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An Efficient Palladium-Catalyzed N-Alkylation of Amines Using Primary and Secondary Alcohols

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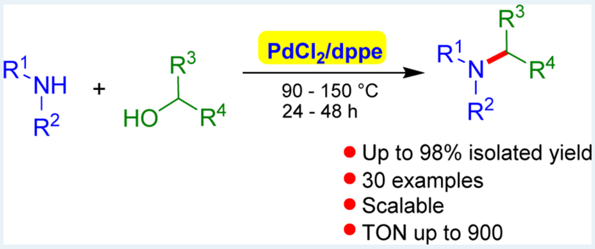
Supporting Information

ABSTRACT: $PdCl_2$ in the presence of dppe or Xantphos(*t*-Bu) as the ligand is found to be an efficient catalyst for the N-alkylation of various primary and cyclic secondary amines using primary alcohols at 90−130 °C under neat conditions. Interestingly, good to excellent yields were achieved when more challenging secondary alcohols were used as alkylating agents at 130−150 °C. The reaction could be easily scaled up, as demonstrated for a 10 mmol scale achieving yields up to 90% with a TON of 900.

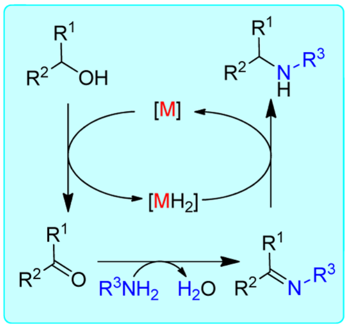


KEYWORDS: *alkylation, alcohol activation, hydrogen borrowing, palladium catalyst, amine synthesis*

INTRODUCTION

Amines are important building blocks for the synthesis of pharmaceuticals, agrochemicals, dyes, and polymers.[1,2] Several catalytic methods for the preparation of amines have been reported, such as reductive amination of carbonyl compounds or reduction of imines, nitriles and nitro compounds;[2] hydroamination;[3] and hydroaminomethylation[4] of unsaturated compounds and metal-catalyzed amination[5] of aryl halides. Alkylation of amines or ammonia with alkyl halides has been practiced as the most convenient method for the synthesis of alkyl as well as alkyl-aryl amines.[2] This method often produces overalkylated products, thereby reducing the yield of the desired product.[2] Moreover, the alkyl halides used are often toxic and have mutagenic properties.[2] Hence, developing more efficient and green alkylation methodologies utilizing nonhazardous and easily available starting materials would be most desirable for future sustainable processes.[2−9] Recently, less toxic and more readily available alcohols were used as the alkylating agents in a greener approach using a catalytic "*hydrogen-borrowing*" strategy.[6] In this method, as shown in Scheme 1, the inactive alcohols are converted in situ to a more reactive and highly electrophilic carbonyl intermediate by temporary removal of hydrogen toward nucleophilic addition reactions. This carbonyl compound undergoes condensation with the amine to form an imine intermediate, which, upon catalytic hydrogenation by transferring the borrowed hydrogen, forms the final alkylated amine. In this overall process, water is produced as the only byproduct and, hence, offers a sustainable method of using alcohols for N-alkylation reactions.[6]

Scheme 1. Hydrogen Borrowing Strategy for the Alkylation of Amines Using Alcohols



Most common catalysts used for the alkylation of amines using alcohols are based on Ru[7] and Ir.[8] Catalysts derived from other metals, such as Au,[9] Ag,[10] Cu,[11] Fe,[12] Ni,[13] Os,[14] and Rh,[15] have also been explored, and many of them showed very good activity and selectivity under moderate to higher temperatures (typically 100−200 °C).

Palladium-based catalysts have generally been employed for alkylation of amines using allylic alcohols.[16] Recently, a few palladium-based catalysts, both heterogeneous[17−19] and homogeneous,[20] have been reported using benzylic and aliphatic primary alcohols as alkylating agents. For example, Corma et al. reported an efficient bifunctional Pd/MgO solid catalyst for the N-alkylation of aniline using benzyl alcohol at 180 °C, giving up to 80% yield of the desired secondary amine product.[17] Shi and co-workers reported up to 90% yield at 160 °C for 2 h using 2.28 wt % Pd/Fe_2O_3 as the catalyst.[18] Reducing the temperature decreased the catalytic activity, and only 65% yield was reported at 140 °C, even in the presence of 100 mol % of base. Aliphatic alcohols gave up to 86% yield at 150 °C after 24 h. Very recently, Shiraishi et al. reported that up to 98% yield can be achieved at room temperature using PdNPs on TiO_2 as the catalyst for the N-alkylation of various anilines

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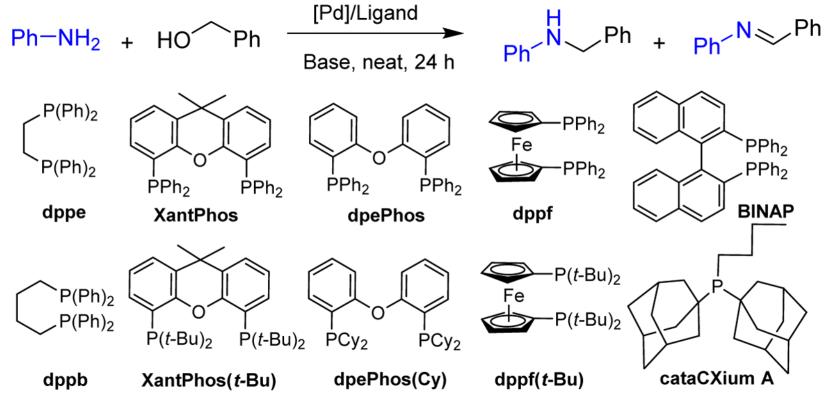
Table 1. Optimization of Catalyst and Conditions for N-Alkylation of Aniline Using Benzyl Alcohol[a]



entry	PdX_2	ligand	base	temp. (°C)	conversion (%)	product (%)	imine (%)
1	Pd(OAc)$_2$	Xantphos	$NaHCO_3$	130	73	26	44
2	$PdCl_2$	Xantphos	$NaHCO_3$	130	100	98	n.d.
3	$PdCl_2$	Xantphos	$NaHCO_3$	110	63	44	20
4	$PdCl_2$	dppf	$NaHCO_3$	110	6	n.d.	5
5	$PdCl_2$	dppf(*t*-Bu)	$NaHCO_3$	110	100	83	17
6	$PdCl_2$	dppf(*t*-Bu)	KOH	110	34	18	16
7	$PdCl_2$	dppf(*t*-Bu)	KO*t*-Bu	110	68	43	25
8	$PdCl_2$	dppf(*t*-Bu)	Cs_2CO_3	110	52	35	17
9	$PdCl_2$	dppf(*t*-Bu)	Et_3N	110	12	9	2
10	$PdCl_2$	dppf(*t*-Bu)	LiOH	110	100	99	n.d.
11	$PdCl_2$	dppf(*t*-Bu)	Na_2CO_3	110	94	87	16
12	$PdCl_2$	dppf(*t*-Bu)	LiOH	100	100	98	n.d.
13	Pd(OAc)$_2$	dppf(*t*-Bu)	LiOH	100	76	35	41
14	$PdCl_2$	dppf(*t*-Bu)	LiOH	90	91	84	6
15	$PdCl_2$	PPh_3	LiOH	100	6	5	2
16	$PdCl_2$	BINAP	LiOH	100	18	11	7
17	$PdCl_2$	dpePhos	LiOH	100	12	8	4
18	$PdCl_2$	cataCXiumA	LiOH	100	62	55	7
19	$PdCl_2$		LiOH	100	18	3	14
20	Pd(OAc)$_2$		LiOH	100	13	n.d.	11
21	$PdCl_2$	dpePhos(Cy)	LiOH	100	98	95	2
22	$PdCl_2$	dppb	LiOH	100	84	82	2
23	$PdCl_2$	dppe	LiOH	100	98	96	2
24	$PdCl_2$	Xantphos(*t*-Bu)	LiOH	100	100	99	n.d.
25	$PdCl_2$	dppe	LiOH	90	96, 58^b	94, 55^b	2, 2^b
26	$PdCl_2$	Xantphos(*t*-Bu)	LiOH	90	97, 76^b	96, 70^b	1, 5^b

[a] Aniline (2 mmol), benzyl alcohol (6 mmol), PdX_2 (1 mol %), ligand (1 mol %), base (20 mol %); conversion and yields were determined by GC using hexadecane as the internal standard. [b] Reaction was carried out for 15 h.

using both benzyl and aliphatic alcohols under photoirradiation conditions.[19] A homogeneous catalyst system was reported by Ramón and co-workers using 1 mol % of Pd(OAc)$_2$ in the presence of 100 mol % of CsOH at temperatures of 130−150 °C in toluene as the solvent. Up to 99% yield of the alkylated amines was reported when benzylic alcohols were used as the alkylating agents.[20] However, the yield decreased drastically to 26% when aliphatic alcohols such as 1-cyclohexyl carbinol was used. Challenging secondary alcohols such as 2-octanol were reported to be inactive under the optimized conditions. Accordingly, we focused our research on developing simple catalyst systems that work under relatively mild operating conditions as well as for challenging substrates. Herein, we report a homogeneous palladium catalyst system that is active at temperatures as low as 90 °C for easily oxidizable alcohols as well as for using aliphatic primary and secondary alcohols as potential alkylating agents under moderate conditions.

■ RESULTS AND DISCUSSION

Our initial investigations using benzyl alcohol as the alkylating agent for N-alkylation of aniline showed that homogeneous palladium catalysts in the presence of a suitable phosphine ligand and substoichiometric amounts of a base performed better under solvent-free conditions. Accordingly, Pd(OAc)$_2$ as the catalyst in the presence of Xantphos as the ligand and 20 mol % of $NaHCO_3$ as the base gave a yield of 26% with 73% conversion at 130 °C for 24 h, as shown in Table 1 (entry 1). In this case, ∼44% imine remained unhydrogenated. To our delight, near quantitative yield was observed when $PdCl_2$ (entry 2) was used as the catalyst instead of Pd(OAc)$_2$ under similar conditions. Reducing the temperature to 110 °C decreased both conversion and yield of the product (entry 3). A quick screening of different phosphine ligands (Xantphos, dppf, dppf(*t*-Bu)) at 110 °C showed that dppf(*t*-Bu) (entry 5) was promising and was selected for further evaluation. Screening different bases showed that LiOH (entry 10) was one of the best bases for this reaction, achieving quantitative yield even at 100 °C (entry 12).

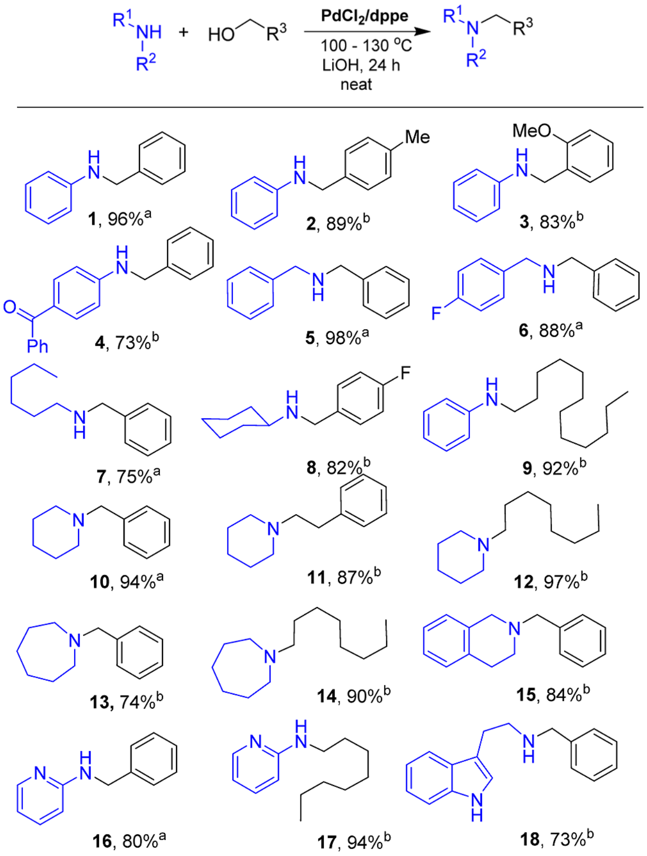
Palladium precursors may have an important role because Pd(OAc)$_2$ gave inferior results (entry 13) under the optimized conditions. Further reduction in temperature to 90 °C (entry 14) gave a slightly lower yield and would require a longer reaction time to achieve quantitative yield.

Under these optimized reaction conditions, some of the common phosphine ligands, such as PPh$_3$, BINAP, dpePhos, etc. (entries 15, 16 and 17) showed very low conversions and very low yield of the product. No product or a negligible amount of the product was observed with very low conversions in the absence of any phosphine ligands (entries 19 and 20). Ligands such as dpePhos(Cy), dppe, and Xantphos(*t*-Bu) (entries 21, 23 and 24) showed near quantitative conversions and product yields similar to that of dppf(*t*-Bu) at 100 °C for 24 h. Decreasing the temperature to 90 °C had only a marginal change in the yield. Though dppe and Xantphos(*t*-Bu) (entry 25 and 26) gave similar results after 24 h, a better performance with Xantphos(*t*-Bu) was observed at 90 °C for a lower reaction time of 15 h. However, we chose dppe for further investigation and to study substrate scope because dppe is a relatively inexpensive and readily available ligand in comparison with Xantphos(*t*-Bu) and dppf(*t*-Bu).

Thus, good to excellent yields were achieved for the alkylation of various primary and cyclic secondary amines using relatively easily oxidizable benzyl alcohols at 100 °C and sterically hindered benzylic alcohols as well as aliphatic alcohols at 130 °C (Table 2). In the case of alkylation of aniline, isolated yields of 96% and 89% were obtained for the secondary amine products **1** and **2**, by using benzyl alcohol and 4-methyl benzyl alcohols as the alkylating agents, respectively. *ortho*-Methoxy-substituted benzyl alcohol was also active as the alkylating agent and gave the corresponding secondary amine **3** in 83% yield. *p*-Substituted aniline, such as *p*-benzoyl aniline, gave good yields of **4** (79%) using benzyl alcohol as the alkylating agent. Benzylic amines and aliphatic amines underwent alkylation smoothly with benzyl alcohol to give **5**, **6**, and **7** in good to excellent yields. Up to 82% yield was obtained for the secondary amine **8** when alkylation of cyclohexylamine was carried out using *p*-fluorobenzyl alcohol. Aliphatic alcohols as alkylating agents generally require higher temperatures, and up to 92% yield of **9** was achieved for the alkylation of aniline with 1-dodecanol using the present catalyst system at 130 °C.

Cyclic secondary amines[21] were also readily alkylated to the corresponding tertiary amines in excellent yields (Table 2). For example, tertiary amine **10** was obtained in 94% yield upon alkylation of piperidine with benzyl alcohol at 100 °C. With aliphatic alcohols such as homobenzylic alcohol and 1-octanol, up to 87% and 97% yields of **11** and **12**, respectively were obtained at 130 °C. Seven-membered cyclic secondary amine was also successfully alkylated using benzyl alcohol and 1-octanol, achieving **13** and **14** in 74% and 90% yields, respectively. Heterocyclic tertiary amine **15** was obtained in 84% yield upon alkylation of tetrahydroisoquinoline using benzyl alcohol. Interestingly, heteroaromatic amines, such as 2-aminopyridine and tryptamine, were also efficiently alkylated under these conditions to give the products **16**, **17**, and **18** in 80%, 94% and 73%, respectively.

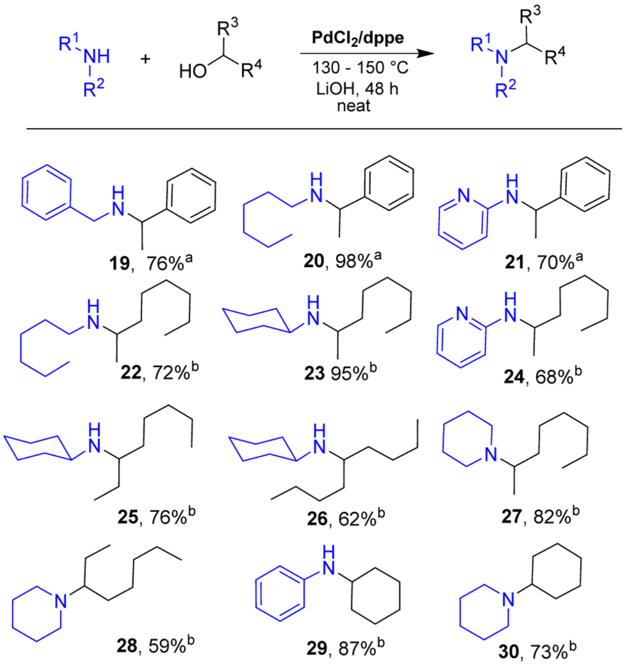
Table 2. Scope of N-Alkylation of Amines Using Primary Alcohols



^{a,b}R^{1}NHR^2 (2 mmol), R^{3}OH (6 mmol), PdCl$_2$ (1 mol %), dppe (1 mol %), LiOH (20 mol %); yields given are isolated yields. ^{a}Reaction carried out at 100 °C. ^{b}Reaction carried out at 130 °C.

Secondary alcohols are challenging alkylating agents compared with primary alcohols using hydrogen borrowing strategy because of the difficulty in its in situ dehydrogenation to the corresponding ketones as well as the hydrogenation of the iminium or enamine intermediates.[6,22] To the best of our knowledge, a promising Pd-catalyzed N-alkylation of amines using secondary alcohols as alkylating agents has not been reported so far.[17−20] To our delight, with the current Pd-catalyst system, *sec*-benzylic as well as aliphatic acyclic and cyclic secondary alcohols gave excellent yields for N-alkylation of amines under neat conditions (Table 3). Using secondary benzyl alcohol, alkylation of benzyl amine, hexylamine, and 2-amino pyridine were achieved in 76% (**19**), 98% (**20**), and 70% (**21**) yields, respectively at 130 °C. More challenging aliphatic secondary alcohols required 150 °C for achieving higher yields. Accordingly, very good yields to the corresponding alkylated amine products were achieved for alkylation of primary aliphatic acyclic (**22**, 72%) and cyclic (**23**, 95%) amines and heteroaromatic amine (**24**, 68%) using 2-octanol as the alkylating agent. Remarkably, more internal secondary alcohols, such as 3-octanol and 5-nonanol, also proved to be excellent alkylating agents, and up to 76% and 62% yields of **25** and **26**, respectively, were obtained for the alkylation of cyclohexylamine. Cyclic secondary amine as substrate also gave promising yields, and up to 82% and 59% yields of **27** and **28**, respectively, were achieved in the case of piperidine when 2-octanol and 3-octanol were used as the alkylating agents. Under the present catalyst system, cyclohexanol can also be used as the alkylating agent, and up to 87% (**29**) and 73% (**30**) yields were achieved with aniline and piperidine as the substrates.

Table 3. Scope of N-Alkylation of Amines Using Secondary Alcohols



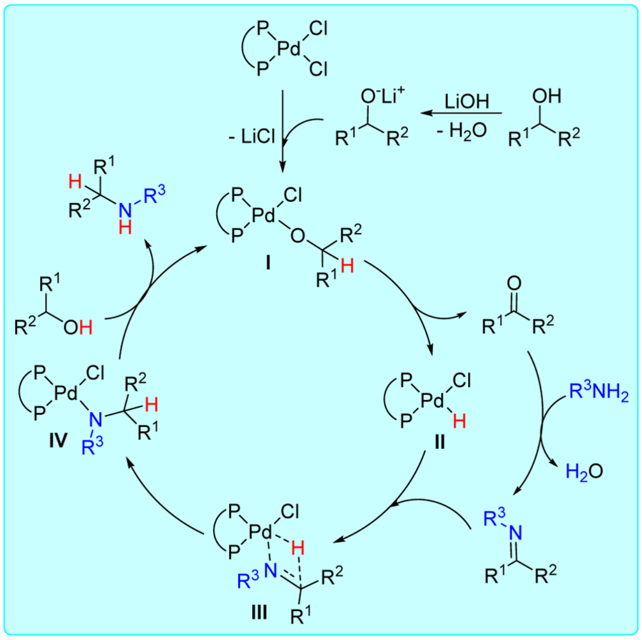
[a,b]R^1NHR^2 (2 mmol), R^3R^4CHOH (6 mmol), $PdCl_2$ (2 mol %), dppe (2 mol %), LiOH (20 mol %); yields given are isolated yields. [a]Reaction carried out at 130 °C. [b]Reaction carried out at 150 °C.

Next, we examined the scalability of this palladium catalyzed methodology. Thus, the standard reaction of N-alkylation of aniline using benzyl alcohol was scaled up to 10 mmol scale using 0.1 mol % catalyst at 100 °C for 72 h, achieving up to 90% yield and a TON of 900. The yield can be improved upon further optimization. For example, near quantitative yield was achieved at 110 °C after 48 h using 0.4 mol % of the catalyst.

A possible catalytic cycle is proposed in Scheme 2 on the basis of the results obtained and the available literature on similar palladium-catalyzed transformations.[23] Reaction of the in situ-formed lithium alkoxide with palladium precursor generates the catalytically active palladium alkoxide species **I**, which upon β-hydride elimination generates the palladium hydride intermediate **II** and the carbonyl compound. Insertion of the in situ-generated imine on to Pd−H bond of **II** generates the species **IV**, which upon reaction with alcohol releases the amine product, thereby regenerating the catalytically active palladium alkoxide **I** for further catalysis. The effective formation of the intermediates **III** and **IV** may depend on the steric and electronic properties of the imine or iminium ion. Accordingly, alkylation of secondary amine and alkylation using secondary alcohol would require harsh reaction conditions compared with that of primary amine and using primary alcohol.

In conclusion, we have reported a simple, convenient and highly efficient homogeneous palladium catalyst system for the N-alkylation of amines using alcohols under solventless conditions. Excellent yields were achieved with benzyl alcohol as alkylating agent at temperatures of 90−100 °C. More challenging aliphatic and secondary alcohols gave good to excellent yields for the alkylation of various primary and cyclic secondary amines under moderate conditions of 130−150 °C. N-Alkylation using the present catalyst system could be easily scaled up, and a TON of 900 is achieved for a 10 mmol scale reaction. Since this catalyst system offers reactions at fairly mild conditions, it would be useful for further applications in the synthesis of complex molecules having various functional groups and is currently in progress.

Scheme 2. Proposed Catalytic Cycle for the Pd-Catalyzed N-Alkylation of Amines Using Alcohols



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data of the products, NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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