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Letter

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Reductive N-Alkylation of Nitro Compounds to *N*-Alkyl and *N,N*-Dialkyl Amines with Glycerol as the Hydrogen Source

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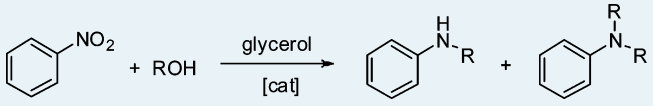
Supporting Information

ABSTRACT: As the sustainable and promising hydrogen source, here, glycerol was directly used as the hydrogen source for the reductive amination of alcohol using nitrobenzene as the starting material. The amination of alcohols, especially aliphatic alcohols with different structures, was realized, and mono- or disubstituted amines were synthesized with excellent yields. The reaction mechanism was also explored.



KEYWORDS: *amines, alcohols, N-alkylation, glycerol, renewable, catalysis*

Renewable biomass has gained extensive attention because of the derivation of fuels and chemicals from petroleum is facing tremendous challenges for environmental and economic sustainability.[1] In recent years, much progress has been made in using biomass as carbon sources for fuel and chemical production. Ethylene, ethanol, glycol, glycerol, and furan derivatives are typical biobased feedstock.[2,3] Moreover, biomass or biobased feedstock is also a renewable source for the generation of CO and H_2 through catalytic cracking or reforming.[4−7] As a successful example, recently, hydrogen generation from glycerol was reported.[7−14] That means biobased feedstock could be a potential hydrogen source, and it would be ideal if biobased feedstock could be directly used as a reducing agent in the synthesis of fine chemicals without thermal cracking. In this way, the carbon dioxide fixation in nature and the synthesis of fine chemicals in industry could be put into one carbon cycle and a balance realized. However, until now, reports about synthesis of fine chemicals using biobased feedstock as the hydrogen source have been few.[15,16]

Carbon−nitrogen bonds are one of the key motifs in medicinal agents and natural products.[17,18] N-substituted amines are usually prepared by the alkylation of amines with alkyl halides.[19,20] In many cases, N-substituted amines could also be synthesized by hydroamination,[21−23] hydroaminomethylation,[24,25] and self-coupling of primary amine.[26−28] In recent decades, many efforts have been focused on the applying of alcohol as the alkylation reagent because of its intrinsic advantages, such as easy availability, inexpensiveness, and low toxicity. So far, metal complexes based on ruthenium, iridium, rhodium, gold, copper, and iron have been studied as catalysts for the coupling reaction of amines and alcohols with excellent performance.[29−44] Recently, it was shown that N-alkylated amines could be synthesized using nitrobenzenes and alcohols as starting materials.[45−50] In this process, except for its role as an alkylation reagent, alcohol was employed as the hydrogen source to reduce nitrobenzene. Thus, a large excess of alcohol was needed, in which the ratio of alcohol to nitrobenzene is in the range of 6:1 to 10:1. It would be a good choice if the coupling reaction could be realized with an equivalent amount of nitrobenzene and alcohol. According to the sustainability perspective, the incorporation of biomass-based feedstock as the hydrogen source for this important transformation should be the ideal way. On the basis of our effort in the clean and economic synthesis of N-substituted amine using primary amine, nitrobenzene, and benzonitrile as starting materials and alcohol as the reducing and alkylation reagent,[49,51−54] we tried to develop a method for a one-pot synthesis of N-substituted amines from nitrobenzene with feedstock glycerol as the hydrogen source. This system showed better generality than our former report using a Au/Ag−Mo catalyst.[55]

First, the catalytic activity of $RuCl_3/PPh_3$ was tested in the presence of different solvents with K_2CO_3 as the cocatalyst (Tables 1 and 2). Clearly, the solvent, ligand, and base have a strong influence on the catalytic efficiency (entries 1−7). The conversion was <50% in the absence of solvent, ligand, or base. A >95% conversion and selectivity of *N*-benzyl aniline was obtained if using (trifluoromethyl)benzene (TFMB) as solvent, possibly because of its suitable polarity and boiling point. Further on, the activities of different ruthenium complexes were tested, but poor activity was observed (entries 8−10). The conversion was 26−62% with 35−77% selectivities when $[Ru(p\text{-cymene})Cl_2]_2$, $[Ru(benzene)Cl_2]_2$, and $Ru_3(CO)_{12}$ were employed, although they were reported to be active catalysts in N-substituted amine synthesis using alcohol or amine as alkylation reagents.[33,40] Then, P- or N-containing ligands with different structures were explored (entries 11−16). P-Containing ligands exhibited better catalytic performance than N-containing ligands and PPh_3. The application of other bases, such as KO-*t*-Bu, Na_2CO_3, and KOH resulted in lower nitrobenzene conversion, but >90% selectivity was maintained

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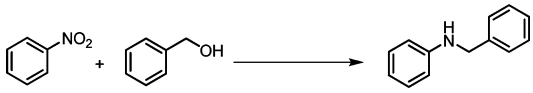
Table 1. Catalyst Screening and Reaction Conditions Optimization[a]



entry	catalyst	solvent	ligand	conversion (%)[b]	selectivity (%)[b]
1	$RuCl_3$		PPh_3	50	88
2	$RuCl_3$	TFMB		50	35
3[c]	$RuCl_3$	TFMB	PPh_3	17	24
4	$RuCl_3$	TFMB	PPh_3	95	96
5	$RuCl_3$	THF	PPh_3	16	52
6	$RuCl_3$	toluene	PPh_3	85	65
7	$RuCl_3$	dioxane	PPh_3	24	56
8	$[Ru(p\text{-cymene})Cl_2]_2$	TFMB	PPh_3	26	35
9	$[Ru(benzene)Cl_2]_2$	TFMB	PPh_3	56	77
10	$Ru_3(CO)_{12}$	TFMB	PPh_3	62	56
11	$RuCl_3$	TFMB	DPPE	76	48
12	$RuCl_3$	TFMB	DPPP	70	86
13	$RuCl_3$	TFMB	DPPB	100	44
14	$RuCl_3$	TFMB	BPy	15	6
15	$RuCl_3$	TFMB	TMEDA	56	37
16	$RuCl_3$	TFMB	Phen	37	25
17[d]	$RuCl_3$	TFMB	PPh_3	62	93
18[e]	$RuCl_3$	TFMB	PPh_3	70	96
19[f]	$RuCl_3$	TFMB	PPh_3	79	91

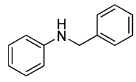
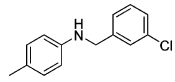
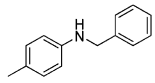
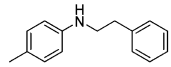
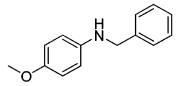
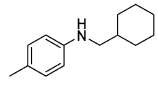
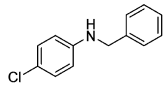
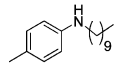
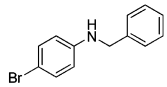
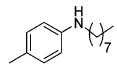
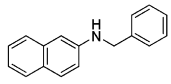
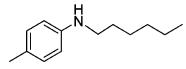
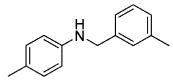
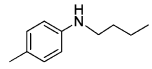
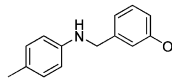
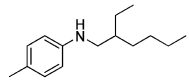
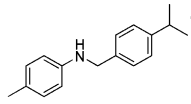
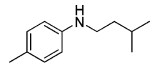
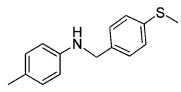
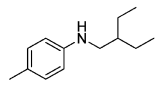
[a]1.0 mmol nitrobenzene, 1.0 mmol benzylalcohol, 1.5 g glycerol, 0.5 mL solvent, 2.5 mol % Ru, 10% mmol ligand, 10 mol % K_2CO_3, 130 °C, Ar, 24 h. TFMB = (trifluormethyl)benzene. THF = tetrahydrofuran. PPh_3 = triphenylphosphine. DPPE = ethylene bis-(diphenylphosphine). DPPP = 1,3-bis(diphenylphosphino)propane. DPPB = 1,4-bis(diphenyl phosphino)butane. BPy = 2,2′-bipyridine. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. Phen=1,10-phenanthroline. [b]By GC/MS. [c]Base -free. [d]10 mol % KO-*t*-Bu. [e]10 mol % Na_2CO_3. [f]10 mol % KOH.

(entries 17−19). The major byproducts in the above reactions were all imine intermediates. If less glycerol was employed (10 equiv), the conversion of the nitrobenzene was 85% and selectivity to the corresponding product was decreased to 57%. Therefore, except for its role as a reducing agent, glycerol may behave as a cosolvent to promote the transfer hydrogenation reaction.

In the reductive coupling reaction of nitrobenzenes with 1 equiv of alcohols, the formation of a trace amount of tertiary amines was also detectable. This result inspired us to try a one-pot synthesis of N,N-disubstituted amines from nitrobenzenes with 2 equiv of alcohols. The results for the one-pot synthesis of N,N-disubstituted amines are given in Table 3. By simply increasing the reaction temperature to 150 °C, good to excellent results were achieved, entries 1−8. The structure and the position of the functional groups did not affect the catalytic activity significantly, and the yields of the desired products were ∼80%. The applying of aliphatic alcohols in the coupling reactions gave 80−90% isolated yields, no matter whether linear or branched alcohols were used (entries 9−16).

The exploration of the reaction mechanism should be interesting. By tracing the coupling reaction of *p*-methylnitrobenzene and benzyl alcohol by GC/MS, *p*-toluidine was observed at the initial stage, and then imine was detectable. Subsequently, both *p*-toluidine and imine were transformed

Table 2. Results for Synthesis of N-Substituted Amines from Different Nitrobenzenes and Alcohols[a]

Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1		86	11		80
2		91 (85[c])	12		90
3		88	13		87
4		81	14		84
5		83	15		83
6		76[d]	16		78
7		86	17		70
8		93	18		88
9		92	19		76
10		86	20		85

[a]Nitrobenzene (1.0 mmol), alcohol (1.0 mmol), glycerol (1.5 g), TFMB (0.5 mL), $RuCl_3$ (2.5 mol %), PPh_3 (10 mol %), K_2CO_3 (10 mol %), 130 °C, Ar, 24 h. [b]Isolated yields. [c]Glycerol with 95% purity was used. [d]140 °C, 24 h.

into the N-substituted aniline (Scheme 1). To check the oxidation product of glycerol, ^1H NMR and LC/MS characterizations were performed. According to ^1H NMR characterization, the signals at 10.05 ppm for benzaldehyde and at 9.64 ppm for glycerol aldehyde could be observed. On the basis of LC/MS characterization, the oxidation product of glycerol could be observed, that is, glyceraldehyde, too ($[glyceraldehyde{\cdot}Cl]^-$, m/z = 125.1). Therefore the oxidation product of glycerol occurred on the terminal hydroxyl group, and a portion of the alcohol was oxidized into the corresponding aldehyde. Next, the *p*-toluidine reacts with the aldehyde to generate *N*-benzylidene-4-methylaniline, and *N*-alkyl amine was produced through the reduction of *N*-benzylidene-4-methylaniline by glycerol because there was no alcohol left at this moment. To test this assumption, *N*-benzylidene-4-methylaniline was used as the starting material, and 90% *N*-alkyl amine was obtained under the same reaction conditions. Interestingly, the in situ-generated glycerol aldehyde did not react with aniline, possibly because of its specific structure.

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Table 3. Results for Synthesis of N,N-Disubstituted Amines from Nitrobenzenes and Alcohols[a]

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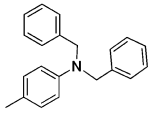
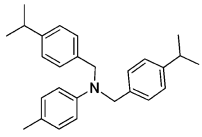
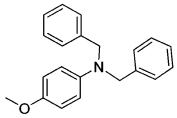
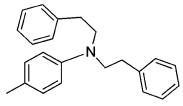
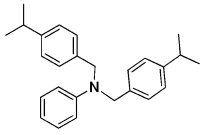
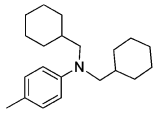
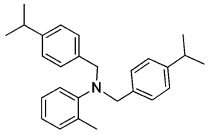
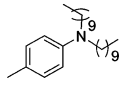
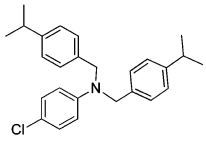
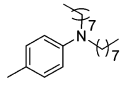
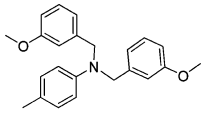
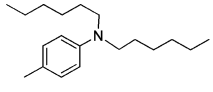
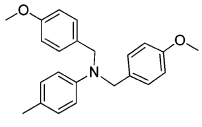
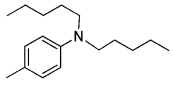
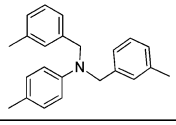
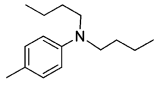
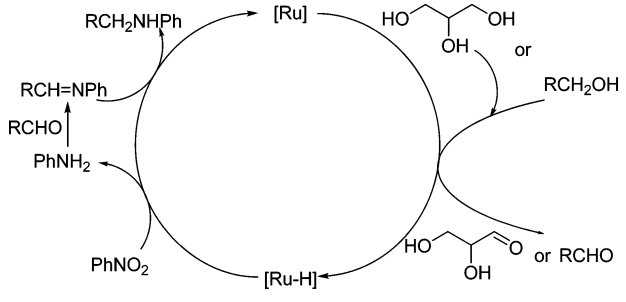
1		85	9		81
2		86	10		82
3		75	11		89
4		81	12		77
5		69	13		87
6		83	14		90
7		87	15		81
8		79	16		86

[a]Nitrobenzene (1.0 mmol), alcohol (2.0 mmol), glycerol (1.5 g), solvent (0.5 mL), Ru (2.5 mol %), ligand (10 mol %), K_2CO_3 (10 mol %), 150 °C, Ar, 24 h. [b]Isolated yields.

Scheme 1. A Possible Mechanism for the N-Alkylation Reactions



The one-pot synthesis of mono- and disubstituted amines from nitrobenzenes with an equivalent amount of alcohols was realized successfully using glycerol as the reducing agent. To the best of our knowledge, this is the first demonstration of the controllable synthesis of mono- and disubstituted amines from nitrobenzenes without the addition of an excess amount of alcohol. It offers an economic and clean method for a one-pot synthesis of amines from nitrobenzenes.

■ ASSOCIATED CONTENT

Supporting Information

Reaction procedures and characterization results of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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