



Phosphine ligand-free RuCl₃-catalyzed reductive N-alkylation of aryl nitro compounds



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ABSTRACT

Without using any additional ligands, RuCl₃ efficiently catalyses the reductive N-alkylation of aryl nitro compounds with alcohols using bio-based glycerol as the hydrogen source and without the need for any added solvents. The reaction can be easily manipulated to produce either imines or secondary amines in high yields. RuCl₃-catalyzed reductive N-alkylation of nitroarenes with alcohols affords the corresponding imine products in good to excellent yields. Under the same reaction conditions, the one-pot sequential reaction of nitroarenes with alcohols and glycerol also gives amines in higher yields.

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1. Introduction

N-substituted amines are an important class of compounds in the pharmaceutical and agrochemical industries.^{1–3} Reactions for their synthesis include alkylation of amines with alkyl halides,^{4–6} direct reductive amination of ketones and aldehydes^{7,8} and hydroamination of unsaturated hydrocarbons with amines.^{9–13} These methods generally require environmentally harmful organic solvents, alkyl halides and/or stoichiometric quantities of reducing agents. In recent decades, much attention has focused on the use of inexpensive and low toxicity alcohols as the alkylation reagent.^{14–27} The N-alkylation of anilines with alcohols using 'borrowing hydrogen (BH)' methodology,^{20,28–33} in which water is the only byproduct, is an environmentally benign method for preparing N-functionalized anilines. Catalysts based on Ru, Ir, Rh, Au, Ag, Cu, Fe, Ni, Os and Pd have been developed for this coupling reaction.^{34–37} However, aromatic amines are genotoxic and are therefore undesirable potential impurities in the product. Recently, the metal catalyzed synthesis of N-alkylated anilines using nitro compounds as the nitrogen source has attracted particular

attention because nitrobenzenes are inexpensive, stable and readily available.^{38–40} Some hydrogen transfer catalysts, particularly of Ru, have been screened for the synthesis of imines and secondary and tertiary amines from nitroarenes, using alcohols as the reducing and alkylation reagents. These methods involve toxic phosphine ligands and very excess alcohol. Deng and Li et al. reported the reaction of nitroarenes and primary alcohols could yield secondary and tertiary amines, which was catalyzed by [Ru(acac)₃]/dppe (dppe=1,2-bis(diphenylphosphino)ethane) or Ru(CO)(H)₂(PPh₃)₃/NHC (NHC=1,3-dimesitylimidazolium chloride).^{41,42} Shi and co-workers demonstrated the controllable synthesis of mono- and di-substituted amines from nitrobenzenes with alcohols using RuCl₃/PPh₃ or [{Ru(*p*-cymene)Cl₂]₂}/dppb (dppb=1,2-bis(diphenylphosphanyl)benzene).^{43,44} Liu and co-workers prepared secondary amines from nitroarenes and alcohols in the presence of (P–N)Ru(CO)₂Cl₂ (P–N=*o*-(diphenylphosphino)aniline) or (PNO)Ru(CO)₂Cl (PNO=2-(((2-(diphenylphosphanyl)phenyl)imino)methyl)phenol).^{45,46} Viswanathamurthi and co-workers found ruthenium(II) carbonyl complexes with phosphine-functionalized type thiosemicarbazone ligands such as [RuCl(CO)(PPh₃)(PNS–Me)] (PNS–Me=2-(2-(diphenylphosphino)benzylidene)-N-methylthiosemicarbazone) were efficient and versatile N-alkylation catalysts.⁴⁷ Zhang et al. reported the synthesis of quinolines from α -2-nitroaryl alcohols and alcohols using Ru₃(CO)₁₂/dppf as the catalyst or 2-nitroanilines and vicinal diols

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using $\text{Ru}_3(\text{CO})_{12}/\text{dpppp}$ as the catalyst.^{48,49} However, despite their versatility as ligands for stabilizing low valent metal transition states and intermediates, phosphines are often toxic, moisture and air sensitive and hard to separate from the organic products. Nano- $\text{Ru}/\text{Fe}_3\text{O}_4$ ⁵⁰ and $\text{Ru}(\text{OH})_3\text{-Fe}_3\text{O}_4$ ⁵¹ have been successfully employed as catalysts for the N-alkylation of amines, sulfonamides, sulfonamides, and nitroarenes using alcohols as the electrophile, which involve a large excess of alcohol. Very recently, Bera et al. have found that a hydroxy appendage substituted on the naphthyridine unit can promote the dehydrogenative coupling of alcohols with amines catalyzed by diruthenium complexes of naphthyridine-functionalized *N*-heterocyclic carbene (NHC) ligands.⁵² Can, therefore, the alcohol substrates themselves work as labile ligands to accelerate Ru-catalyzed coupling of nitroarenes and alcohols?

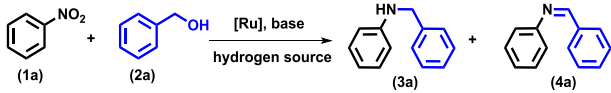
In general, excess alcohol is used in these reductive N-alkylations of aryl nitro compounds. The utilization of renewable biomass derivatives as the hydrogen source represents a more sustainable alternative.^{53–55} Among various possible biomass derived alcohols, glycerol is now a readily available and cheap resource and has received much attention as a green solvent and reagent. Glycerol can be converted to various fuel units and is used as a starting substrate for 'bio'-hydrogen production via aqueous-phase reforming. Glycerol has been utilized as an environmentally benign hydrogen source for the reduction of various functional groups such as benzaldehyde, acetophenone, nitroarenes and several unfunctionalized olefins.^{56–61} Herein, we present our findings of N-alkylation of nitro/imine compounds catalyzed by RuCl_3 , using renewable glycerol as the hydrogen source in the absence of any additional organic ligands and solvents.

2. Results and discussion

Our initial investigations focused on the N-alkylation reaction of commercially available and inexpensive nitrobenzene (**1a**) and benzyl alcohol (**2a**) using the borrowing hydrogen strategy (Table 1). When **1a** (1.0 mmol) was reacted with excess **2a** (3.0 mmol) in the presence of 3.0 mol% $\text{RuCl}_2(\text{PPh}_3)_3$ as catalyst and stoichiometric K_2CO_3 , none of the desired compound N-benzylaniline (**3a**) was formed, as determined by GC analysis. Instead, the compound 1-diphenylmethanimine (**4a**) was formed as the major product (98%) together with a large amount of benzaldehyde (Table 1, entry 1). This preliminary result implied that RuCl_3 could catalyze the formation of imine without extra organic ligands. Most importantly, it prompted us to suspect that the amine could also be obtained under suitably modified conditions. Subsequently, different ruthenium salts were investigated with this reaction under a nitrogen atmosphere (Table 1, entries 2–4). None of the desired product **3a** was observed when $\text{Ru}_3(\text{CO})_{12}$, $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ or $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ was used as the catalyst, but **4a** was obtained in moderate to excellent yields (49%–99%). Bases such as carbonates, hydroxides alkoxides and phosphates worked approximately equally well (Table 1, entries 5–10). Reaction with triethylamine (Table 1, entry 11) also provided **4a**, but in a reduced yield under these conditions. Increasing the amount of benzyl alcohol did not increase reduction of imine to amine (Table 1, entry 12). However, less than three equivalents of benzyl alcohol decreased the yield of imine **4a**, approximately proportionately (entries 13–15).

Since excess benzyl alcohol could not further reduce imine to amine in our catalytic system, we wondered if an additional

Table 1
Optimizing the reaction conditions for the synthesis of amine and imine



Entry ^a	Cat.	1a/2a (mol/mol)	Additive	Base	Yield of 3a (%) ^c	Yield of 4a (%) ^c
1	$\text{RuCl}_2(\text{PPh}_3)_3$	1/3		K_2CO_3	—	98
2	$\text{Ru}_3(\text{CO})_{12}$	1/3		K_2CO_3	Trace	49
3	$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	1/3		K_2CO_3	Trace	71
4	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3		K_2CO_3	—	99
5	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3		NaOH	Trace	92
6	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3		KOH	Trace	90
7	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3		K_3PO_4	Trace	82
8	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3		Cs_2CO_3	—	98
9	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3		^t BuOK	—	98
10	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3		EtONa	Trace	87
11	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3		Et_3N	Trace	62
12	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/10		K_2CO_3	—	99
13	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/2		K_2CO_3	Trace	82
14	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/1.5		K_2CO_3	Trace	63
15	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/1		K_2CO_3	Trace	45
16	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	K_2CO_3	84	Trace
17	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	2-Propanol	K_2CO_3	Trace	Trace
18	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Pinacol	K_2CO_3	Trace	Trace
19	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	NaOH	32	67
20	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	KOH	30	69
21	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	^t BuOK	81	Trace
22	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	EtONa	53	38
23	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	K_3PO_4	6	87
24	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	Cs_2CO_3	69	Trace
25	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	Et_3N	3	89
26 ^b	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/3	Glycerol	K_2CO_3	85	Trace
27	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/2	Glycerol	K_2CO_3	83	Trace
28	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/1.5	Glycerol	K_2CO_3	84	Trace
29	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/1.2	Glycerol	K_2CO_3	61	Trace
30	$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	1/1	Glycerol	K_2CO_3	45	1

^a Reaction conditions: 1.0 mmol nitrobenzene, benzyl alcohol, 3 mol% catalyst, 1.0 mmol base, 10 mmol additive, under nitrogen atmosphere, at 130 °C, for 24 h.

^b At 150 °C.

^c GC yield.

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