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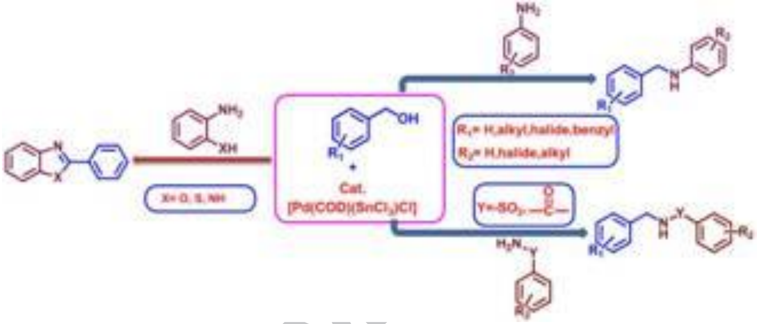

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Re-entry of Tin in N-alkylation: First Example of a Homogeneous Heterobimetallic Pd-Sn Catalyst for Base and Additive Free alkylation of Amine and Surrogates with Alcohol

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ABSTRACT

The *N*-alkylation of amines, and amides with benzyl alcohols is catalyzed by bimetallic catalyst $[Pd(COD)(SnCl_3)Cl]$ in *o*-xylene. The reaction does not require additional base, additive or ligand, and is insensitive towards air and moisture and involves minimal work-up. These features make the reaction attractive, simple and practical

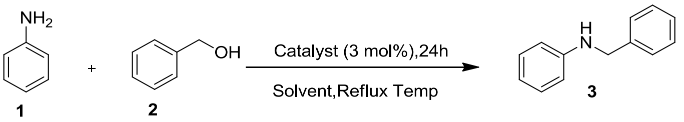
Amines find widespread application in both the bulk and fine chemical industries as basic intermediates, additives, dyes, and agrochemicals, as well as in the pharmaceutical industry.[1] The development of simple methods for the selective formation of C-N bonds is therefore of great importance. The best known method for the alkylation of amines is their nucleophilic substitution reaction with haloalkanes.[2] However, this method can be problematic due to over alkylation and toxic nature of many alkyl halides and related alkyl agents and also produce large amount of inorganic salt. The so-called "borrowing hydrogen methodology"[3] or "hydrogen auto transfer reaction"[4] has aroused great interest in recent years and is an excellent protocol for the selective alkylation of amines using simple, nontoxic alcohols.[5] The use of alcohols as alkylating agents make the process relatively greener since the by-product is only water. In past few years many homogenous transition metal complexes such as ruthenium, iridium, rhodium, platinum, gold, nickel, copper, and iron catalysts are used for the synthesis of *N*-alkylation of amines with alcohols.[6-15] However these catalysts require the use of co-reagents such as a base, a promoter or an additive. While an additive free *N*-alkylation strategy in the homogeneous regime is yet to emerge, a few heterogeneous nobel-metal catalysts (Pd, Ru, Ag, Au, and Pt)[16-20] have been reported. Yet many of these catalysts require high pressure (5 atm of N_2), H_2 atmosphere or co-catalyst/support. We presume that development of an efficient catalyst for direct *N*-alkylation will be rewarding**.**

Thirty years ago Migita and co-workers noted that palladium compounds can catalyze the regiospecific *N*-alkylation from aryl halides and stoichiometric tin amides.[21] This hetero cross-coupling is remarkable, considering its relationship to Stille type carbon-carbon bond-forming cross couplings.[22] In 1994, Buchwald and Hartwig independently reported the catalytic amination reactions of aryl halide with palladium complexes with Tin amide.[23] They used *ex-situ* or *in-situ* generated tin amide in stoichiometric amount. Due to the toxicity of tin amides and related disposal problems, alternative routes were explored, which led to the development of Buchwald-Hartwig amination in the absence of tin reagent, but utilizing stoichiometric amount of strong bases such as $LiN(SiMe_3)_2$, NaO-*t*-Bu and Cs_2CO_3.

Use of an alcohol instead of a halide in the *N*-alkylation of amines has been attempted by various groups. In this regard recent reports on the use of benzylic and aliphatic primary alcohols as alkylating agent by homogenous[16e-f] or heterogeneous[16a-d] palladium based catalyst are noteworthy. In continuation of our success with bimetallic catalysis for carbon–carbon bond formation,[24] here we report a homogenous heterobimetallic 'Pd–Sn' catalyst which promotes the C-N bond formation through *N*-alkylation of anilines with alcohol under base and additive free condition.

The *N*-alkylation of aniline with benzyl alcohol in the absence of base and additive was explored using various Lewis acids, monometallic salts, and bimetallic complexes as catalysts. In model studies, we examined the reaction of aniline **1** (0.25 mmol) with benzyl alcohol **2** (0.25 mmol) at 140 °C for 24h leading to the formation of *N*-benzyl aniline **3** as the desired product varying the solvents and catalysts (3 mol%) (table 1). To our delight, the heterobimetallic catalyst namely $[Pd(COD)(SnCl_3)Cl]$ showed excellent catalytic efficiency in *o*-xylene as solvent under reflux giving rise to the desired product **3** (table 1, entry 9). The reaction did not require exclusion of air or moisture (entry 10). The distinct importance of the bimetallic catalyst may be understood from the fact that individually [Pd(COD)Cl_2] was inactive (entry 5), while $SnCl_2$ (entry 2) and the other bimetallic 'Pd–Sn' catalyst (table 1, entry 8) showed poor reactivity. Under similar reaction condition, catalysts such as $AlCl_3$, $FeCl_3$, $PdCl_2$, Pd$(OAc)_2$ were also poorly efficient (table 1, entries 1-5). It may be noted that heterobimetallic Pd-Sn catalyst generated *in-situ* from [Pd(COD)Cl_2] with $SnCl_2$ was equally efficient but a mere combination of $PdCl_2$ with $SnCl_2$ was not so (entries 6, 7). Furthermore toluene, dichloroethane, acetonitrile and water as solvents were ineffective (entries 11-14).

Table 1. Catalyst Screening and Optimization



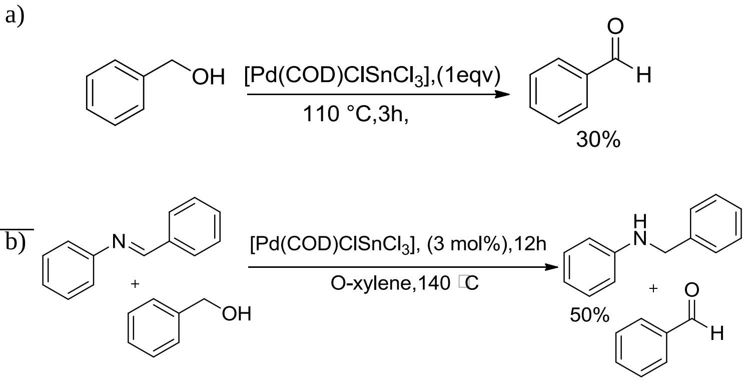
#	Catalyst	Solvent	Converstion (%)^b	Yield of 3 (%)^c
1	$AlCl_3$	*o*-xylene	<5	-
2	$FeCl_3$	*o*-xylene	<10	-
3	$SnCl_2$	*o*-xylene	<20	15
4	$PdCl_2$	*o*-xylene	<5	-
5	Pd$(OAC)_2$	*o*-xylene	<10	-
6	$PdCl_2(PPh_3)_2$	*o*-xylene	0	0
5	$PdCl_2$(COD)	*o*-xylene	0	0
6	$PdCl_2$+$SnCl_2$	*o*-xylene	70	60
7	$PdCl_2$(COD)+ $SnCl_2$	*o*-xylene	95	87
8	$Pd(PPh_3)_2ClSnCl_3$	*o*-xylene	<30	20
9	Pd(COD)$ClSnCl_3$	*o*-xylene	>98	90
10^d	Pd(COD)$ClSnCl_3$	*o*-xylene	95	88
11	Pd(COD)$ClSnCl_3$	Toluene	<10	-
12	Pd(COD)$ClSnCl_3$	DCE	0	0
13	Pd(COD)$ClSnCl_3$	water	0	0
14	Pd(COD)$ClSnCl_3$	acetonitrile	0	0

^{a} Reaction condition: Aniline (0.25 mmol), benzyl alcohol (0.25 mmol), catalyst (3 mol%) in 3 mL of solvent at reflux temperature for 24 h; ^{b} From ^{1}H NMR; ^{c} Isolated yield of pure product; ^{d} argon atmosphere

Having established the optimum condition, we tested the scope and limitation of the *N*-alkylation reaction using various amine and surrogates with other benzyl alcohols. The C-N coupling between aniline **1** and substituted benzyl alcohols **2** afforded the desired product **3** in moderate to excellent yields (table 2). For example with alcohol variation, 88–94% yields of desired product **3b**, **3c**, and **3d** were obtained from 3-methyl benzyl alcohol, 3-methoxy benzyl alcohol, and 2-methoxy benzyl alcohol as the alkylation reagents (table 2, entries 2-4). On the other hand, with alcohols bearing halogen substituent, the corresponding products **3e-3h** were isolated in 60-75% yields. Amines such as 2, 3, 5-trimethyl aniline, 4-floroaniline could also react with benzyl alcohol to afford the *N*-benzyl amine **3k** and **3l** in >85% yields (entries 11, 12). The alkylation of carboxamide with alcohol was further explored. With benzamide as the starting material, the coupling reactions could be realized by using benzyl alcohol (entry 10). To our delight, it was also observed that Pd-Sn catalyst was also active for the *N*-alkylation of sulfonamides. Sulfonamides such as *p*-toluene sulfonamide and benzene sulfonamide reacted with benzyl alcohol to generate the corresponding *N*-alkylated products **3m** and **3n** in excellent yields (entries 13, 14).

The condensation reaction of *o*-substituted (–NH_2 or –SH or –OH) anilines with aldehydes is the most commonly used method for the synthesis of benzazoles. The synthesis of benzazoles directly from alcohols is also reported. Interestingly we found that our catalyst also showed good efficiency for the synthesis of benzazoles from alcohols. In order to explore the scope of the present method, the reactions of *o*-substituted (–NH_2 or –SH or –OH) anilines were explored with a variety of alcohols (table 3). The reaction of *o*-phenylenediamine with benzyl alcohol and 4-methyl benzyl alcohol proceeded smoothly to give the desired product in high yield (table 3, entries 1, 2). Reaction of substituted benzyl alcohols with 2-aminothiophenol afforded the desired 2-substituted benzothiazoles in excellent yields (table 3, entry 5, 6). In the case of benzyl alcohol (table 3, entry 5) and 4-methyl benzyl alcohol (table 3, entry 6) good yields of the coupling product were observed. The present protocol was also applied for the synthesis of 2-phenylbenzoxazole from 2-aminophenol and benzyl alcohol (table 3, entry 3) or 4-methyl benzyl alcohol (table 3, entry 4).

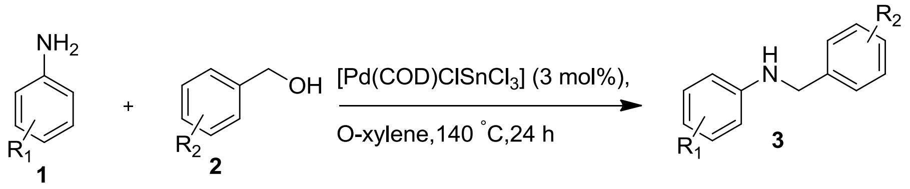
While mechanistic explorations are underway, taking cue from the "borrowing hydrogen methodologies", it may be anticipated that the present process undergoes a three-step pathway involving alcohol oxidation, imine formation, followed by imine hydrogenation. In independent experiments (Scheme 1) we found that in the absence of amine, the oxidation of benzyl alcohol to benzaldehyde takes place in presence of stoichiometric Pd-Sn complex, confirming the first step. With catalytic Pd-Sn complex and in presence of amine, when the reaction was carried out at low temperature (110 °C) or stopped in between, imine was observed as the major product, which confirms the second step. The hydrogenation of the imine afforded the corresponding amine under the present reaction conditions, which further confirmed the third step.

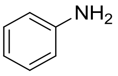
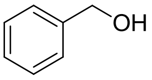
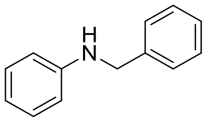
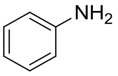
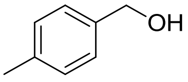
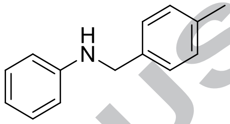
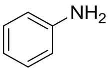
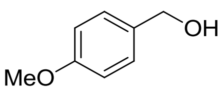
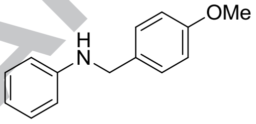
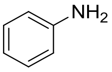
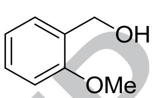
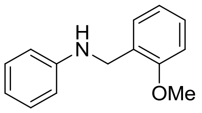
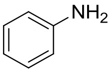
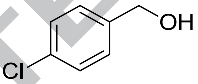
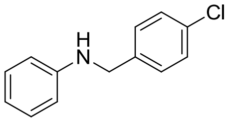
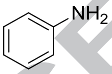
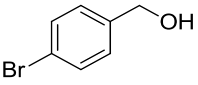
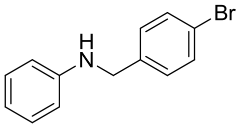
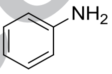
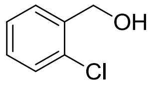
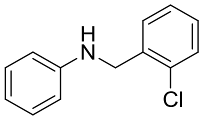
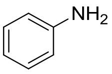
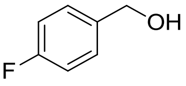
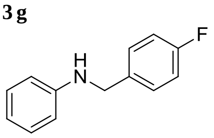
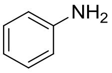
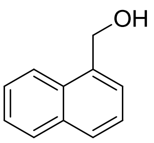
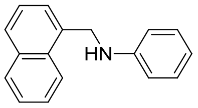
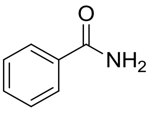
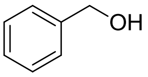
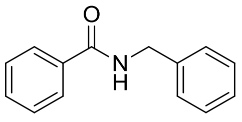


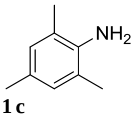
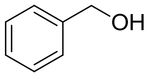
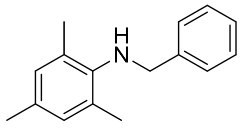
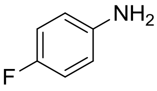
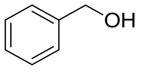
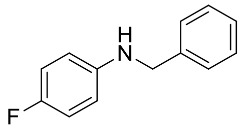
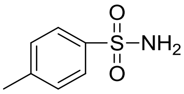
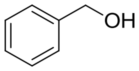
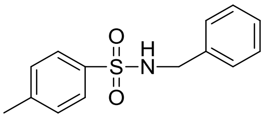
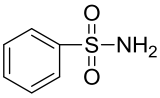
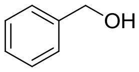
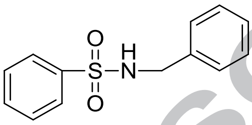
Scheme-1: (a) oxidation of alcohol; (b) hydrogenation of imine

We therefore propose that [Pd(COD)$(SnCl_3)$Cl] promotes the oxidation of the alcohols to aldehydes, followed by the formation of imine and finally to *N*-alkylated product. A tentative outline of the mechanistic proposal is presented in Scheme 2. This involves initial coordination of alcohol to Pd-Sn catalyst followed by the formation of the hydridopalladium(II) species along with the aldehyde. The imine formed *in situ* from aldehyde and amine is activated by the bimetallic core in Pd-Sn catalyst. We have earlier shown that the Sn(IV) center in TM-Sn system is a hard Lewis acidic center.[24] Thus coordination of the hard nitrogen to tin(IV) is expected. Formation of the final organic product is a result of internal rearrangement as shown. The detailed mechanistic description, in particular the role of the two metals in the bimetallic catalyst must await further studies.

Table 2. Pd–Sn catalyzed *N*-Alkylation of Anilines with Benzylic Alcohols: Substrate Scope [a]



#	Aniline	Alcohol	Product	Yield(%)[b]
1	 1a	 2a	 3a	90
2	 1a	 2b	 3b	88
3	 1a	 2c	 3c	94
4	 1a	 2d	 3d	90
5	 1a	 2e	 3e	78
6	 1a	 2f	 3f	65
7	 1a	 2g	 3g	70
8	 1a	 2h	 3h	65
9	 1a	 2i	 3i	78
10	 1b	 2a	 3j	68

11	 **1c**	 **2a**	 **3k**	84
12	 **1d**	 **2a**	 **3l**	60
13	 **1e**	 **2a**	 **3m**	75
14	 **1f**	 **2a**	 **3n**	70

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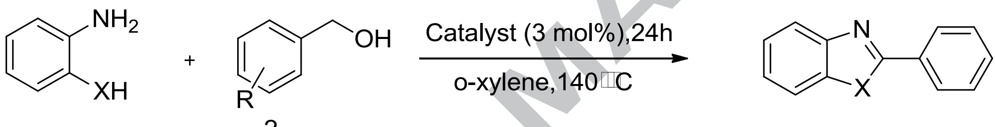
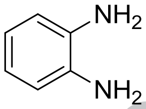
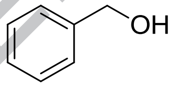
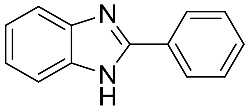
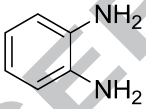
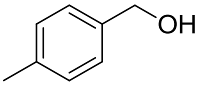
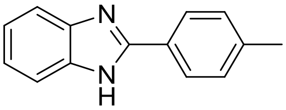
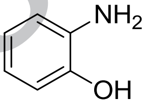
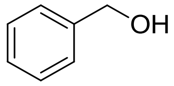
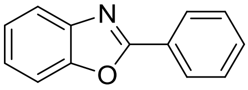
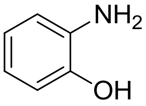
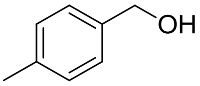
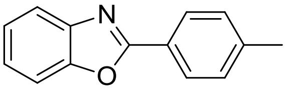
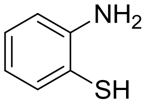
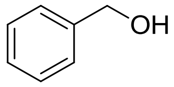
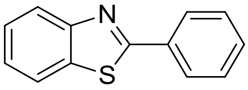
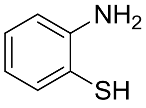
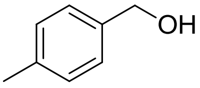
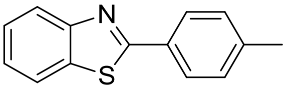
[a] Unless otherwise mentioned, reaction conditions are as follows: **1** (0.25 mmol), **2** (0.25 mmol), catalyst (3 mol%); [b] refers to isolated yield

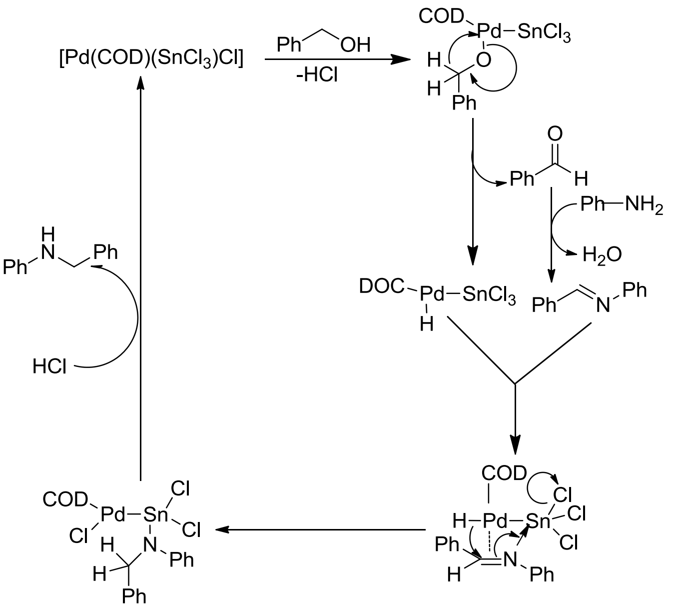
Table 3: *N*-Alkylation of *O*-substituted anilines with benzyl alcohols [a,b]



4 2 5

Entry	Aniline	Alcohol	Product	Yield(%)
1	 **4a**	 **2a**	 **5aa**	80
2	 **4a**	 **2b**	 **5ab**	85
3	 **4b**	 **2a**	 **5ba**	70
4	 **4b**	 **2b**	 **5bb**	72
5	 **4c**	 **2a**	 **5ca**	75
6	 **4c**	 **2b**	 **5cb**	73

[a] All the reactions were carried out with *o*-substituted aniline (0.25 mmole), benzyl alcohol (0.25 mmole) and catalyst (3 mol%) in 2mL *o*-xylene at 140 ºC



Scheme-2: Proposed Mechanism

In summary [Pd(COD)(SnCl$_3$)Cl] has been found to be an effective catalyst for the N-alkylation reaction of amine with substituted benzyl alcohol; water being the by-product. Catalyst screening clearly established the importance of the bimetallic core in the catalyst; however further mechanistic studies are warranted to understand the precise roles of the two metals. From synthetic point of view, it is promising to note that no additive and acids/bases are required in this alkylation. Additionally, the ease of handling of the catalyst (insensitive towards air and moisture) makes the protocol attractive, simple, and bench-friendly.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, http://dx.doi.org/XX.XXXX/j.tetlet.XXXX.XX.XXX.

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Highlights

- *N*-alkylation of amines and amides is achieved with benzyl alcohols using [Pd(COD)($SnCl_3$)Cl] as a heterobimetallic catalyst.
- The major advantage of the protocol is that it does not require any co-catalyst, base, additive, or external ligand.
- The catalyst is insensitive to air and moisture.