

Ruthenium-Catalyzed Tertiary Amine Formation from Nitroarenes and Alcohols

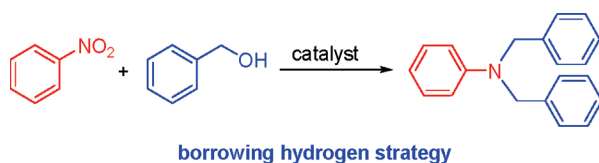
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ABSTRACT



A highly selective ruthenium-catalyzed C–N bond formation was developed by using the hydrogen-borrowing strategy. Various tertiary amines were obtained efficiently from nitroarenes and primary alcohols. The reaction tolerates a wide range of functionalities. A tentative mechanism was proposed for this direct amination reaction of alcohols with nitroarenes.

Nitrogen-containing compounds are of great importance as building blocks for pharmaceuticals, agrochemicals, dyes, and ligands.¹ Much effort has been paid on the development of methods for the synthesis of the C–N bonds.² Traditional routes to C–N bond formations, e.g., amide synthesis, require functionalized substrates such as carboxylic acids and amines as well as stoichiometric amounts of activating reagents.^{3,4} Transition-metal-catalyzed amination of aryl halides and pseudohalides has proven to be an efficient method for the construction of C–N bonds, especially for amine prepara-

tion.⁵ Various efficient catalysts for such transformations have been reported.⁶ Direct amination of C–H bonds has also been realized by transition-metal catalysis.⁷

Alcohols are cheap and readily available organic compounds, and alcohol oxidation is a key step in the preparation of many pharmaceutical agents and fine chemicals.⁸ The use of alcohols as starting materials to form C–C and C–N bonds is highly attractive, and great progress has been made

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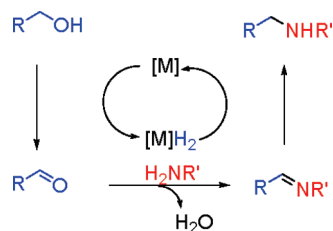
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on the subject during the past three decades. The alkylation of amines by alcohols under harsh conditions was reported independently by Grigg and Watanabe in the early 1980s.⁹ In recent years, milder conditions have been achieved by Yamaguchi and co-workers with Cp*IrCl₂ as catalyst¹⁰ and by Beller et al. using Ru₃(CO)₁₂ together with bulky phosphines.¹¹ Williams et al. developed an efficient [Ru-(*p*-cymene)Cl₂]₂/phosphine catalyst system and realized the alkylation of amines and sulfonamides with alcohols under mild reaction conditions.¹² The first step in these reactions is the dehydrogenation of alcohols to their corresponding aldehydes with the release of dihydrogen (Scheme 1).¹³

Scheme 1. Borrowing Hydrogen Strategy in the Alkylation of Amines with Alcohols



Subsequently, the aldehyde reacts with amines to form imines,¹⁴ which could be reduced to secondary amines. The latter step is known as a borrowing hydrogen methodology, and no external molecular hydrogen is necessary.¹⁵ The metal acts as both an alcohol oxidation catalyst and an imine hydrogenation catalyst. The borrowing hydrogen methodology has been used in the synthesis of primary amines,

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secondary amines, tertiary amines, and *N*-alkylated sulfonamides in high yields under mild conditions.¹⁶ On the other hand, Milstein et al. developed a ruthenium-catalyzed dehydrogenative amide formation from alcohols and primary amines with the liberation of H₂ without using a hydrogen acceptor.¹⁷

Nitroarenes are readily available compounds and can be reduced to amines by reducing reagents such as iron or zinc in aq HCl.¹⁸ Using hydrogen as a reducing reagent is greener and more economical; however, selective reduction of nitro groups is still a challenging problem.¹⁹ The direct amination of nitroarenes with alcohols is rare compared with the great breakthroughs being made in the amination of amines with alcohols.²⁰ We envisioned a direct amination of nitroarenes with alcohols by using a hydrogen-borrowing strategy: alcohol is oxidized to aldehyde and releases hydrogen, nitroarene is reduced by hydrogen, and subsequently the reaction follows the same route as alkylation of amines. *Herein, we report a highly selective ruthenium-catalyzed direct amination of nitroarenes with alcohols* (Figure 1).

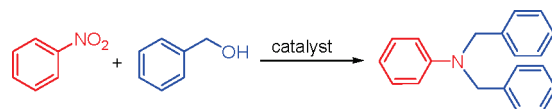


Figure 1. Forming tertiary amines via borrowing hydrogen strategy.

To begin our study, the reaction of commercially available and inexpensive nitrobenzene (**1a**) and benzyl alcohol (**2a**) was chosen as a model using RuCl₃ as a catalyst. When nitrobenzene was reacted with excess benzyl alcohol in the absence of any ligand, no 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).

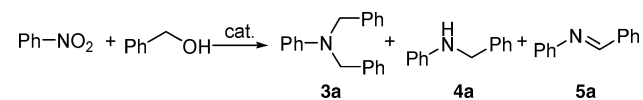
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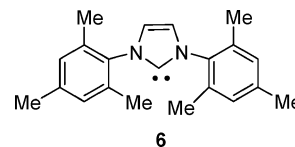
Table 1. Reaction of Nitrobenzene (**1a**) and Benzyl Alcohol (**2a**) under Various Conditions^a

entry	Ru catalyst	ligand (mol %)	yield ^b (%)		
			3a	4a	5a
1	RuCl ₃		n.d.	n.d.	n.d.
2	RuCl ₃	PPh ₃ (15.0)	7	n.d.	n.d.
3	RuCl ₃	dppp (7.5)	n.d.	n.d.	n.d.
4	RuCl ₃	dppb (7.5)	n.d.	n.d.	n.d.
5	RuCl ₃	dppe (7.5)	n.d.	n.d.	n.d.
6	RuCl ₃	dppf (7.5)	n.d.	n.d.	5
7	RuCl ₃	binap (7.5)	19	41	n.d.
8	RuCl ₃	phen (7.5)	n.d.	n.d.	n.d.
9	RuCl ₃	NHC (7.5)	47	3	n.d.
10	Ru(acac) ₃	NHC (7.5)	56	21	3
11	[Ru(<i>p</i> -cymene)Cl ₂] ₂	NHC (7.5)	48	2	2
12	[RuCl ₂ (COD)] _n	NHC (7.5)	61	2	1
13	RuCl ₂ (PPh ₃) ₃	NHC (7.5)	48	1	n.d.
14	Ru(CO)(H)Cl(PPh ₃) ₃	NHC (7.5)	71	2	n.d.
15	Ru(CO)(H)₂(PPh₃)₃	NHC (7.5)	96	1	n.d.
16	Ru(CO)(H) ₂ (PPh ₃) ₃		44	24	n.d.
17	Ru(CO)(H) ₂ (PPh ₃) ₃	NHC (5.0)	77	1	n.d.
18 ^c	Ru(CO)(H) ₂ (PPh ₃) ₃	NHC (3.75)	40	25	n.d.
19 ^d	Ru(CO)(H) ₂ (PPh ₃) ₃	NHC (7.5)	67	2	n.d.
20 ^e	Ru(CO)(H) ₂ (PPh ₃) ₃	NHC (7.5)	4	32	n.d.
21 ^f	Ru(CO)(H) ₂ (PPh ₃) ₃	NHC (7.5)	18	5	32

^a Conditions: **1a** (0.2 mmol), **2a** (0.15 mL, 1.5 mmol), catalyst (0.01 mmol), 150 °C, 16 h under argon unless otherwise noted. ^b GC–MS yields based on nitrobenzene. In most cases, benzyl benzoate, dibenzyl ether, and benzaldehyde were observed. ^c 0.005 mmol of catalyst was used. ^d 130 °C. ^e In 0.5 mL of xylenes. ^f Two equiv of **2a** was used.

With PPh₃, the desired product, *N,N*-dibenzylaniline (**3a**), was obtained in 7% yield. A 19% yield was obtained with bidentate phosphine binap [(1,2-bis(diphenylphosphino)-1,1'-binaphthyl)] as a ligand (entry 7). However, only a trace amount of the desired product was observed using other bidentate phosphines such as dppe [1,2-bis(diphenylphosphino)ethane], dppp [1,3-bis(diphenylphosphino)propane], dppb [1,4-bis(diphenylphosphino)butane], and dppf [1,1'-bis(diphenylphosphino)ferrocene]. A nitrogen-containing ligand, 1,10-phenanthroline, was also investigated, and no product was observed under similar conditions (entry 8). To our delight, a moderate yield was obtained with a NHC ligand **6**, generated in situ from 1,3-dimesitylimidazolium chloride (entry 9). Then various ruthenium complexes were investigated in the presence of the NHC ligand (entries 10–15). Ru(acac)₃, [Ru(*p*-cymene)Cl₂]₂, and Ru(PPh₃)₃Cl₂ all catalyzed the reaction efficiently. The best result was obtained when Ru(CO)(H)₂(PPh₃)₃/NHC was used as catalyst, giving the desired product in 96% yield (entry 15). The presence of both NHC ligand and phosphine ligand is important for the reaction; the reaction yield decreased dramatically in the absence of either ligand (entries 12 and 16). The ratio of NHC/ruthenium also affected the reaction significantly, and a lower yield was obtained when the ratio

of NHC/ruthenium was decreased (entry 17). Decreasing the catalyst loading or the reaction temperature decreased the product yield (entries 18 and 19). The concentration of substrates is also important; only 4% yield was observed when xylenes was used as solvent (entry 20).²¹



With the optimized conditions in hand, the scope of the reaction with respect to nitrobenzene derivatives and alcohols was investigated (Tables 2 and 3). The substituent at different

Table 2. Reaction of Nitroarenes with Benzyl Alcohol^a

entry	nitroarene	product	yield (%) ^b
1			88
2			82
3			72
4			81
5			77
6			43
7			32
8			54
9			82
10			84
11			54
12			77

^a Conditions: **1** (0.2 mmol), **2a** (1.5 mmol), NHC (0.015 mmol), Ru(CO)(H)₂(PPh₃)₃ (0.01 mmol), 150 °C, 16 h in argon unless otherwise noted. ^b Isolated yield based on nitroarenes.

positions on the nitroarenes affected the reaction yield significantly. The yield decreased to 72% when 4-methoxy-nitrobenzene (**1c**) was used as a substrate (Table 2, entry 3).

Table 3. Reaction of Nitrobenzene with Alcohols^a

entry	alcohol	product	yield (%) ^b
1			91
2			67
3			74
4			90
5			40
6			40
7			67
8			68
9			54

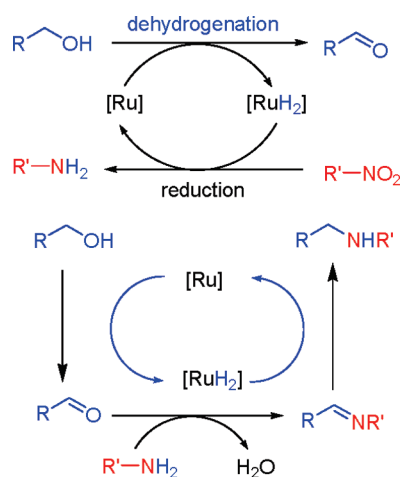
^a Conditions: **1a** (0.2 mmol), **2** (1.5 mmol), NHC (0.015 mmol), Ru(CO)(H)₂(PPh₃)₃ (0.01 mmol), 150 °C, 16 h in argon unless otherwise noted. ^b Isolated yields based on nitrobenzene.

The reaction tolerates the presence of halogens (entries 4–6); however, a lower yield was obtained when the substituent was changed from fluoride to bromide, partially due to the poor solubility of substrate. Nitroarene bearing an ester group at the para position reacted with benzyl alcohol to give the corresponding product in a moderate yield (entry 7). A methyl group para to the nitro group only slightly affected the product yield (entry 2); however, only a moderate yield was observed when the methyl group was at the ortho position (entry 8). Interestingly, a chloride group at the ortho position of the nitro group affected the reaction only slightly (entry 9). The influence of substituents at the meta position of the nitro was also investigated (entries 10–12). Good yields were obtained with 3-methylnitrobenzene and 3-chloronitrobenzene as substrates.

(21) In some cases, a large amount of benzaldehyde, dibenzyl ether, and/or benzyl benzoate was observed. For example, in Table 1, entry 15, benzaldehyde and benzyl benzoate were formed in 57% and 66% yields (based on nitrobenzene), respectively. When only 2 equiv of **2a** was used, tertiary amine, secondary amine **4a**, and imine **5a** were formed, with imine being a major product (entry 21).

Other alcohols were also investigated under similar conditions (Table 3). Alcohols with halogens reacted smoothly with nitrobenzene to give the corresponding products in good yields (entries 3 and 4). Again, a bromide substituent dramatically decreased the product yield, and only 40% yield was obtained when 4-bromobenzyl alcohol was used (entry 5). The substituent at the ortho position has a great impact on the reaction; a moderate yield was obtained when 2-chlorobenzyl alcohol or 2-methylbenzyl alcohol was used (entries 6 and 7). To our delight, besides benzyl alcohol and its derivatives, simple aliphatic alcohols also reacted with nitrobenzene to give the desired product in moderate yields (entries 8 and 9). However, attempts to react secondary alcohols with nitroarenes were unsuccessful.

In summary, we have developed a selective ruthenium-catalyzed tertiary amine formation reaction using nitroarenes and primary alcohols as starting materials via a hydrogen-borrowing strategy. The ruthenium catalyst plays a key role in this reaction. Excess alcohol is necessary to get satisfied reaction yields. The alcohol oxidation, nitro reduction and imine reduction were realized in a cascade. The reaction proceeded well for a range of different substrates. A tentative mechanism for this reaction was also proposed (Scheme 2).

Scheme 2. Tentative Mechanism for the Direct Amination of Nitroarenes

Further investigation including the scope, mechanism, and application of C–N bond formations from nitroarenes and alcohols are in progress in our laboratory.

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Supporting Information Available: General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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