aniline provided the corresponding N-alkylated product in good isolated yield of more than 72 % (Table 5, compounds 19, 20, 21 and 22). The reactions of benzyl alcohol with *p*-trifluoromethylaniline and 2-phenylethanol with *p*-methoxyaniline progressed well to give the corresponding secondary amines in 76 % and 72 % isolated yields respectively (Table 5, compounds 31 & 23). To our delight, a good yield of N-alkylated morpholine was achieved with 2-phenylethanol as an alkylating reagent (Table 5, compound 32). When we applied this approach to the more challenging secondary alcohols such as 1-phenylpropanol, 1-phenylethanol,1-(3-methylphenyl)ethanol, 1-(4-methylphenyl)-1-propanol, 2-hexanol, 2-decanol, 1-phenyl 2-propanol and cylohexanol at 120 °C (or) 130 °C, they were successfully alkylated to the corresponding amines (Table 5, compounds 25-30, 33-35).

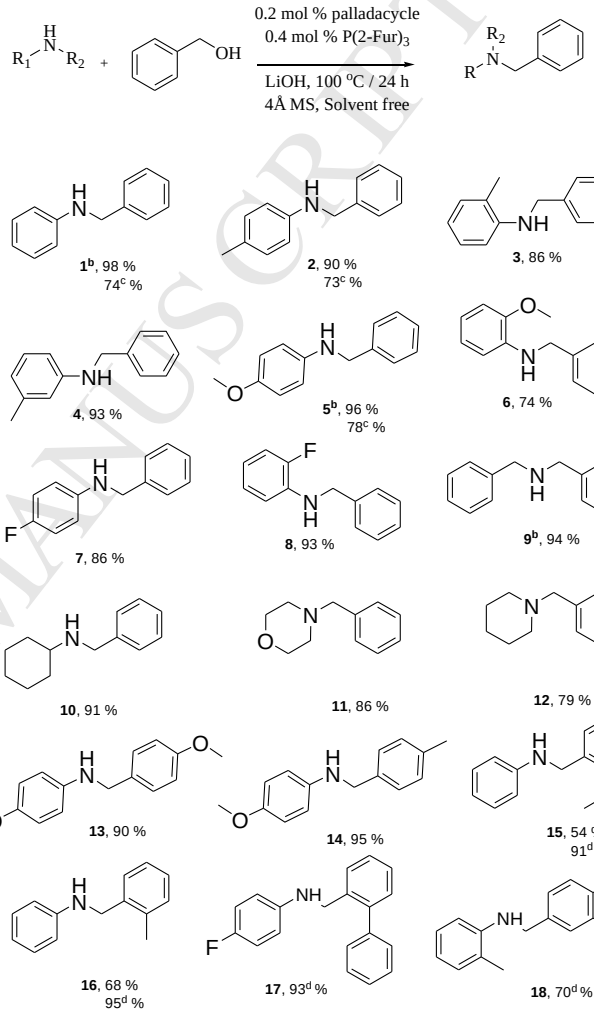
Table 3. A study of catalyst efficiency for N-alkylation of aniline using benzyl alcohol[a]



Entry	Y	T (°C)	Time (h)	Yield[b] (%)	TON[c]
1	0.2	100	24	98	245
2	0.1	100	24	91	453
3	0.05	100	24	85	845
4	0.025	100	24	81	1621
5	0.1	110	24	96	482
6	0.05	110	24	92	917
7	0.025	110	24	87	1734
8	0.01	110	24	83	4142
9	0.01	110	48	93	4643
10[d]	0.001	120	48	61	30013
11[d]	0.001	130	48	89	43358

[a]Reaction condition: aniline (5.3 mmol), benzyl alcohol (6.4 mmol), LiOH (2.65 mmol), [b]Isolated yield after column chromatography, [c]Turn Over Number (TON) based on the isolated product, [d]Gram scale: aniline (10.7 mmol), benzyl alcohol (12.8 mmol), LiOH (5.3 mmol); average isolated yield of two runs.

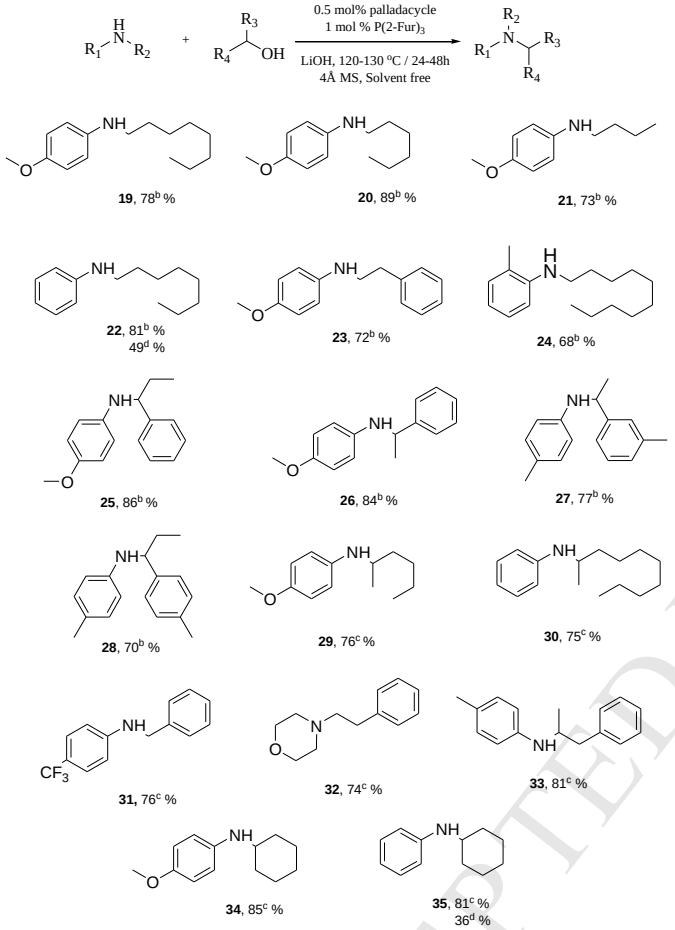
Table 4. N-Alkylation of various amines using benzyl alcohol[a]



[a]Reaction condition: amine (3 mmol), benzyl alcohol (3.6 mmol), LiOH (1.5 mmol), palladacycle (6 X 10^{-3} mmol), $P(2\text{-Fur})_3$ (12 X 10^{-3} mmol), [b]Average isolated yields of two runs, [c]In *tert*-butylbenzene (concentration = 1M), [d]Reactions were performed at 120 °C.

regioselective N-alkylation of 2-amino benzothiazoles with benzylic alcohols. Compared to the solvent free condition, the use of representative reactions using non-polar solvent (*tert*-butylbenzene) gave relatively low yields for the N-alkylation of amines (Table 4, compounds 1, 2, 5; Table 5, compounds 22, 35; Table 6, compound 37).

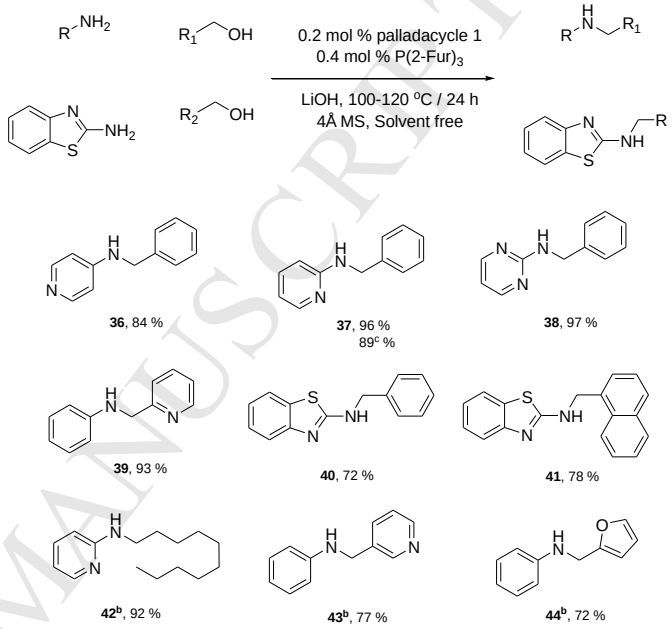
Table 5. N-Alkylation of various amines using primary and secondary alcohols[a]



[a]Reaction condition: amine (3.0 mmol), alcohol (6.0 mmol), LiOH (1.5 mmol), palladacycle (1.5 x 10^{-2}mmol), $P(2\text{-Fur})_3$ (3.0 x 10^{-2} mmol), [b] Reactions were performed at 120 °C for 24 h, [c] Reactions were performed at 130 °C for 48 h, [d]In *tert*-butylbenzene (concentration = 1M)

Heteroaromatic amines, such as 4-aminopyridine, 2-aminopyridine and 2-aminopyramidine, were also efficiently alkylated under these conditions to give the products 36, 37, and 38 in 84 %, 96 % and 97 % yields respectively (Table 6). 2-Aminopyridine was successfully alkylated with 1-decanol and gave quantitative yield of the corresponding product (Table 6, compound 42). Heteroaromatic aryl alcohols such as 2-pyridinemethanol, 3-pyridinemethanol and furfuryl alcohol were also efficiently utilized as alkylating reagents at moderate temperatures (Table 6, compounds 39, 43 and 44). Interestingly, 2-amino benzothiazole (Table 6, compounds 40 and 41) selectively alkylated at the primary amine position with benzyl alcohol and 1-naphthyl methanol.[13] As reported in the literature the regioselective N-alkylation of 2-amino benzothiazole is a challenging task, here we show that our pre-catalyst has the potential to prepare 2-(N-alkyamine)benzothiazoles *via*

Table 6. N-Alkylation of amines using aryl (hetero) amines and aryl (hetero) alcohols[a]



[a] Reaction condition: amine (3.0 mmol), benzyl alcohol (6.0 mmol), LiOH (1.5 mmol), palladacycle (6 x 10^{-3} mmol), $P(2\text{-Fur})_3$ (12 x 10^{-3} mmol), [b] Reactions were performed using 0.5 mol% palladacycle 1, 1 mol% $P(2\text{-Fur})_3$ and at 120 °C, [c]In *tert*-butylbenzene (concentration = 1M)

3.4 Regioselective N-alkylation of sulfanilamide using benzyl alcohols

Inspired by the regioselective N-alkylation of sulfanilamides using alcohols reported by Feng Li and co-workers[14a,14b] we attempted N-alkylation of sulfanilamide using alcohols. To our delight our pre-catalyst successfully alkylated sulfanilamide, regioselectively, at moderate temperatures (Table 7, compounds 45 – 49). As representative examples, single crystals of product 49, were grown and analysed using X-ray crystallography to confirm the regioselectivity (Figure 2). Benzyl alcohol having electron withdrawing group such as $-CF_3$ gave the N-alkylated product in 64% yield. Furthermore, benzyl alcohol bearing electron donating group such as methyl and methoxy gave the desired products 46 and 47 in 71% and 64% yield respectively.

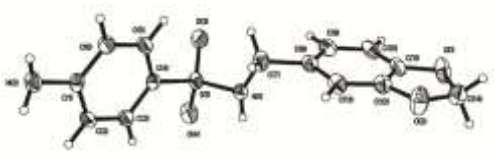
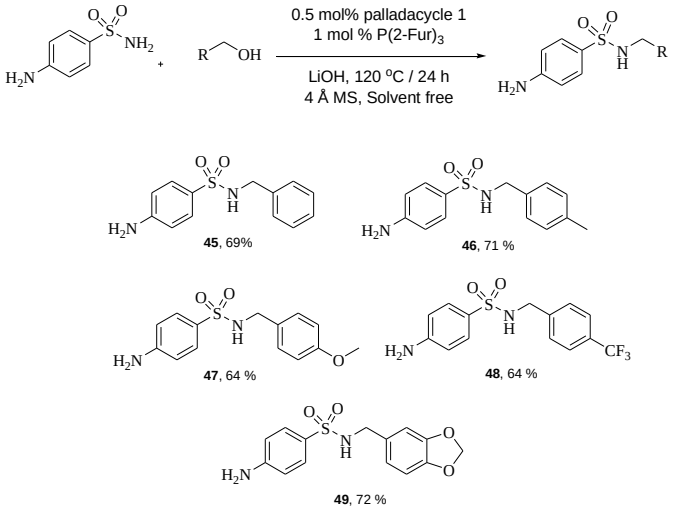


Fig. 2. Molecular structure of product 49 with thermal ellipsoids at the 50% probability level

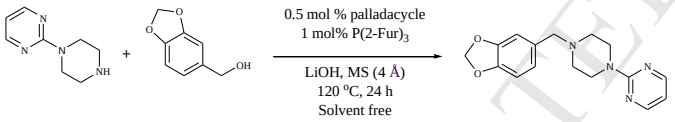
Table 7. Regioselective N-Alkylation of sulfanilamide using aryl alcohols [a]



[a]Reaction condition: sulfanilamide (3.0 mmol), aryl alcohol (6.0 mmol), LiOH (1.5 mmol), palladacycle (1.5 x 10^{-2} mmol), $P(2\text{-Fur})_3$ (3.0 x 10^{-2} mmol)

3.5 Synthesis of piribedil by using our palladacycle

Furthermore, we established the synthetic utility of our palladacyle in the synthesis of piribedil,[3d] which is clinically used for the treatment of Parkinson's disease. To our delight the reaction of 1-(pyrimidin-2-yl)piperazine with piperonyl alcohol in the presence of 0.5 mol % of palladacycle afforded 76 % isolated yield (Scheme 3).



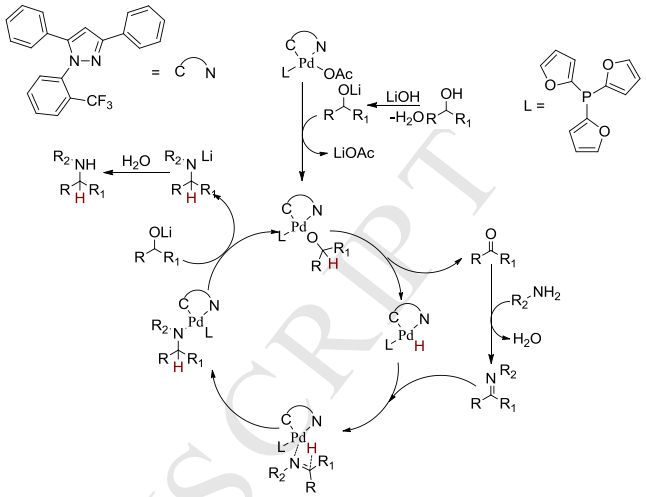
Scheme 3. Synthesis of piribedil using palladacycle (1)

3.6 Proposed mechanism

A plausible mechanism is proposed based on the control experiment. As shown in Scheme S1, under our optimized reaction conditions, 3 mmol of aniline and 3.6 mmol of benzyl alcohol was refluxed for 12 h. The resultant crude product was analysed using ^{1}H NMR (Figure S1). The formation of aldehyde and imine was observed, suggesting that abstraction of hydrogen atoms takes place to generate benzaldehyde followed by condensation of amine to form imine. Finally, the desired product is obtained by hydrogenation of the imine as shown in Scheme 4.[5c, 15]

4. Conclusions

In summary, we have demonstrated that a pyrazole based palladacycle synthesized from simple starting materials is a highly active and versatile catalyst or pre-catalyst for the N-alkylation of amines using alcohols as reagent under solvent free condition. Our palladacycle provided very high turnover numbers for N-alkylation of amines compared to the palladium based homogeneous catalysts or pre-catalysts reported in the literature. Notably, our palladacycle has been shown to be an active regioselective catalyst for the monoalkylation of sulfanilamide.



Scheme 4: Proposed catalytic pathway for N-alkylation of amines using alcohols

Acknowledgements

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Supplementary Material

Supplementary material associated with this article can be found in the online version.