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Methylation of Aromatic Amines and Imines Using Formic Acid over Heterogeneous Pt/C Catalyst†‡

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We describe here that a commercially available Pt/C catalyst is capable of catalyzing methylation of aniline and aromatic imine with formic acid in the presence of a hydrosilane reductant. Both primary aniline and secondary aniline can be methylated. The advantage of this newly described method includs the operational simplicity, high TON, ready availability of the catalyst, and also good functional group compatibility.

Due to the prevalence of N-methylated aniline structures in both fine and bulk chemical industries,[1] new methodologies for methylation of aniline continuously attract the interest of chemists from both synthetic laboratories[2] and industry.[3] Classic methods of aniline methylation include substitution reactions with toxic and volatile methyl electrophiles[4] and also the well-known Eschweiler-Clarke reaction using excess formaldehyde and formic acid through a reductive amination.[5] Recently, catalytic methods utilizing renewable and non-toxic C1 source such as carbon dioxide,[6-8] carbonate[9] and formic acid[10] have received intensive attention. Among these C1 sources, formic acid (FA) is a non-toxic liquid that is generated as one of the major product from biomass industries[11] and CO_2 hydrogenation.[12] Recently, Beller et al. developed catalytic methylation of amine using commercially available Karstedt's catalyst.[10a] Cantat et al. reported a different formylation/ transfer hydrogenation catalyzed by Ru/triphos catalyst using excess amount of formic acid in the absence of external reducing agent.[10b] Shang and Fu et al. also discovered that a boron-based catalyst is capable of catalyzing amine methylation using formic acid.[10c] However catalytic methylation of amines with formic acid has been reported mainly by using homogeneous Pt,[10a] Ru[10b] or B catalysis.[10c] Development of alternative new catalytic system based on utilizing easily available, highly efficiency and low cost heterogeneous catalyst is still highly desirable. In this work, we describe a new catalytic methylation of aniline and aromatic imine over a commercialized heterogeneous Pt/C catalyst[13]

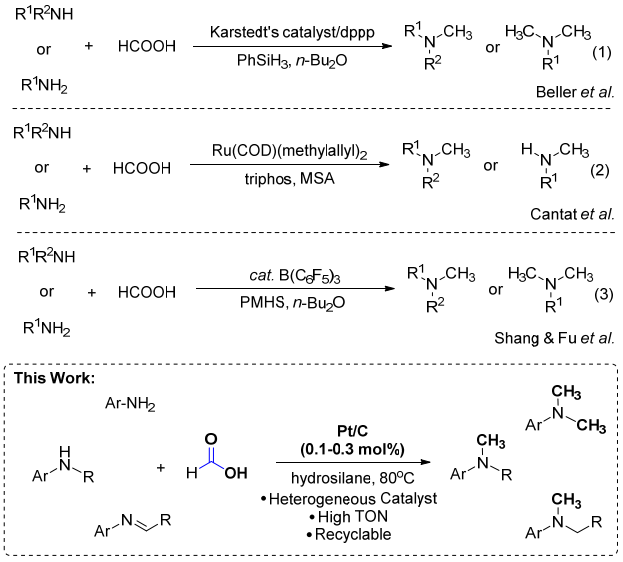

Figure 1 Catalytic methylation of amine using Formic Acid (FA).

using hydrosilane as reductant. Both primary and secondary amine can be methylated with good functional group tolerance. Aromatic imine can be reductively methylated in a cascade style in one pot. The commercially available heterogeneous catalyst exhibits high efficiency at a low catalyst loading (0.1 mol%-0.3 mol%) and has been demonstrated for a broad scope of substrates. TON number as high as 1700 was also achieved. The Pt/C catalyst retains its catalytic activity after 2 time of recycling by centrifugation for this reaction. This method offers a new way to produce N-methylated anilines utilizing renewable carbon source and an easily available low cost heterogeneous catalyst.

Our studies started with a discovery that commercially available Ru/C can catalyze N-methylation of N-methylaniline with formic acid (Table 1, Entry 1). This result inspired us that a heterogeneous metal catalyst on activated carbon may serve as a suitable catalyst. We tested three commercialized metal carbon catalyst, and found Pt/C catalyst gave the best result (Table 1，Entry 2), whereas using Pd/C mainly caused the formation of formamide (Table 1，Entry 3). The moderate

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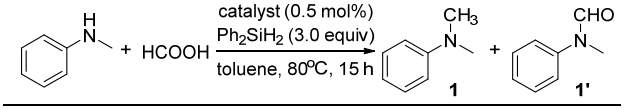
†Dedicated to Prof. Tien-Yau Luh on the occasion of his 70th birthday.

‡Electronic Supplementary Information (ESI) available: General information, experimental procedures, characterization data and H^1 and ^{13}C NMR spectra of products. See DOI: 10.1039/x0xx00000x

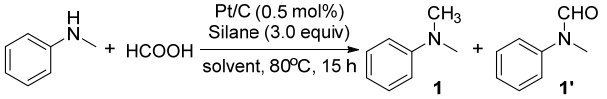
Table 1 Screening heterogeneous metal-carbon catalysts[a]



Entry	Cataylst	Conv. (%)[b]	Yield (%)[b]	
			1	**1'**
1	Ru/C	99	53	34
2	Pt/C	96	60	6
3	Pd/C	99	10	85

[a] Reaction conditions: N-methylaniline (0.3 mmol), silane (3.0 equiv), catalyst(0.5 mol%), HCO_2H (2.0 equiv), toluene (1.0 mL), 80 °C, 15 h. Ru/C (5 wt % of Ru) , Pt/C (5 wt % of Pt) and Pd/C (10 wt % of Pd) are commercialized catalyst [b] Determined by GC using n-dodecane as internal standard.

Table 2 Optimization of reaction conditions[a]



Entry	Silane	Solvent	Conv. (%)[b]	Yield (%)[b]	
				1	**1'**
1	Et_3SiH	Toluene	77	trace	71
2	$(EtO)_3SiH$	Toluene	97	3	91
3	Et_2MeSiH	Toluene	70	61	3
4	$PhSiH_3$	Toluene	99	98	-
5	PMHS	Toluene	92	67	2
6	$PhSiH_3$	Cyclohexane	99	98	trace
7[c]	**$PhSiH_3$**	**Cyclohexane**	**99**	**98**	**-**
8[c]	**$PhSiH_3$**	**Toluene**	**99**	**97**	**trace**
9[d]	$PhSiH_3$	Cyclohexane	78	77	trace
10[d]	$PhSiH_3$	Toluene	90	85	trace

[a] Reaction conditions: N-Methylaniline (0.3 mmol), Silane (3.0 equiv), catalyst (0.5 mol%), HCO_2H (2.0 equiv), solvent (1.0 mL), 80 °C, 15 h. [b] Determined by GC using n-dodecane as internal standard. [c] Catalyst (0.1 mol%), silane (2.5 equiv). [d] Catalyst (0.05 mol%).

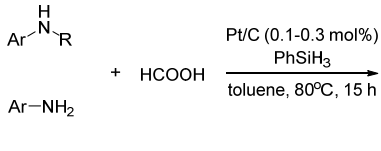
yield compared with a full conversion may be ascribed to the formation of $(ArMeN)_2$-$SiPh_2$ compound.

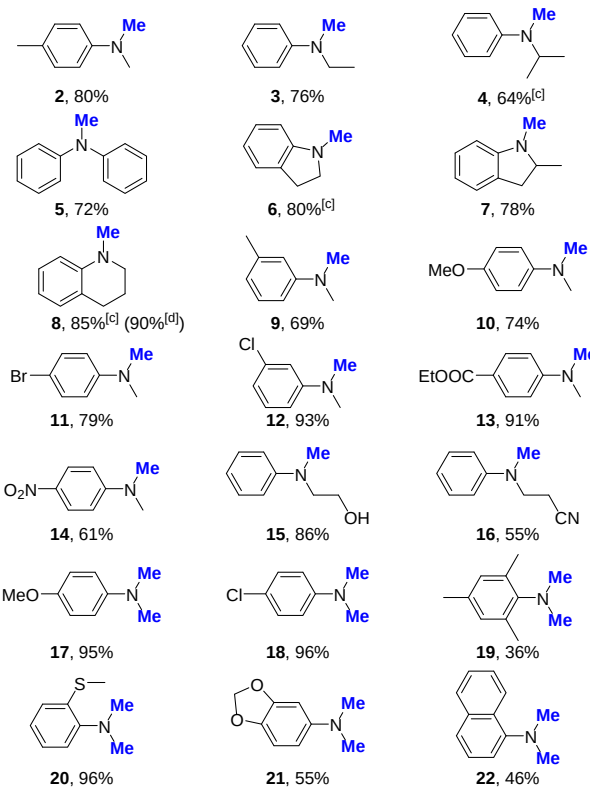
After finding the catalytic activity of Pt/C for this amine methylation, we intensively screened various factors including solvents and hydrosilanes to optimize this reaction. Among all the solvents tested, toluene and cyclohexane gave comparably good yields and best methylation/formylation selectivity (See SI, Table S1). Screening different hydrosilanes revealed that using triethylsilane is totally ineffective for methylation and only leads to formylation (Tabel 2, Entry 1). Triethoxysilane is also ineffective (Entry 2). Utilizing a less sterically hindered hydrosilane, methyl diethyl silane, significantly improved yield and selectivity for methylation (Entry 3). Polymethylhydrosiloxane (PMHS), a byproduct of the silicone industry,[14] gave methylation product in 67% yield, accompanying only 2% of formylation (Entry 5). The best result was achieved when $PhSiH_3$ was used. N,N-dimethyl aniline was exclusively formed in 98% yield (Entry 4 and 6). The reaction selectively delivered methylation product with only trace amount of formylated byproduct detected. The catalyst loading could be reduced from 0.5 mol% to 0.1 mol% without obviously decreasing the yield (Entry 7 and 8). It is worth noting, when the catalyst loading is as low as 0.05 mol%, methylation still proceeds to 85% yield with only trace amount of formylation byproduct. In this case, the TON value reached 1700 (Entry 10).

We noticed that the Pt/C catalyst remained insoluble during the reaction process and after the completion of the reaction. The catalyst can be easily separated from the reaction mixture through centrifugation. After simply washing it with methanol and toluene, the recovered Pt/C catalyst remained catalytically reactive. It is demonstrated that the heterogeneous Pt/C catalyst is still catalytically reactive after recycle for two times (See SI, Table S2). Inductively coupled plasma (ICP) analysis of the centrifuged and filtered toluene solution after reaction shows no detectable leaching of Pt presented in the filtrate, and the filtrate is catalytic inactive, which strongly suggest the observed catalysis is heterogeneous in nature. The decrease of yield and selectivity of methylation/formylation could probably be ascribed to the deactivation by absorbed species such as siloxane byproduct on Pt/C surface

After obtaining the optimized reaction conditions, the scope of aniline was studied. It is worth mentioning that only a low

Table 3 Scope of methylation of secondary and primary anilines[a,b]





[a] Reaction conditions for secondary amines: substrate (0.3 mmol), $PhSiH_3$ (2.5 equiv), Pt/C (0.1 mol%), HCO_2H (2.0 equiv), toluene (1.0 mL), 80 °C, 15 h; for primary amines: substrate (0.3 mmol), $PhSiH_3$ (5.0 equiv), Pt/C (0.3 mol%), HCO_2H (3.0 equiv), toluene (1.0 mL), 80 °C, 15 h. [b] Yield of isolated product. [c] Cyclohexane instead of toluene. [d] reacted in 10 mmol scale, 1.32 g product was obtained and TON was 900.

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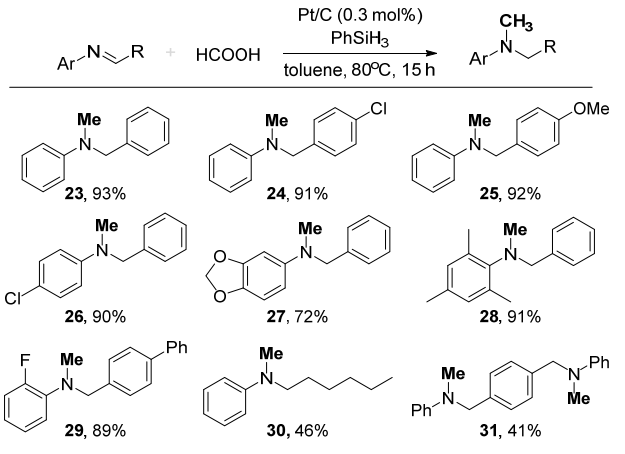
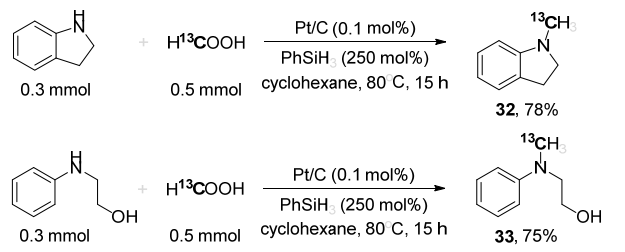
catalyst loading of 0.1 mol% and 0.3 mol% of Pt/C were applied for the substrate scope investigations of secondary aniline and primary aniline respectively. Both N-alkylated aniline **(2, 3, 4)** and N-arylated aniline **(5)** are suitable substrates. Cyclic substrates such as indoline **(6, 7)** and tetrahydroquinoline **(8)** are also compatible substrates. It is remarkable that various functional group can be tolerated. Ether **(10)**, aryl bromide **(11)**, aryl chloride **(12)**, ester **(13)**, nitro **(14)**, alcohol **(15)**, nitrile **(16)**, sulfide **(20)** and acetal **(21)** are all tolerated. This reaction is easily scalable to gram-scale without decreasing the yield and turn-over-number **(8)**. Besides secondary aniline, primary aniline can be smoothly dimethylated by slightly increasing the catalyst loading to 0.3 mol% **(17-22)**. For primary amine the dimethylation product is still the major product when the amount of formic acid is reduced. This observation reveals methylation of secondary amine is faster than primary amine. It is noteworthy that aniline with large steric hindrance adjacent to nitrogen gives reduced yield **(7, 22)**. This observation may be ascribed to the reduced nucleophilicity of amine by steric hindrance. Attempts to use acetic acid and hexanoic acid failed under the optimized reaction conditions.

Except for primary and secondary aniline, aromatic imine was also discovered as suitable substrate. Klankermayer et al. reported that imine could be consecutively reduced and methylated with CO_2 by using a homogeneous Ru/triphosphine catalyst.[7d] However, using formic acid and a heterogeneous catalyst system to methylate aromatic imine have not been investigated to date. Table 4 shows various aromatic imines can be successfully methylated using Pt/C catalyst. It is interesting to observe that imine substrate containing large steric-hindrance can also be methylated in high yield **(28)**.

Table 4 Scope of aromatic imines[a,b,c]

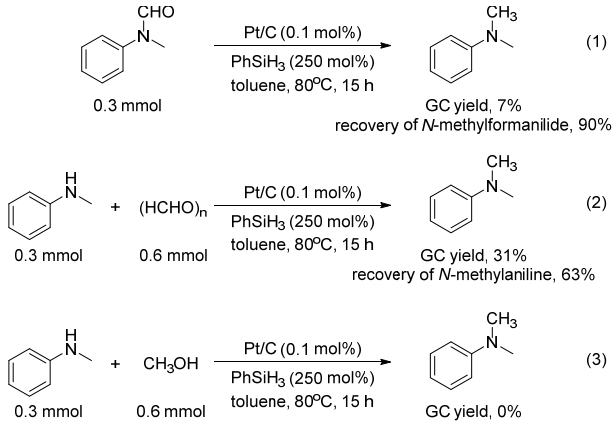


[a] substrate (0.3 mmol), $PhSiH_3$ (3.0 equiv), Pt/C (0.3 mol%), HCO_2H (2.0 equiv), toluene (1.0 mL), 80 °C, 15 h. [b] Yield of isolated product. [c] Pt/C (0.5 mol%), $PhSiH_3$ (5.0 equiv), HCO_2H (3.0 equiv).



Scheme 1. Synthesis of ^{13}C-label N-methyl amines using H^{13}COOH.

^{13}C-labeled N-methyl amines are significantly important in medical biology for ^{13}C-NMR spectroscopic analysis and tracking metabolites.[15] By using H^{13}COOH, ^{13}C-labeled N-methyl anilines can be easily accessed in good yields (Scheme 1). Several control experiments were performed and the results offer mechanistic insights that are different from reported homogeneous Pt-catalysis.[10a] First, we were surprised to find that N-methyl-N-phenylformamide can not be smoothly reduced to N,N-dimethylaniline under the optimized condition (Scheme 2, Eq. 1). This clearly rules out the mechanism of forming formamide followed by sequential reduction, which was proposed in homogeneous Pt/phosphine catalyzed N-alkylation of amines.[16] Second, when polyoxymethylene was applied instead of formic acid, methylation only proceeded in low yield (Scheme 2, Eq. 2). Using methanol as methylation reagent[17] was failed (Scheme 2, Eq. 3). The result of using polyoxymethylene suggests that reducing formic acid to formaldehyde followed by reductive amination is less possible. When deuterated silane was used, $PhNMeCD_3$ was detected by GC-MS, demonstrating that the hydrogen atoms in installed methyl group are from hydrosilane reductant.



Scheme 2 Control experiments.

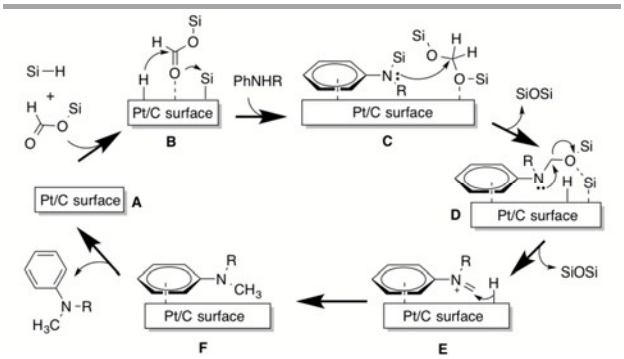


Figure 2. A possible reaction mechanism.

Based on the scope studies and the results from the control experiments, a possible mechanism for this heterogeneous Pt/C catalyzed methylation is demonstrated in Figure 2. Since

control experiments ruled out the possibility through amide and aldehyde intermediates, it is reasonable that *silyl acetal* intermediate may form and act as electrophile to react with amine to form C-N bond. As depicted in Figure 2, first, Si-H bond is activated on the surface of Pt/C, and formic acid is also absorbed on Pt/C (**B**). Formic acid is reduced by hydrosilane to form disilyl geminal diol ether, and disilyl geminal diol ether was attacked by absorbed amine (**C**). It is worth mentioning the reason why aliphatic amine is unreactive may be ascribed to the weak adsorption on Pt/C due to the lack of aromatic π-Pt interaction. After forming the C-N bond by nucleophilic attack and generation of siloxane, silyl aminomethanol ether intermediate is formed (**D**). **D** may release siloxane via intramolecular nucleophilic attack and generate iminium cation. Reduction of the iminium intermediate (**E**) and desorption deliver N-methylation product (**F** to **A**). The failure of higher carboxylic acids as alkylation reagent may be attributed to steric hindrance of the silyl acetal intermediate proposed in this mechanism.

Conclusions

In conclusion, we have demonstrated N-methylation of aniline and aromatic imine with formic acid as carbon source by using a commercially available Pt/C catalyst. Both primary aniline and secondary aniline can be methylated in the presence of various functional groups including reducible ester, nitro and cyano substituents. Aromatic imine can also be reduced and methylated under the same conditions in a cascade manner. The advantage of this newly described method includes the operational simplicity, high TON, ready availability of the catalyst, and also good functional group compatibility.

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