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Ruthenium-catalyzed direct amination of alcohols with tertiary amines

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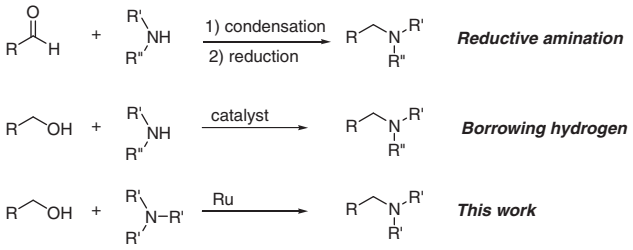
ABSTRACT

A highly selective phosphine-based ruthenium catalyst system efficiently catalyzes the direct amination of alcohols with aliphatic tertiary amines, yielding unsymmetric tertiary amines in yields up to 87%. Ligand and solvent both affect the reaction yields significantly. The reaction can be performed with a wide variety of functionalities.

Amines are of great importance as building blocks for pharmaceuticals, agrochemicals, dyes, ligands, and material chemistry.[1] Thus, the development of versatile and efficient methods for the synthesis of amines has attracted much attention.[2] The best-known reaction for the alkylation of amines is the nucleophilic substitution reaction of amines with haloalkanes, although this procedure can be problematic due to overalkylation and the toxic nature of many alkyl halides and related alkylating reagent.[3] The reductive amination of ketones and aldehydes with primary and secondary amines has been used as a useful tool for N-alkylation of amines. The process generally proceeds in two tandem steps, condensation between carbonyl compounds and amines to generate an imine intermediate and reduction of the imine by a reducing agent (Scheme 1).[4] Using this method, secondary and tertiary amines can be selectively synthesized from primary and secondary amines, respectively.

Alcohols are cheap and readily available organic compounds and can be readily oxidized to aldehydes and ketones.[5] The use of alcohols as starting materials to form C–N bonds is, therefore, potentially atom economical and less hazardous. The alkylation of amines by alcohols under harsh conditions was reported independently by Grigg and Watanable in the early 1980s.[6] In recent years, milder conditions have been achieved by Yamaguchi and co-workers with $[Cp*IrCl_2]_2$ as catalyst[7] and by Beller and co-workers using $Ru_3(CO)_{12}$ together with bulky phosphines.[8] Williams and co-workers developed an efficient $[Ru(p\text{-cymene})Cl_2]_2$/phosphine catalyst system and realized the alkylation of amines and sulfonamides with alcohols under mild reaction conditions.[9] In recent years, various amines,[10] imines[11] and even amides[12] can be selectively synthesized from alcohols and primary amines, secondary amines, and even ammonium or ammonium salts in one-pot. In a typical process of secondary and tertiary amine synthesis, alcohol was oxidized to aldehyde or ketone which can be condensed with amine to form an imine intermediate which can be reduced by hydrogen which was released during alcohol oxidation step and no additional reducing agent is necessary. The overall process is termed as the 'borrowing hydrogen' methodology (Williams and co-workers) or 'hydrogen autotransfer' reaction (Yus and co- workers).[13,14] In sharp contrast to amination of alcohols with primary and secondary amines, little has known for that with tertiary amines.[15,16]



Scheme 1. Tertiary amine formation with amine.

Recently, we developed a ruthenium-catalyzed tertiary amine formation from nitroarenes and alcohols via borrowing hydrogen strategy.[17] During the optimization of reaction conditions, we observed a reaction occurred between alcohols and tertiary amines. This prompted us to investigate the reaction between alcohols and tertiary amines systematically. *Herein, we report an unprecedented*

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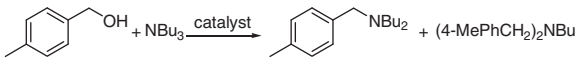
ruthenium-catalyzed direct amination of alcohols with tertiary amines.

To begin our study, the reaction of commercially available *p*-methylbenzyl alcohol (**1a**) and tributylamine (**2a**) was chosen as a model using $RuCl_3{\cdot}3H_2O$ as a catalyst in chlorobenzene at 145 °C. When **2a** was reacted with 3 equiv of **1a** in the absence of any ligand, 35% of desired product was formed as determined by GC–MS and ^1H NMR methods (Table 1, entry 1). Subsequently, various ligands were investigated for this reaction under an atmosphere of argon (entries 2–8). Moderate yields were obtained when dppp [1,3-bis(diphenylphosphino)propane] and dppb [1,4-bis(diphenylphosphino)butane] were used as ligands. The yields increased when PPh_3 and dppe [1,2-bis(diphenylphosphino)ethane] were used. The best yield was obtained when dppf [1,1′-bis(diphenylphosphino)ferrocene] was used as the ligand, and the desired product was achieved in 92% yield along with 7% bis-alkylated byproduct (entry 6). PCy_3HBF_4 is also efficient for this tranformation. However, only a trace amount of the product was found when binap [(1,2-bis(diphenylphosphino)-1,1′-binaphthyl)] was used as a ligand. Other ruthenium complexes were also investigated by using dppf as the ligand and lower yields were obtained (entries 9–12). The solvent effect on the reaction was also investigated (entries 13–16). Lower yield was achieved when the reaction was carried out in other solvents. Almost no desired product was obtained when DMF and DMSO were used as solvents. Interestingly, the bis-alkylated product was the major product when the reaction was run in no solvent and only 2% of the desired product was observed (entry 17). Decreasing the reaction temperature decreased the product yield (entry 18). The desired product was obtained in 73% yield by using 2 equiv of alcohol (entry 19).

With the optimized conditions in hand, the scope of the reaction with respect to tertiary amines and alcohols was investigated (Table 2). The nature of the alcohol and amine has great influence on the results. Benzyl alcohol and 4-methoxybenzyl alcohol reacted with tributylamine and gave the desired products in 81% and 78% yield, respectively (entries 2 and 3). Halogen-substituted benzyl alcohols reacted smoothly with tribuylamine to give the corresponding products in good yields (entries 4–6). Only a trace amount of the product was observed when 4-nitrobenzyl alcohol was used (entry 7). *Ortho*-substituted benzyl alcohols gave slightly lower yields (entries 8 and 9). Similar result was obtained when 3-methylbenzyl alcohol was used (entry 10). Good yields were obtained when 1-naphthalenemethanol and 2-furanmethanol reacted with tributylamine (entries 11 and 12). To our delight, besides benzyl alcohol and its derivatives, simple aliphatic alcohols also turned out to be good substrates for this transformation. The length of chain affected the selectivity significantly. When 1-dodecanol was used as substrate, the mono-substituented product was the major product (entry 13). However, 1-octanol and 1-hexanol reacted with tributylamine and gave the bis-substituented amines as the major products in moderate yields (entries 14 and 15). Unfortunately, attempts to react secondary alcohols with tertiary amines were unsuccessful.[18]

Table 1
Optimization of reaction conditions[a]

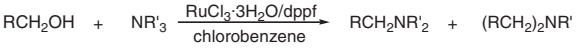


1a **2a** **3a** **4a**

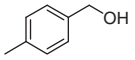
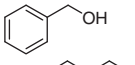
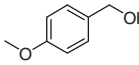
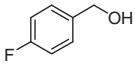
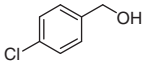
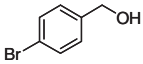
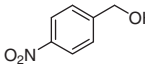
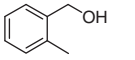
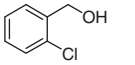
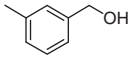
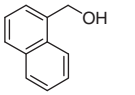
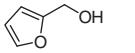
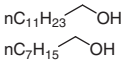
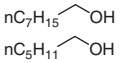
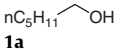
Entry	Catalyst	Ligand	Solvent	Yield[b] (%)	
				3a	**4a**
1	$RuCl_3{\cdot}3H_2O$	None	PhCl	35	Trace
2	$RuCl_3{\cdot}3H_2O$	dppp	PhCl	47	Trace
3	$RuCl_3{\cdot}3H_2O$	dppb	PhCl	52	Trace
4	$RuCl_3{\cdot}3H_2O$	PPh_3	PhCl	71	3
5	$RuCl_3{\cdot}3H_2O$	dppe	PhCl	70	2
6	**$RuCl_3{\cdot}3H_2O$**	**dppf**	**PhCl**	**92**	**7**
7	$RuCl_3{\cdot}3H_2O$	PCy_3HBF_4	PhCl	86	10
8	$RuCl_3{\cdot}3H_2O$	BINAP	PhCl	Trace	0
9	$[Ru(p\text{-cymene})Cl_2]_2$	dppf	PhCl	70	5
10	$[RuCl_2(COD)]n$	dppf	PhCl	35	0
11	$Ru(acac)_3$	dppf	PhCl	73	4
12	$Ru(CO)(H)_2(PPh_3)_3$	dppf	PhCl	Trace	0
13	$RuCl_3{\cdot}3H_2O$	dppf	Xylene	85	9
14	$RuCl_3{\cdot}3H_2O$	dppf	DMF	Trace	0
15	$RuCl_3{\cdot}3H_2O$	dppf	DMSO	Trace	0
16	$RuCl_3{\cdot}3H_2O$	dppf	NMP	32	0
17	**$RuCl_3{\cdot}3H_2O$**	**dppf**	**None**	**2**	**85**
18[c]	$RuCl_3{\cdot}3H_2O$	dppf	PhCl	49	4
19[d]	$RuCl_3{\cdot}3H_2O$	dppf	PhCl	73	Trace

[a] Conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), catalyst (0.01 mmol), ligand (0.01 mmol), solvent (0.8 mL), 145 °C, 15 h under argon.
[b] GC yields based on tributyamine.
[c] Reaction was carried out at 130 °C.
[d] 2 equiv of **1a** was used.

Table 2
Amination of alcohols with tertiary amines[a]



1 **2** **3** **4**

Entry	Alcohol(**1**)		Amine(**2**)	Yield[b] (%)	
				3	**4**
1		**1a**	NBu_3	84	7
2		**1b**	NBu_3	81	9
3		**1c**	NBu_3	78	3
4		**1d**	NBu_3	87	9
5		**1e**	NBu_3	76	Trace
6		**1f**	NBu_3	64	7
7		**1g**	NBu_3	10	Trace
8		**1h**	NBu_3	58	3
9		**1i**	NBu_3	75	2
10		**1j**	NBu_3	61	4
11		**1k**	NBu_3	63	Trace
12		**1l**	NBu_3	68	7
13		**1m**	NBu_3	45	Trace
14		**1n**	NBu_3	9	56
15		**1o**	NBu_3	11	62
16	**1a**		$N(nC_6H_{17})_3$	74	4
17	**1a**		$N(nC_6H_{13})_3$	70	3
18	**1a**		NPr_3	52	11
19	**1a**		$N(CH_2Ph)_3$	Trace	Trace
20	**1a**		**3a**		76

[a] Conditions: **1** (0.6 mmol), amine (0.2 mmol), $RuCl_3{\cdot}3H_2O$ (0.01 mmol), dppf (0.01 mmol), PhCl (0.8 mL), 145 °C, 15 h under argon.
[b] Isolated yields for the major products and GC yields for the minor products based on amines.