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VIP

Development of a General Non-Noble Metal Catalyst for the Benign Amination of Alcohols with Amines and Ammonia

Xinjiang Cui,[a, b] Xingchao Dai,[a, b] Youquan Deng,[a] and Feng Shi*[a]

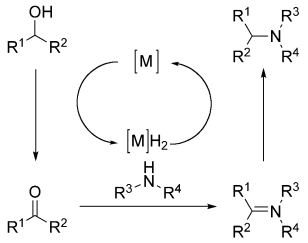
Abstract: The N-alkylation of amines or ammonia with alcohols is a valuable route for the synthesis of N-alkyl amines. However, as a potentially clean and economic choice for N-alkyl amine synthesis, non-noble metal catalysts with high activity and good selectivity are rarely reported. Normally, they are severely limited due to low activity and poor generality. Herein, a simple NiCu-FeO_x catalyst was designed and prepared for the N-alkylation of ammonia or amines with alcohol or primary amines. N-alkyl amines with various structures were successfully synthesized in moderate to excellent yields in the absence of organic ligands and bases. Typically, primary amines could be efficiently transformed into secondary amines and N-heterocyclic compounds, and secondary amines could be N-alkylated to synthesize tertiary amines. Note that primary and secondary amines could be produced through a one-pot reaction of ammonia and alcohols. In addition to excellent catalytic performance, the catalyst itself possesses outstanding superiority, that is, it is air and moisture stable. Moreover, the magnetic property of this catalyst makes it easily separable from the reaction mixture and it could be recovered and reused for several runs without obvious deactivation.

Keywords: alcohols · amination · ammonia · heterogeneous catalysis · non-noble metals

Introduction

N-alkyl amines are extensively applied in the syntheses of functional materials, pharmaceuticals, and pesticides.[1] Generally, N-alkyl amines are produced through the reaction of amines with alkyl halides with the addition of stoichiometric amounts of inorganic bases or by applying reductive amination reactions of aldehydes or ketones.[1b] These processes often suffer from drawbacks, such as generation of inorganic salts and the use of unstable and expensive carbonyl compounds. Besides the known routes for N-alkyl amine synthesis mentioned above, modern transition-metal-catalyzed processes, that is, reaction of amines with amines,[2] hydroaminations,[3] and hydroaminomethylations,[4] were realized and elegant results were obtained.

In recent decades, the coupling reaction of amines with alcohols has been examined as a potentially clean and economic route for the synthesis of N-alkyl amines by using a borrowing-hydrogen methodology (Scheme 1).[5] In this reaction, theoretically, water is produced as the sole byproduct and alcohols are readily available, inexpensive, and nontoxic. Initially, this transformation was realized in the presence of homogeneous metal catalysts, such as ruthenium-,[2g,6] iridium-,[7] palladium-,[8] rhodium-,[9] copper-,[10] or iron-based[11] complexes and excellent results were obtained. To build a simple and easily reusable catalyst system for the N-alkylation of amines with alcohols to produce N-substituted amines, many heterogeneous catalysts have been explored recently. Since 2009, ruthenium-,[12] palladium-,[13] platinum-,[14] gold-,[15] silver-,[16] nickel-,[17] manganese-,[18] copper-,[19] and iron-based[20] heterogeneous catalysts have been studied extensively. However, in comparison with the homogeneous catalysts, the development of heterogeneous catalyst, especially heterogeneous non-noble metal catalyst, has to date been severely limited due to poor generality or specific catalytic activity for specific reactions. Therefore, one of the major tasks for catalyst researchers is to develop active and general heterogeneous non-noble metal catalysts for the N-alkylation of amines with alcohols.



Scheme 1. Alcohol amination by using the borrowing-hydrogen mechanism.

[a] X. Cui, X. Dai, Prof. Dr. Y. Deng, Dr. F. Shi
Centre for Green Chemistry and Catalysis
Lanzhou Institute of Chemical Physics
Chinese Academy of Sciences
No. 18, Middle Tianshui Road
Lanzhou, 730000 (P. R. China)
Fax: (+86) 931-8277088
E-mail: fshi@licp.cas.cn

[b] X. Cui, X. Dai
University of Chinese Academy of Sciences
Beijing, 100049 (P. R. China)

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As discussed above, nickel and copper have been used as heterogeneous catalysts in N-alkyl amine synthesis in coupling reactions of amines and alcohols.[17,19] Unfortunately, only moderate results were obtained and some of the reaction conditions were rigorous. However, as known for a long time, nickel is an excellent catalyst in the catalytic activation of molecular hydrogen to generate nickel hydride[21] and copper is a potential catalyst for borrowing-hydrogen reactions.[10] Inspired by these interesting results, we speculated that the combination of nickel and copper into one catalyst with a suitable method might generate an active catalyst for the N-alkylation of amines or ammonia with alcohols.

Based on our continuing study of the coupling reaction of amines and alcohols through borrowing-hydrogen methodology,[11b,13c,15e,16a,22] herein we present the preparation, characterization, and catalytic activity study of an air- and moisture-stable $NiCuFeO_x$ catalyst. This heterogeneous and non-noble metal catalyst exhibits excellent catalytic activity and generality in the coupling reaction of amines and alcohols. Typically, primary amines could be efficiently transformed into secondary amines or N-heterocyclic compounds and secondary amines could be N-alkylated to synthesize tertiary amines. Note that primary and secondary amines could be produced through a one-pot reaction of ammonia and alcohols. Moreover, because the catalyst is air and moisture stable it could be separated easily from the reaction mixture, and could be recovered and reused for several runs without obvious deactivation.

Results and Discussion

Characterization of the catalyst: The $NiCuFeO_x$ catalyst was characterized by using XRD, photoelectron spectroscopy (XPS), TEM, BET, and inductively coupled plasma atomic emission spectroscopy (ICP-AES) techniques. The XRD diffraction patterns (Figure 1) indicated that the major crystal structure of the catalyst might be NiO (400). A small amount of Cu_2O (111) was also observed. The same surface structure could be obtained by using XPS characterization. The typical binding energies of NiO (855.8 eV), Cu_2O (932.9 eV), and Fe_3O_4 (711.5 eV) were observed. TEM characterization suggested that the catalyst was composed of nanoparticles with a size of 20 to 30 nm (Figure 2a), which is favorable for the dispersion of catalyst particles in the reaction mixture. The HR-TEM image shown in Figure 2b confirms the observations from the XRD diffraction patterns and XPS spectra. The crystal lattices of NiO (400) and Cu_2O (111) can be observed clearly. Similar morphology and crystal lattices were maintained after the reaction (Figure 2c and d), which suggests that the catalyst is stable enough during the reaction. The stability of the catalyst sample was confirmed by XPS and XRD characterization of the catalyst after use, that is, XPS spectra and XRD diffraction patterns similar to the fresh sample were observed.

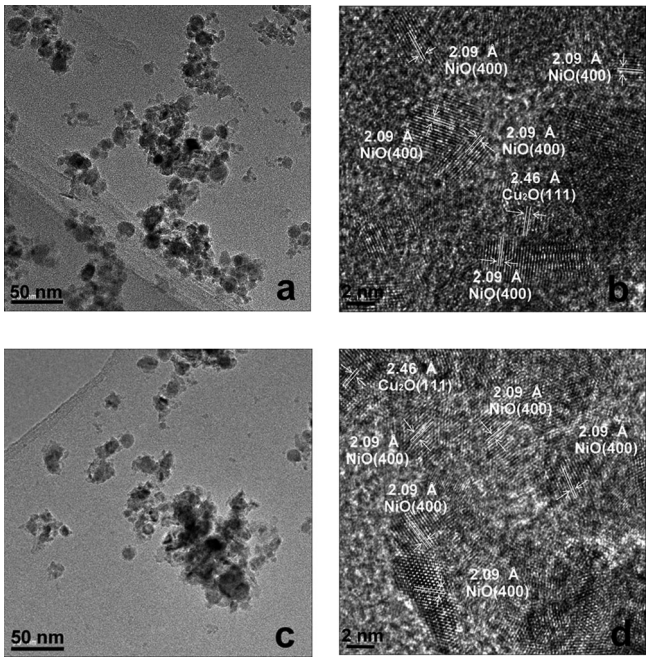


Figure 2. TEM and HR-TEM images of $NiCuFeO_x$ a,b) before and c,d) after use. Scale bars: a,c) 50 nm; b,d) 2 nm.

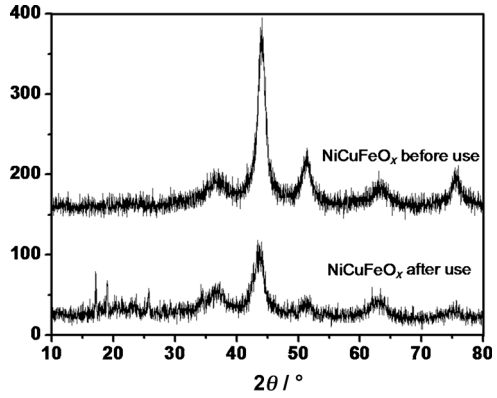
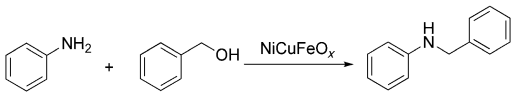


Figure 1. XRD diffraction patterns of $NiCuFeO_x$.

Optimization of the reaction conditions: The reaction of aniline with benzyl alcohol was chosen as a model for catalyst screening and optimization of the reaction conditions (Scheme 2). The reactions were performed in 40 or 20 mL pressure tubes under an argon atmosphere. The solvents toluene, xylene, tetrahydrofuran, benzotrifluoride, and 1,4-dioxane were tested at different reaction temperatures and



Scheme 2. Synthesis of *N*-benzyl aniline.

optimized reaction conditions were obtained. For the coupling reaction of primary amines and alcohols, the conditions used were amine (1.0 mmol), alcohol (1.0 mmol), NiCuFeO$_x$ (50 mg), xylene (2 mL), Ar, 24 h at reflux. Under these optimized reaction conditions, the yield of the target product was >90%. If NiFeO$_x$ and CuFeO$_x$, which were prepared by using the same procedure as NiCuFeO$_x$, were used as the catalysts, the yields of *N*-(1-phenylethyl)aniline were <50%. In view of the characterization results discussed above, it can be supposed that the synergism between the Ni, Cu, and Fe species might be crucial to realize the borrowing-hydrogen transformation.

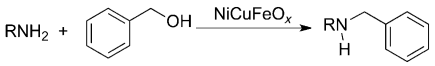
N-Alkylation of amines with benzyl alcohol: After optimization of the reaction conditions, the N-alkylation reactions of amines with benzyl alcohol were tested (Table 1). Clearly, a range of N-benzyl amines could be synthesized successfully. Aromatic amines, including aniline, *p*-methylaniline, *p*-methoxyaniline, *p*-chloroaniline, and *o*-phenylaniline, could be transformed into the corresponding N-benzyl amines in isolated yields of 76 to 94% (Table 1, entries 1–5). The use of 2-aminopyridine, 1-naphthylamine, and 1-phenylethanamine as substrates gave good yields of the corresponding products, that is, 81 to 92% (Table 1, entries 6–8). Note that aliphatic amines, such as cyclohexylamine, butylamine, and octylamine, could also be used as starting materials for the N-benzylation reaction. The yields of the corresponding secondary amines were 69 to 83% (Table 1, entries 9–11).

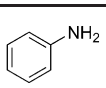
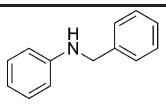
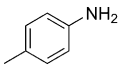
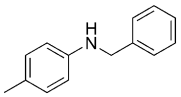
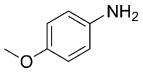
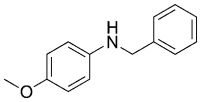
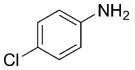
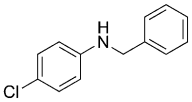
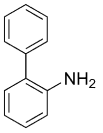
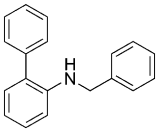
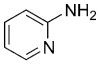
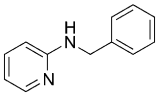
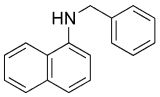
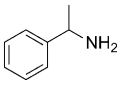
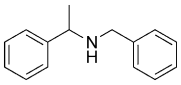
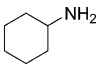
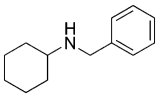
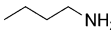
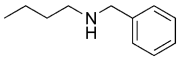
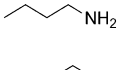
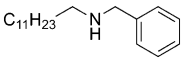
It is interesting to explore the byproducts of the N-alkylation reactions. By tracing the reactions by using GC-MS, imine was observed as the major byproduct in all of the reactions between benzyl alcohol and primary amines. Because the catalyst is magnetic, it could be separated easily in the presence of an external magnetic field. After washing with Et_2O and drying in air, the catalyst was directly reused and a yield of 85% was obtained in the second run in the reaction of aniline and benzyl alcohol. By repeating the operation, a yield of 82% was obtained in the fifth run (Table 1, entry 1). Thus, this catalyst is potentially reusable.

Based on the above results, it can be concluded that NiCuFeO$_x$ is a good catalyst for the monoalkylation of primary amines. Therefore, it was further used in the monoalkylation of 2-(pyridin-2-yl)ethanamine to synthesize *N*-methyl-2-(pyridin-2-yl)ethanamine, which is used as a drug for Meniere's disease and vertigo.[23] To our delight, a yield of 79% was obtained (Scheme 3).

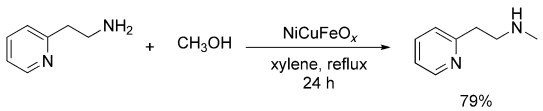
N-Alkylation of *p*-methyl aniline with alcohols: Subsequently, the amination reactions of different alcohols with *p*-methylaniline were explored (Table 2). Clearly, aromatic alcohols, including *p*-methylbenzyl alcohol, *p*-methoxylbenzyl alcohol, *p*-chlorobenzyl alcohol, and *p*-isopropylbenzyl alcohol, could react smoothly with *p*-methylaniline to give yields of 75 to 91% (Table 2, entries 1–4). Note that if aliphatic alcohols were used as starting materials, the N-alkylated products were also synthesized in excellent yields (Table 2, entries 5–10). The structures of the aliphatic alcohols did not influence the reaction very much and the yields of the corresponding N-alkyl amines were 76 to 91%.

Table 1. N-Alkylation of amines with benzyl alcohol.[a]



Entry	Amine	Product	Yield [%][b]
1			94/85[c]/82[d]
2			87
3			83
4			76
5			79
6			81
7			92
8			86
9			89
10			69
11			83

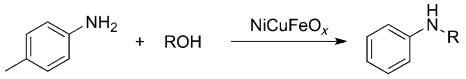
[a] Conditions: amine (1.0 mmol), benzyl alcohol (1.0 mmol), NiCuFeO$_x$ catalyst (50 mg), xylene (2 mL), Ar, 40 mL pressure tube, reflux, 24 h. [b] Yield of isolated product. [c] The catalyst was recovered and reused for a second cycle. [d] The catalyst was recovered and reused for a fifth cycle.

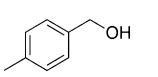
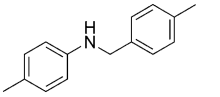
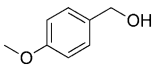
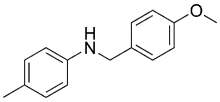
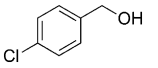
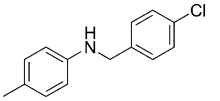
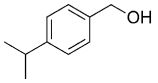
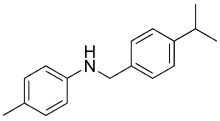
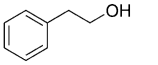
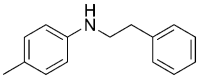
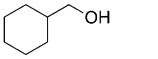
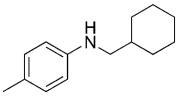
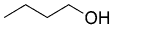
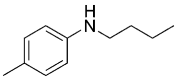
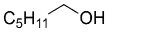
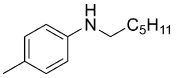
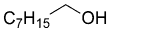
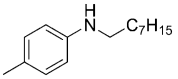
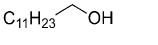
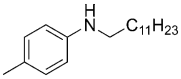


Scheme 3. Synthesis of *N*-methyl-2-(pyridin-2-yl)-ethanamine.

N-Alkylation of secondary amines with benzyl alcohol: During the reaction of primary amines and alcohols, the for-

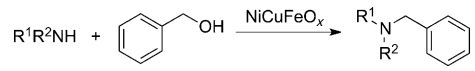
Table 2. N-Alkylation of *p*-methyl aniline with alcohols.[a]

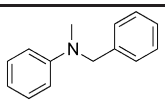
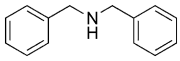
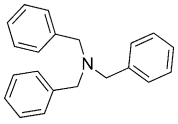
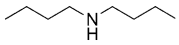
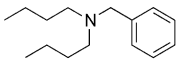
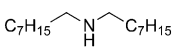
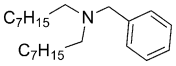
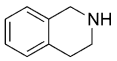
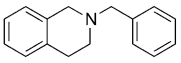
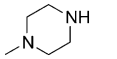
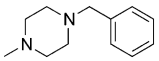
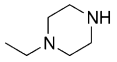
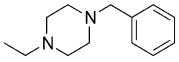
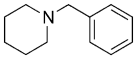
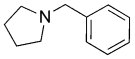


Entry	Alcohol	Product	Yield [%][b]
1			91
2			89
3			75
4			86
5			91
6			89
7			76
8			83
9			79
10			84

[a] See the reaction conditions given in Table 1. [b] Yield of isolated product.

Table 3. N-Alkylation of secondary amines with benzyl alcohol.[a]



Entry	Amine	Product	Yield [%][b]
1			78
2			95
3			86
4			88
5			85
6			79
7			86
8			95
9			93

[a] See the reaction conditions given in Table 1. [b] Yield of isolated product.

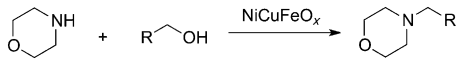
mation of a trace amount of tertiary amine was observed if excess alcohol was added. This suggests that the N-alkylation of secondary amine to tertiary amine might be possible if secondary amines were used as starting materials (Table 3). As expected, secondary amines, such as *N*-methylaniline and *N*,*N*-dibenzyl, could be N-benzylated with yields of 78 and 95%, respectively (Table 3, entries 1 and 2). Furthermore, tertiary amines in yields of 86 and 88% could be achieved for the N-benzylation of dibutylamine and dioctylamine, respectively (Table 3, entries 3 and 4). The reactions were also successful for the N-benzylation of cyclic amines, that is, 1,2,3,4-tetrahydroisoquinoline, 1-methylpiperazine, 1-ethylpiperazine, piperidine, and pyrrolidine. The yields of the corresponding tertiary amines were 79 to 95% (Table 3, entries 5–9). Therefore, this catalyst is active for the N-alkylation of secondary amines with various structures.

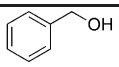
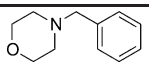
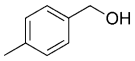
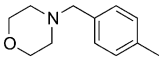
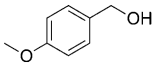
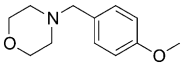
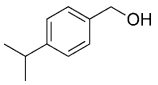
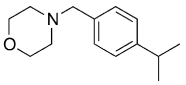
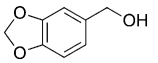
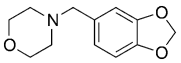
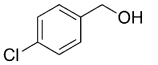
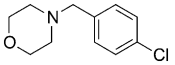
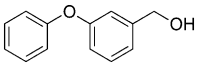
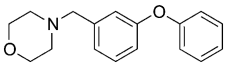
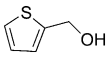
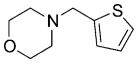
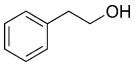
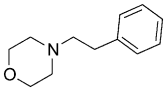
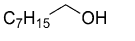
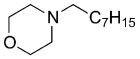
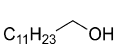
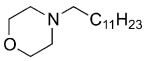
Because piperazine derivatives could be N-alkylated efficiently, the synthesis of piribedil, a piperazine-based dopamine agonist used in the treatment of Parkinson's disease,[24] was attempted by using commercially available 2-(1-piperazinyl) pyrimidine and piperonyl alcohol as starting materials. To our delight, under the same reaction conditions and with $NiCuFeO_x$ as the catalyst, piribedil could be synthesized in 93% yield (Scheme 4).

Scheme 4. Synthesis of piribedil by a reaction of 2-(1-piperazinyl) pyrimidine with piperonyl alcohol.

N-Alkylation of morphine with alcohols: As an important moiety in many pharmaceutical molecules and organic chemical intermediates, the structure of morphine is distinct from other amines and thus the synthesis of *N*-alkyl morphine was explored separately (Table 4). Clearly, the N-alkylation of morphine with benzylic alcohols could be realized with up to 98% isolated yields (Table 4, entries 1–7). The presence of sulfur often deactivates noble metal catalysts; herein 2-thiophenylmethanol was used as a starting material to check the activity of the $NiCuFeO_x$ catalyst. To

Table 4. N-Alkylation of morphine with alcohols.[a]

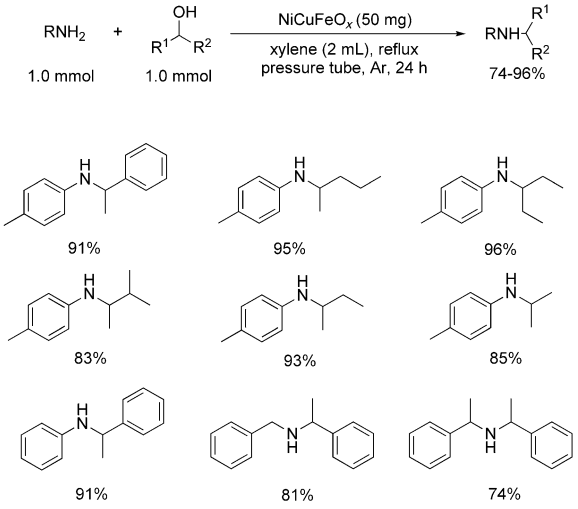


Entry	Alcohol	Product	Yield [%][b]
1			89
2			93
3			91
4			90
5			87
6			84
7			98
8			79
9			97
10			95
11			94

[a] See the reaction conditions given in Table 1. [b] Yield of isolated product.

our delight, an isolated yield of 79% for 4-(2-thiophenylmethyl)-morphine was obtained. Excellent yields of *N*-alkyl morphine were also achieved if using phenylethanol, 1-octynol, and 1-dodecanol as alkylation reagents (Table 4, entries 9–11).

N-Alkylation of amines with secondary alcohols: Due to the low reactivity, the application of secondary alcohols as alkylation reagents with a non-noble metal catalyst continues to be a challenging topic. Herein, the results suggest that NiCuFeO$_x$ is also an excellent catalyst for the amination of secondary alcohols (Scheme 5). First, the reaction of *p*-methylaniline and 1-phenylethanol was explored and a yield of 91% was obtained. It is known that short-chain secondary aliphatic alcohols are difficult to activate and thus we tried the amination reaction of secondary aliphatic alcohols. To our delight, the reactions of *p*-methylaniline with 2-amyl alcohol, 3-amyl alcohol, 3-methyl-2-butanol, and 2-butanol progressed well to give isolated yields of 83 to 96%. Even by using the smallest secondary alcohol, isopropanol, as the starting material, *N*-isopropyl *p*-methylaniline was obtained in an isolated yield of 85%. Further on, the coupling reactions of several amines with different structures were also checked by using 1-phenylethanol as starting material. The yields of *N*-(1-phenylethyl)aniline and *N*-benzyl-1-phenylethanamine were 81 and 91%, respectively. This catalyst could also be applied in the reaction of secondary amines with secondary alcohols. Typically, 1-phenylethanamine can react with 1-phenylethanol to produce bis(1-phenylethyl)-amine in 74% isolated yield.



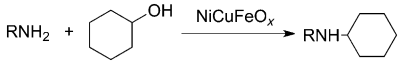
Scheme 5. N-alkylation of amines with secondary alcohols.

N-Alkylation of amines with cyclohexanol: As a secondary alcohol with a specific structure, the use of cyclohexyl alcohol as an alkylation reagent in the N-alkylation of amines with different structures was explored (Table 5). Obviously, both aromatic and aliphatic primary amines could react with cyclohexyl alcohol to produce the corresponding N-cyclohexyl amines in yields of up to 98% (Table 5, entries 1–9). Even *N*-methyl phenyl, which is a typical secondary amine, could be transformed into the corresponding product, that is, *N*-methyl-*N*-cylcohexyl aniline, in 72% isolated yield (Table 5, entry 10). Therefore, the NiCuFeO$_x$ catalyst exhibits its excellent activity and generality in the amination of cyclohexanol.

N-Alkylation of amines with diols: The reaction of amines with diols is an attractive route for the synthesis of N-heterocyclic compounds. Thus, the N-alkylation of amines with diols was performed (Table 6). Anilines with different substituents reacted well with 1,2-ethanediol and isolated yields of 84 to 95% were obtained (Table 6, entries 1–5). Yields of 86 to 89% were obtained if using benzylamine and octanamine as starting materials (Table 6, entries 7, 8). Excellent results were achieved if 1,6-hexanediol and 2,2′-oxydiethanol were used as alkylation reagents (Table 6, entries 9, 10). Interestingly, 4,4′-methylenedianiline reacted smoothly with 1,2-ethanediol to give an isolated yield of 81% (Table 6, entry 11).

N-Alkylation of dimethyl amine with alcohols: Dimethyl amine is extensively observed in functional compounds, so the N-alkylation of dimethyl amine with alcohols was tested

Table 5. N-Alkylation of amines with cyclohexanol.[a]



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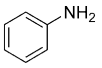
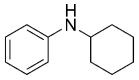
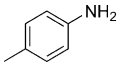
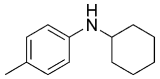
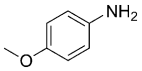
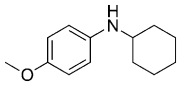
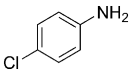
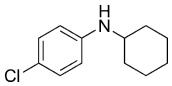
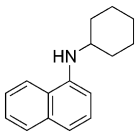
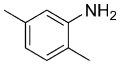
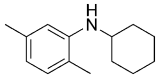
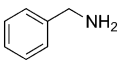
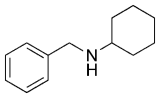
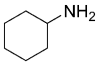
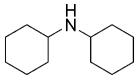
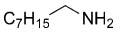
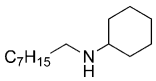
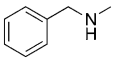
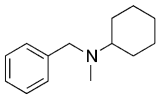
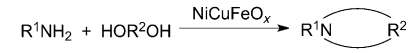
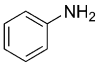
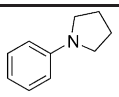
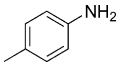
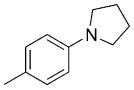
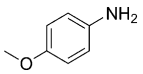
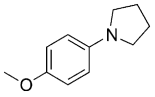
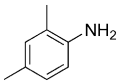
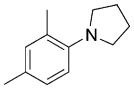
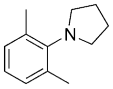
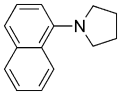
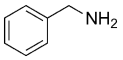
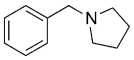
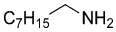
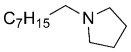
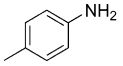
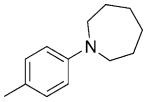
1			98
2			89
3			92
4			76
5			87
6			83
7			83
8			92
9			86
10			72

[a] See the reaction conditions given in Table 1. [b] Yield of isolated product.

Table 6. N-Alkylation of amines with diols.[a]



Entry	Amine	Product	Yield [%][b]
1			89
2			84
3			89
4			95
5			92
6			76
7			86
8			89
9			93
10			73
11[c]			81

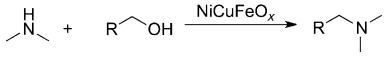
[a] See the reaction conditions given in Table 1. [b] Yield of isolated product. [c] 1,4-butane diol (2.2 mmol) was used.

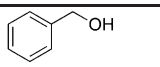
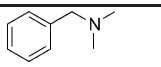
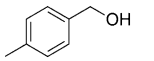
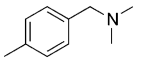
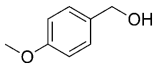
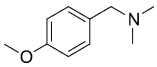
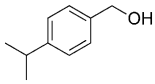
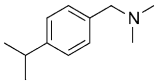
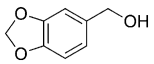
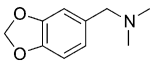
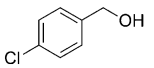
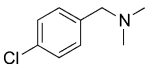
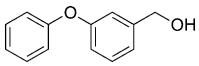
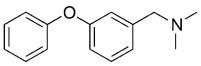
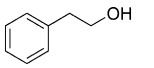
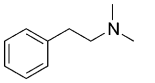
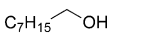
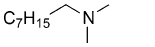
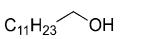
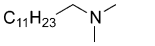
using our catalyst (Table 7). Here, aqueous dimethylamine (33 wt%) was used as the dimethylamine source. Benzylic alcohols with different functional groups on the aromatic ring could react with dimethylamine and the corresponding tertiary amines were obtained in yields of 75 to 92% (Table 7, entries 1–7). The amination reactions of aliphatic alcohols, such as 2-phenylethanol, 1-octynol, and 1-dodecanol, with dimethylamine proceeded smoothly and the yields of the corresponding tertiary amines were 65 to 85% (Table 7, entries 8–10).

Pheniramine is an antihistamine with anticholinergic properties that used to treat allergic conditions such as hay fever or urticaria.[25] By applying the $NiCuFeO_x$ catalyst and using dimethylamine as amination reagent, it could be synthesized with high efficiency. Under the reaction conditions given in Table 7, the yield of pheniramine was 87% (Scheme 6).

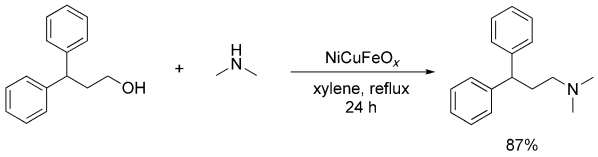
N-Alkylation of ammonia with alcohols: The direct C–N bond formation of alcohols with ammonia is an ideal route for N-alkyl amine synthesis.[7c,26] However, to date reports concerning the selective coupling of alcohols and ammonia by using heterogeneous catalysts are still scarce. Therefore, the $NiCuFeO_x$ catalyst was chosen to investigate the reaction of alcohols with ammonia (Table 8). To add ammonia quantitatively, ammonium carbonate, which has a decomposition temperature of 58°C, was used as the ammonia source. As the results in Table 8 show, symmetric *N*,*N*-disubstituted amines were obtained as the major products although the molar ratio of alcohol to ammonia was 1:1. First, the amination reactions of primary alcohols were examined (Table 8, entries 1–12). Both aromatic and aliphatic primary alcohols could be transformed into the corresponding *N*,*N*-disubstituted amines with isolated yields of up to 90%. It is worth mentioning that secondary alcohols with different structures could react with ammonia to afford the desired products with isolated yields of about 80% as well (Table 8, entries 13–19).

Table 7. N-Alkylation of dimethyl amine with alcohols.[a]



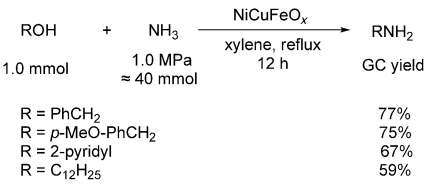
Entry	Alcohol	Product	Yield [%][b]
1			83
2			85
3			92
4			91
5			91
6			75
7			87
8			79
9			85
10			65

[a] See the reaction conditions given in Table 1. [b] Yield of isolated product.



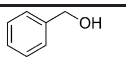
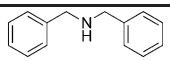
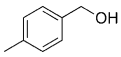
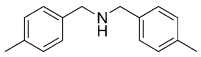
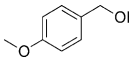
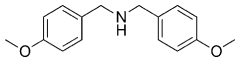
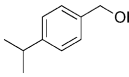
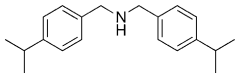
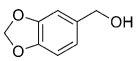
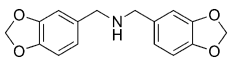
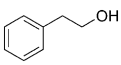
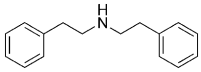
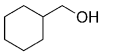
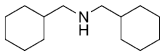
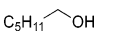
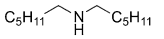
Scheme 6. Synthesis of pheniramine.

During the synthesis of *N*,*N*-disubstituted amines with alcohols and ammonia, small amounts of primary amines were detectable. We were encouraged by this result to see whether it might be possible to convert alcohols into primary amines by using ammonia. To inhibit the formation of secondary amines and stop the reaction at primary amines, we tried the alcohol amination reaction with an excess amount of gaseous ammonia, that is, 1.0 MPa (Scheme 7). To our delight, the syntheses of primary amines were realized. The



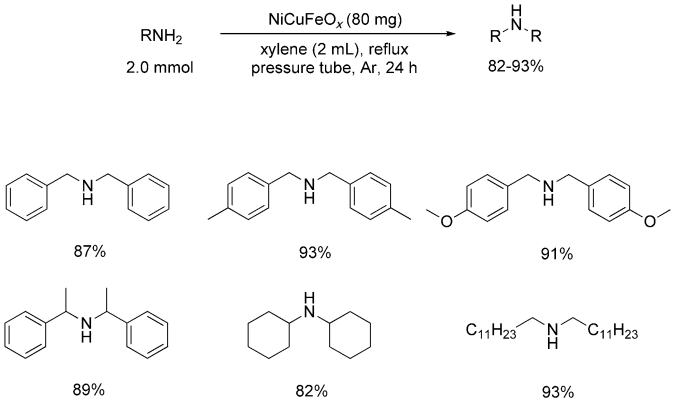
Scheme 7. Synthesis of primary amine from alcohol and gaseous ammonia.

Table 8. N-Alkylation of ammonia with alcohols.[a]

Entry	Alcohol	Product	Yield [%][b]
1			84
2			90
3			68
4			75
5			69
6			85
7			85
8	C_5H_{11} 	C_5H_{11}  C_5H_{11}	60
9	C_7H_{15}	C_7H_{15} C_7H_{15}	61
10	$C_{11}H_{23}$	$C_{11}H_{23}$ $C_{11}H_{23}$	81
11			90
12			87
13			55
14			79
15			76
16[c]			83
17[c]			67
18[c]			73
19[c]			81

[a] Conditions: ammonia (1.2 mmol; 0.6 mmol $(NH_4)_2CO_3$), benzyl alcohol (1.0 mmol), $NiCuFeO_x$ catalyst (80 mg), xylene (2 mL), Ar, 20 mL pressure tube, reflux, 24 h. [b] Yield of isolated product. [c] GC yield.

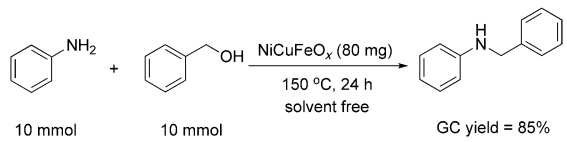
catalytic amination reactions of several typical amines, that is, benzyl alcohol, *p*-methoxybenzyl alcohol, 2-pyridinylmethanol, and *n*-dodecanol, were studied. It can be seen that moderate to good yields of the corresponding primary amines were obtained. The major byproducts were secondary amines and imines. This should be a big breakthrough in the study of amination reactions of alcohols because primary and secondary amines can be selectively synthesized by using ammonia as the nitrogen source and using a heterogeneous catalyst under base- and organic-ligand-free conditions.



Scheme 8. Self-coupling of primary amines.

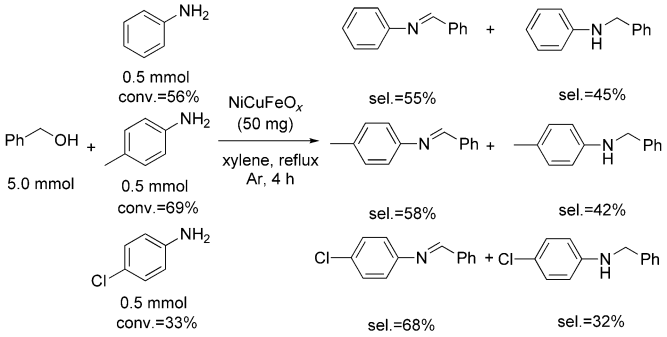
Self-N-alkylation of primary amines: The N-alkylation of amines with amines is also an attractive route for the synthesis of secondary amines, and has been reported to undergo the borrowing-hydrogen strategy.[2] In the above discussion, it was shown that the one-pot synthesis of *N*,*N*-dialkyl amines from alcohols and ammonia could be realized with high efficiency. Additionally, the self-coupling of amines was detectable occasionally during the N-alkylation of primary amines with alcohols. Therefore, we suppose that $NiCuFeO_x$ might possess catalytic activity in the coupling reaction of amines with amines. Several typical amines were chosen for the exploration. As shown in Scheme 8, both benzylic and aliphatic amines could be transformed into the corresponding symmetrical secondary amines in yields of 82 to 93%.

Scaling-up of the reaction under solvent-free conditions: Although good results were obtained by using xylene as the solvent, it would be ideal if the reaction could progress under solvent-free conditions. Therefore, a reaction was performed with 10 mmol aniline and 10 mmol benzyl alcohol without the addition of xylene (Scheme 9). After being heated at 150 °C for 24 h, *N*-benzyl aniline was obtained in 85% yield. This result is very significant because it offers the possibility of developing a practical system for the synthesis of N-alkyl amines.



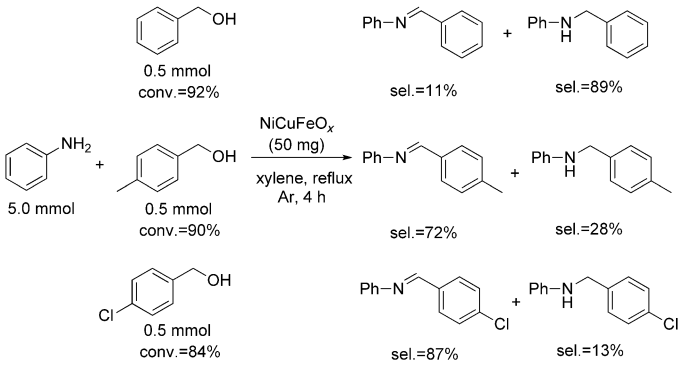
Scheme 9. Reaction of aniline and benzyl alcohol under solvent-free conditions.

The influence of substituents on the activity of amines and alcohols: To investigate the substitution effects of different functional groups, competitive reactions of aniline, *p*-methylaniline, and *p*-chloroaniline with benzyl alcohol were carried out. Based on GC-MS analysis, the conversions of the anilines were 56, 69, and 33% (Scheme 10). Meanwhile, the selectivities for the corresponding *N*-benzyl amines were 45, 42, and 32%. Thus the electron-poor group on the aromatic ring of aniline retarded the coupling reaction and the reduction of imine to *N*-benzyl amine.



Scheme 10. Competitive reactions of anilines and benzyl alcohol with different functional groups.

Additionally, the competitive reaction of aniline with different benzyl alcohols was performed (Scheme 11). In contrast to the above reactions, the presence of functional

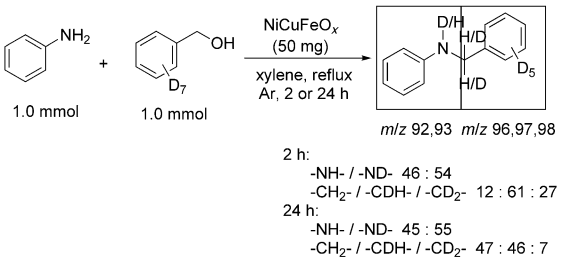


Scheme 11. Competitive reactions of aniline and benzyl alcohols with different functional groups.

groups on the aromatic ring of benzylic alcohols did not influence their dehydrogenation reactions. The conversions of the benzylic alcohols were all around 90%. However, the presence of methyl and chloride groups disfavored the transfer-hydrogenation of imine to secondary amine. The selectivity for *N*-benzyl aniline was 89% but selectivities of only 13 and 28% were obtained for *N*-*p*-methyl aniline and *N*-*p*-chlorobenzyl aniline. Moreover, it could be seen that the conversions of anilines in Scheme 10 were lower than the conversions of benzylic alcohols in Scheme 11 even though the corresponding benzyl alcohol and aniline were all in large excess. Based on these results, we can envisage that the coupling reaction of aniline with benzaldehyde promotes

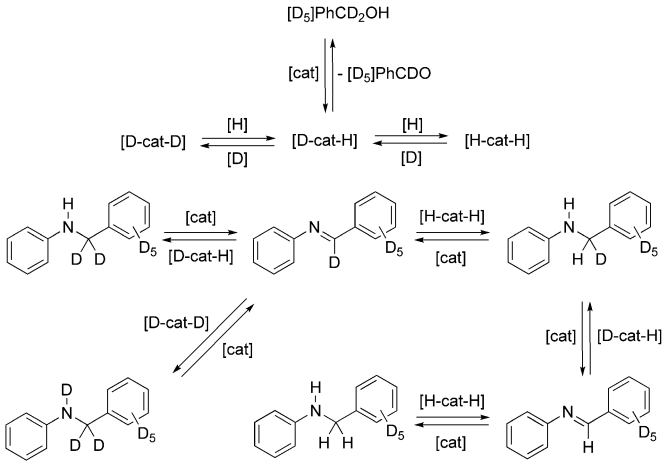
the dehydrogenation of benzyl alcohol because it consumes the dehydrogenation product, that is, benzaldehyde.

Proton shifting between amine and methylene groups: Although it has been extensively accepted that the alcohol amination reaction undergoes a reversible borrowing-hydrogen methodology, the proton shifting between amine and methylene groups has not been studied before. We chose the synthesis of *N*-benzyl aniline as a model reaction to explore the proton shifting in amine and methylene groups. First, the N-alkylation of aniline with [D_7]benzyl alcohol was employed (Scheme 12). In the final product, according



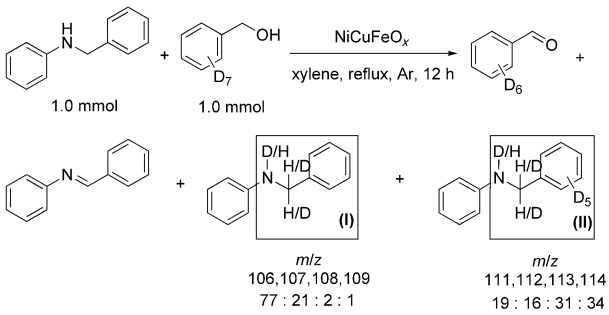
Scheme 12. Reaction of aniline and [D_7]benzyl alcohol.

to a GC-MS analysis of the reaction after 2 h, the *m*/*z* of the aniline group is 92, that is, PhNH, and 93, that is, PhND, and their ratio is 46:54. At the same time, the ratio of *m*/*z* values of [D_5]PhCH$_2$, (96), [D_5]PhCDH (97), and [D_5]PhCD$_2$ (98) is 12:61:27. If the reaction was checked again after 24 h, the ratio of -NH- to -ND- is 45:55 and the ratio of [D_5]PhCH$_2$, [D_5]PhCDH, and [D_5]PhCD$_2$ groups is 47:46:7. The variation in H and D and the increase in the amount of -CH$_2$- in the final product after a longer reaction time suggests the slow shifting of H to the methylene group through a reversible mechanism (Scheme 13).



Scheme 13. H–D shifting in amine and methylene groups of *N*-benzyl aniline.

Further GC-MS analysis of the experiment between N-benzyl aniline and [D_7]benzyl alcohol confirmed the above observations. After reacting for 12 h, two interesting compounds were observed, that is, the methylene- and amine-deuterated *N*-benzyl aniline (**I**) and [D_5]-*N*-benzyl aniline (**II**). In compound **I**, the *m*/*z* values of PhNH and PhCHD overlap each other, so the *m*/*z* values of [D_x]PhCH$_2$NH, that is, 106, 107, 108, and 109, were used to estimate the deuteration of the product. As shown in Scheme 14, the correspond-

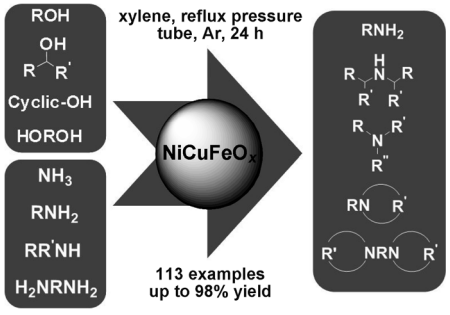


Scheme 14. Reaction of *N*-benzyl aniline and [D_7]benzyl alcohol.

ing ratio is 77:21:2:1. In the deuterium-free *N*-benzyl aniline, the corresponding ratio is 93:6.6:0.4:0. Comparison of these results leads to the conclusion that deuterated *N*-benzyl aniline (**I**) is formed. In addition, the ratio of the *m*/*z* values 111, 112, 113, and 114 is 19:16:31:34, which is typical for the formation of [D_{5-8}]-*N*-benzyl aniline.

Conclusion

An air- and moisture-stable NiCuFeO$_x$ catalyst was designed and prepared for the synthesis of N-substituted primary, secondary, tertiary, and cyclic amines by using ammonia, primary amines, or secondary amines as the nitrogen source and alcohols as the alkylation reagents (Scheme 15). In the absence of bases and organic ligands, 113 samples of primary, secondary, and tertiary amines with various structures could be synthesized with up to 98% isolated yields. The magnetic property of the catalyst makes it easy to separate



Scheme 15. Scope and limitations of the NiCuFeO$_x$-catalyzed alcohol amination.

from the reaction mixture, and it can be reused for several runs without obvious deactivation. To the best of our knowledge, several transformations were realized for the first time by using a heterogeneous non-noble metal catalyst, that is, selective alcohol amination with ammonia to produce primary or secondary amines, secondary aliphatic alcohol amination, diol amination, and alcohol amination with dimethylamine. This offers a clean and economic route for N-substituted amine synthesis.

Experimental Section

All solvents and chemicals were obtained commercially and were used as received.

Typical procedure for catalyst preparation: $Cu(NO_3)_2{\cdot}3H_2O$ (1.25 g, 5.1 mmol), $Ni(NO_3)_2{\cdot}6H_2O$ (6.0 g, 20.7 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (2.0 g, 5.0 mmol), and $Al(NO_3)_3{\cdot}9H_2O$ (2.0 g, 5.3 mmol) were added to deionized water (150 mL) and agitated until complete dissolution. Then, aqueous Na_2CO_3 (50 mL, 1.7 M) was added dropwise and the mixture was stirred for a further 2 h at RT. The reaction mixture was centrifuged and washed with water to remove the base until the pH value of the aqueous solution was ≈7. Subsequently, the solid was dried at 120 °C for 4 h, calcined in air at 450 °C for 5 h, and reduced under a hydrogen flow for 2 h. The solid catalyst sample was treated with aqueous NaOH (10 M) to remove the aluminum, then the solid sample was washed with EtOH (2× 20 mL) and Et_2O (2×20 mL) and vacuum dried for 0.5 h. About 1.8 g of a black solid sample, that is, moisture- and air-stable Raney-type catalyst, was obtained and denoted as $NiCuFeO_x$. According to the ICP-AES measurement, the Ni, Cu, and Fe contents are 43.4, 13.4, and 12.1 wt%. The BET surface area of the obtained catalyst is 127 m^2g^{-1}.

Typical procedure for the N-alkylation of amines with alcohols: Amine (1.0 mmol), alcohol (1.0 mmol), catalyst (50 mg), and xylene (2 mL) were added to a 40 mL pressure tube equipped with a magnetic stirrer. The pressure tube was exchanged three times with argon and reacted under xylene at reflux for 24 h, then cooled to RT. Acetone (≈10 mL) was added to dissolve the reaction mixture, which was filtered with Celite. The crude reaction mixture was concentrated in vacuo and purified by column chromatography (eluent: petroleum ether/ethyl acetate/methanol) to give the N-alkyl amine in good yields.

Typical procedure for the N-alkylation of ammonia with alcohols: $(NH_4)_2CO_3$ (0.6 mmol; 1.2 mmol of ammonia the decomposition temperature of ammonium carbonate is 58 °C), alcohol (1.0 mmol), catalyst (80 mg), and xylene (2 mL) were added to a 20 mL pressure tube equipped with a magnetic stirrer. The pressure tube was sealed and exchanged three times with argon, then reacted under xylene at reflux for 24 h before being cooled to RT. Acetone (≈10 mL) was added to dissolve the reaction mixture, which was filtered with Celite. The crude reaction mixture was concentrated in vacuo and purified by column chromatography (eluent: petroleum ether/ethyl acetate/methanol) to give the N-alkyl amine.

Characterization of catalysts and products: XRD measurements were conducted by using a STADI P automated transmission diffractometer (STOE) equipped with an incident beam curved germanium monochromator with $Cu_{K\alpha1}$ radiation. The catalyst samples were dried in air and pressed on a glass slide for analysis. The XRD patterns were scanned in the 2θ range of 10–80°. For data interpretation, the software WinXpow (STOE) and the database of powder diffraction file (PDF) of the International Centre of Diffraction Data (ICDD) were used. Transmission electron microscopy (TEM) characterization was carried out by using a Tecnai G2 F30 S-Twin transmission electron microscope operating at 300 kV. Single-particle EDX analysis was performed by using a Tecnai G2 F30 S-Twin Field Emission TEM in STEM mode. For TEM investigations, the catalysts were dispersed in ethanol by ultrasonication and deposited on carbon-coated copper grids. The X-ray photoelectron spectroscopy (XPS) measurements were carried out by using a VG ESCALAB 210 instrument equipped with a dual Mg/Al anode X-ray source, a hemispherical capacitor analyzer, and a 5 keV Ar^+ ion gun. All spectra were recorded by using nonmonochromatic $Mg_{K\alpha}$ (1253.6 eV) radiation. The samples were fixed to a stainless steel sample holder by using double-sided adhesive carbon tape. The electron binding energy was referenced to the C_{1s} peak at 284.8 eV. The peaks were fitted by Gaussian–Lorentzian curves after a Shirley background subtraction. For quantitative analysis, the peak area was divided by the element-specific Scofield factor and the transmission function of the analyzer. The background pressure in the chamber was less than 10^{-7} Pa. Nitrogen adsorption–desorption isotherms were measured at 77 K by using a Micromeritics 2010 instrument. The pore-size distribution was calculated from the desorption isotherm by using the Barrett, Joyner, and Halenda (BJH) method. The Cu, Ni, and Fe contents of the catalysts were measured by using inductively coupled plasma atomic emission spectrometry (ICP-AES), by using an Iris advantage Thermo Jarrel Ash device. NMR spectra were measured by using a Bruker ARX 400 or ARX 100 spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C). All spectra were recorded in $CDCl_3$ or $[D_6]$DMSO and chemical shifts (δ) are reported in ppm relative to tetramethylsilane referenced to the residual solvent peaks.

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