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Selective N-monoalkylation of anilines catalyzed by a cationic ruthenium(II) compound

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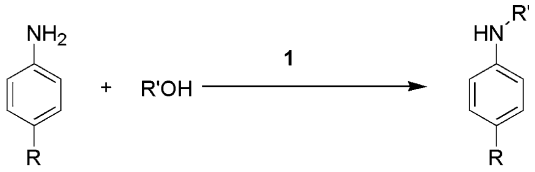
Abstract—$[(PPh_3)_2Ru(CH_3CN)_3Cl][BPh_4]$ has been found to catalyze the selective monoalkylation of anilines by alcohols.

Selective monoalkylation of amines is of fundamental importance.[1–6] For example, monoalkylation of aniline is important in industry.[6] The most common method of N-alkylation is reaction of an alkyl halide and an amine in the presence of base.[7] However, this method is undesirable from an environmental point of view.[7] Since the monoalkylated products have a tendency to react further to produce di- and tri-alkylated amines,[1,8] N-alkylation using alkyl halides suffers from non-selectivity. There are a large number of reports on the alkylation of aniline by reaction with alcohols in the presence of solid acid catalysts.[9] However, in most cases, mono- and dialkylated products are obtained. A recent report describes the monoalkylation of aniline with alcohols in the presence of an iridium catalyst in toluene.[7] Ruthenium complexes have also been used as catalysts for N-alkylation with alcohols.[10,11] In most cases, dialkylated products were obtained as the major products.[10,11] Recently, we reported the synthesis and structure of the cationic ruthenium complex, $[RuCl(PPh_3)_2(CH_3CN)_3]^+[BPh_4]^-$, which was found to be an effective catalyst for transfer hydrogenation of aldehydes and ketones.[12] Also, $[RuCl(PPh_3)_2(CH_3CN)_3]^+[BPh_4]^-$ was found to catalyze selective reduction of C=C double bonds in α,β-unsaturated ketones by formic acid.[13] We were interested in exploring the catalytic activity of this ruthenium complex for alkylation of amines. We report herein $[RuCl(PPh_3)_2(CH_3CN)_3]^+[BPh_4]^-$ (**1**) catalyzed selective monoalkylation of aniline by alcohols under solvent-free conditions.

A mixture of aniline (1 mmol) and **1** (0.01 mmol) was treated with an excess of alcohol (10 cm^3) and anhydrous K_2CO_3 (1 mmol) under argon in a Schlenk flask. The reaction mixture was then heated at 80–110 °C for 10 h. (Scheme 1). The reaction mixture was cooled to room temperature, diluted with water (50 cm^3), extracted with ether and after work-up, the products were isolated and purified by column chromatography. The reactions were monitored by TLC and the products were isolated in low to high yield (Table 1). The products were characterized by elemental analyses and ^1H NMR spectroscopy.

The conversion is dependent on the chain length of the alkyl group of the alcohol. The highest conversion was observed when methanol was used as the alkylating agent and the conversion gradually decreases as the chain length increases (Table 1). The most noteworthy fact is that only monoalkylation was observed, although, an excess of alcohol was used in all the reactions. When secondary alcohols, such as 2-propanol and 2-butanol, were used as alkylating agents, we did



R = H, CH_3
R' = CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $CH_3CH_2CH_2CH_2$

Scheme 1.

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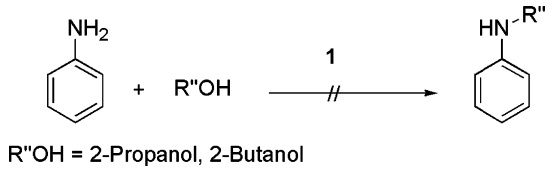
Table 1. N-Alkylation of aromatic and heteroaromatic amines with alcohols catalyzed by Ru-complex **1**[a]

Entry	Substrate	Alcohol	Product(s)	Yield[b] (%)	Conversion	Turnover number[c]
1	Aniline	Methanol	*N*-Methylaniline	76	78	78
2	Aniline	Ethanol	*N*-Ethylaniline	61	65	65
3	Aniline	1-Propanol	*N*-Propylaniline	50	55	55
4	Aniline	1-Butanol	*N*-Butylaniline	42	45	45
5	Aniline	Benzyl alcohol	*N*-Benzylaniline	30	95	95
			N,*N*-Dibenzylaniline	17		
			Benzylidinephenyl amine	46		
6	*p*-Tolylamine	Methanol	*N*-Methyl-*p*-tolylamine	69	70	70
7	*p*-Tolylamine	Ethanol	*N*-Ethyl-*p*-tolylamine	52	55	
8	*p*-Tolylamine	1-Propanol	*N*-Propyl-*p*-tolylamine	46	50	
9	*p*-Tolylamine	1-Butanol	*N*-Butyl-*p*-tolylamine	44	45	
10	Aniline	2-Propanol	—	—	—	—
11	Aniline	2-Butanol	—	—	—	—
12	4-Aminopyridine	Methanol	—	—	—	—
13	4-Nitroaniline	Methanol	—	—	—	—
14	1,4-Diaminobenzene	Methanol	—	—	—	—
15	4-Bromoaniline	Methanol	*N*-Methyl-4-bromoaniline	Poor	—	—
16	Butylamine	Methanol	—	—	—	—
17	Ethylene diamine	Methanol	—	—	—	—

[a] Reagents and conditions: substrate, 1 mmol; **1**, 0.01 mmol; alcohol, 10 cm^3; K_2CO_3, 1 mmol; reaction time, 10 h, temperature, refluxing temperature of the alcohol.
[b] ^1H NMR yield.
[c] Mol of product/mol of catalyst.



Scheme 2.

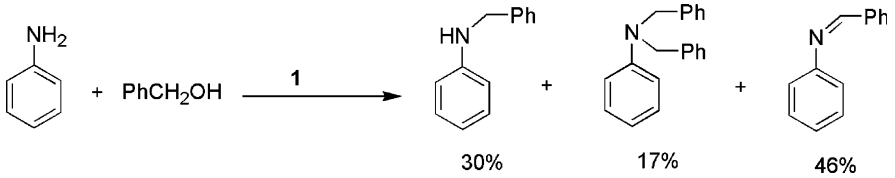
not observe any product formation and only starting materials were recovered (Scheme 2). Thus the reaction is specific for primary alcohols. The reason behind the specificity may be related to the steric bulk of the secondary alcohol. When benzyl alcohol was used as alkylating agent, both mono- and dialkylated products were isolated along with the corresponding imine (Scheme 3). The major products were found to be the imine and *N*-benzylaniline.

We have also studied the alkylation of heteroaromatic amines and did not observe any alkylation of the amino group in 4-aminopyridine under similar reaction conditions. The effect of substituents on the aromatic ring was also studied. 4-Nitroaniline and 1,4-diaminobenzene failed to give any product and only starting materials were recovered. In the case of 4-bromoaniline, we isolated the monoalkylated product in very low yield (Table 1). Similarly, aliphatic amines such as ethylene diamine and butylamine failed to give any product under similar reaction conditions.

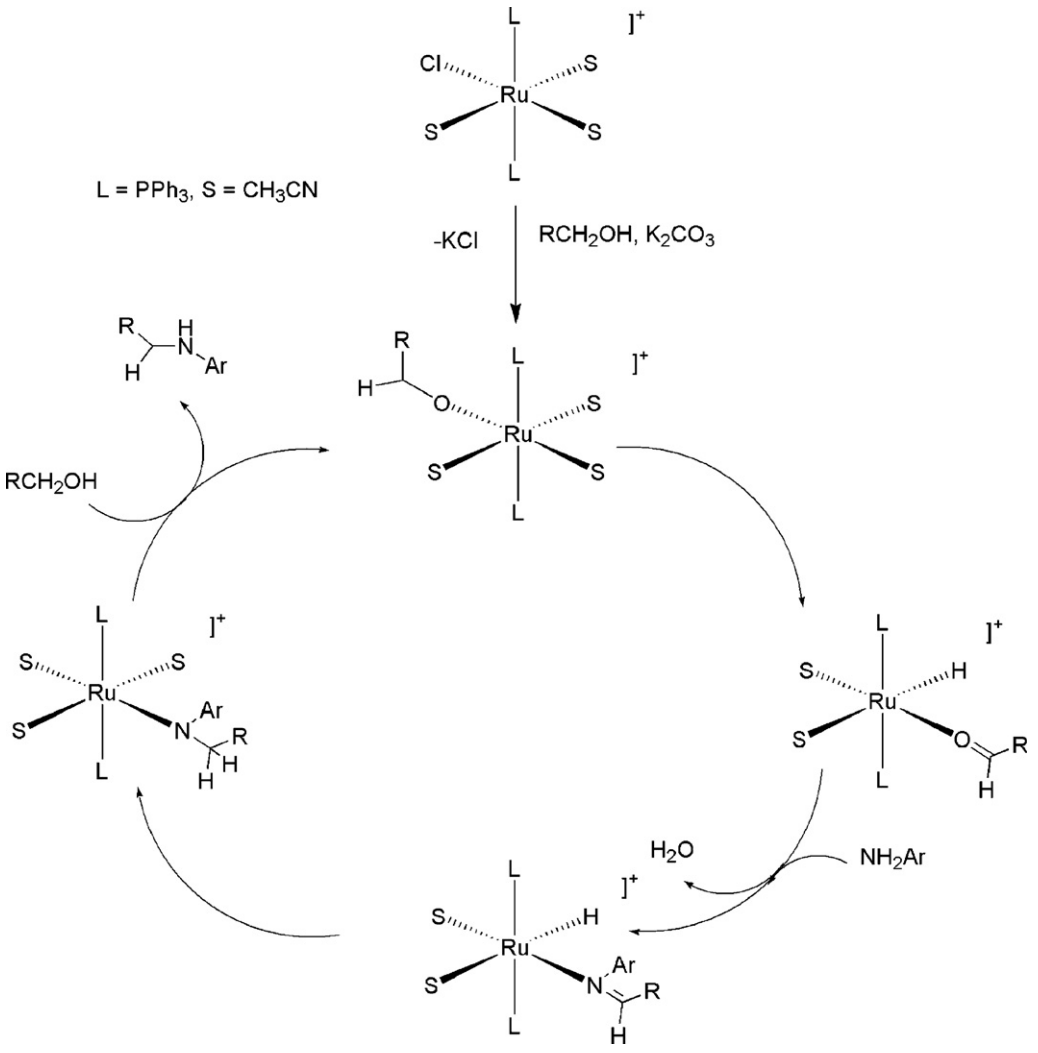
Thus, it is clear that, **1** is a selective catalyst for alkylation of anilines. The mechanism of the reaction is not clear at this stage. However, based on mechanistic work on the $[Ru(PPh_3)_3Cl_2]$ catalyzed alkylation of heteroaromatic amines[10] a possible reaction pathway is proposed and is shown in Scheme 4. The reaction may proceed through an imine intermediate, which is reduced to an amine.

We also carried out the reaction of methanol and benzyl alcohol with benzylidenephenyl amine catalyzed by **1** (Scheme 5) and isolated the corresponding amines in high yield. This observation suggests that, an imine is indeed a reaction intermediate.

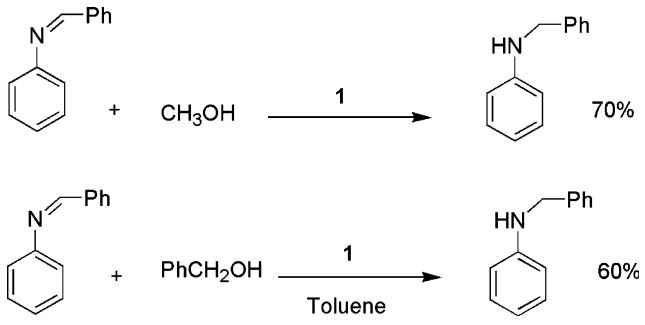
Watanabe et al. have reported that reaction of aniline and heteroaromatic amines with alcohols in the presence of $[Ru(PPh_3)_3Cl_2]$ gave dialkylated amines as the major products.[10] However, in our case, we only observed



Scheme 3.



Scheme 4.



Scheme 5.

monoalkylated products, except in the case of benzyl alcohol. Thus, the catalytic behavior of cationic complex **1** is different from that of the parent compound from which it is generated.[12]

In conclusion, the cationic ruthenium complex, $[RuCl(PPh_3)_2(CH_3CN)_3]^+[BPh_4]^-$ has been found to be an effective catalyst for selective reductive monoalkylation of aniline by primary alcohols.

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