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N-Monomethylation of amines using paraformaldehyde and H₂

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The selective N-monomethylation of amines is an improtant topic in fine chemical synthesis. Herein, for the first time, we described a selective N-monomethylation reaction of amines with paraformaldehyde and H_2 in the presence of CuAlOx catalyst. A variety of amines, including primary aromatic amines, benzylamine and cyclohexylamine, as well as secondary amines are shown to be compatible with this reaction.

Secondary amines are important structural motifs whose synthesis is one of the hottest topics in chemical industry.¹ Nmethyl amines, in particular, are not only recognized as fundamental building blocks in a broad range of biologically active compounds, but also serve as key intermediates in the preparation of pharmaceuticals, dyes and agrochemicals, etc.² The traditional approaches for N-methylation of amines frequently employ activated methyl compounds, such as methyl iodide.^{1b} However, generation of stoichiometric amounts of wasteful (in)organic salts is prejudicial for these protocols. Recently, methanol, carbon dioxide, dimethyl carbonate (DMC) and formic acid have been presented as green alternatives for the preparation of the N-methyl amines.³ The reductive amination using formaldehyde in the presence of suitable reductant (Eschweiler-Clarke methylation) still prevails in industrial production of N-methyl amines.4

Despite a series of nice results were achieved in the synthesis of N-methyl amines, the selective N-monomethylation of primary amines is still limited. This limitation normally originates from the N-monomethyl amines with higher reactivity than primary amines, so it is further transformed into N,N-dimethyl amines. The applying of

specific electrophililic methylating agents, such as MeOTf, dimethyl phosphite, is a choice to circumvent this problem.⁵ Yebeutchou and Dalcanale also described the selective Nmonomethylation of primary amine with excess of Mel via host-guest sequestration.⁶ However, the formation of stoichiometric amounts of salt wastes makes such methods environmentally unfriendly.

In the past years, the utilization of methanol as environmentally benign methylating agent based on the "hydrogen autotransfer process" was reported as a promising alternative methylation strategy. In 1981, Grigg et al. described rhodium-catalyzed selective N-monomethylation of amine with methanol.⁷ Supercritical MeOH was also severed as methylating agent for the selective N-monomethylation of primary amines in the presence of acid-base bi-functional catalysts.⁸ However, these protocols were limited to aliphatic primary amines. Recently, the complementary Nmonomethylation of aniline with methanol in the presence of iridium⁹ or ruthenium catalyst in basic media was accomplished.¹⁰ An attractive strategy using CO₂ and H₂ in the presence of ruthenium,^{11a} palladium^{11b} or copper catalyst^{11c} for N-monomethylation was reported, but suffers from high pressure (35-100 bar) and temperature (150-160 °C) as well as incompatibility with aliphatic primary amines. In addition, Nmonomethylation of primary arylamines was also realized in the presence of a large amount of zeolites as catalysts when DMC was used.¹² However, the aliphatic primary amines were shown to be inactive in these processes.

Compared with above methods, only one example¹³ with paraformaldehyde as methylating agent for the selective N-monomethylation of primary amines has been reported. In that elegant work, heterogeneous Pd/C was used as catalyst and CaH₂ served as reductant. However, the employment of CaH₂ as reductant significantly reduced the appeal of this method in industrial application. In comparison with CaH₂, H₂ is a clean, atom-economical and economic reductant. Furthermore, products are prone to be isolated from the reaction mixtures when H₂ was released. Thus, the development of selective N-monomethylation of amines with

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formaldehyde and H₂ is highly desired. Nevertheless, the activation of H₂ usually needs high temperature, which makes it difficult to realize selective N-monomethylation of amines.¹⁴ In on our previous work, CuAlOx displayed high reactivity and selectivity for the N-monomethylaton of amines with CO₂ and H₂.^{11c} We envisioned that CuAlOx could possess better reactivity and selectivity for the N-monomethylaton of amines with paraformaldehyde and H₂. Herein we describe for the first time the selective synthesis of N-monomethyl amines with paraformaldehyde and H₂ in the presence of a simple CuAlOx catalyst (Scheme 1).



Scheme 1 Selective reductive N-monomethylation of amines.

The catalyst used here was prepared by a co-precipitation method via adding an aqueous solution of Na₂CO₃ into a Cu(NO₃)₂ and Al(NO₃)₃ solution. The precipitates were washed by deionized water, dried in air and reduced under H₂ flow at 450 °C. A series of CuAlOx catalysts were obtained and denoted as CuAlOx (m : n) (m : n = molar ratios of Cu and Al). These catalysts were characterized by ICP-AES, BET surface area analysis, XPS, XRD, EXAFS and TEM.

Table 1 The physicochemical properties of catalysts					
Entry	Catalysts	Cu [°] wt%	SA^{b} (m ² /g)	APS ^b (nm)	PV ^b (cm ³ /g)
1	CuAlOx (2 : 8)	17	59.2	15.4	0.46
2	CuAlOx (3 : 7)	27	85.9	7.0	0.30
3	CuAlOx (5 : 5)	57	58.7	9.5	0.28
4	CuAlOx (7 : 3)	82	52.4	10.0	0.27
5	CuAlOx (8 : 2)	83	36.3	15.5	0.26

^{*a*} Determined by ICP-AES. ^{*b*} Determined by an IQ₂ automated gas sorption analyser. SA: BET surface area; APS: Average pore size; PV: Pore volume.

The contents of Cu in these catalysts were tested by ICP-AES, and the copper loadings in CuAlOx increased from 17% to 83% (Table 1, entries 1-5). Then, the surface areas and pore size distributions of these catalysts were investigated by BET surface area analysis. With the increasing of Cu : Al ratios, the BET surface area of the CuAlOx catalysts increased first and then decreased. However, the average pore size changed in the opposite tendency. The CuAlOx (3 : 7) possessed the highest BET surface area, i.e. 85.9 m²g⁻¹, and smallest pore volume, i.e. 7 nm (entry 2). The pore volume gradually decreased as the Cu : Al ratios of the catalysts increased.











Fig. 3 TEM (a), HR-TEM (b), HAADF (c) and the line-scan EDS analysis (d) images of the fresh CuAlOx (5 : 5) catalyst.

Fig. 1a shows the Cu2p XPS spectra of fresh and used CuAlOx (5 : 5). The XPS spectra of fresh CuAlOx (5 : 5) display two main peaks at 932.8 and 952.6 eV that can be attributed to $Cu_{2p3/2}$ and $Cu_{2p1/2}$ binding energies of Cu^0 or $Cu^{^+}\!.$ In order to verify the valent state of copper species, Cu_{LMM} Auger spectra were collected and are shown in Fig. 1b. A peak at 916.2 eV, which can be attributed to $\mathrm{Cu}^{\scriptscriptstyle +},$ are observed. $^{^{15}}$ In addition, the XRD diffraction patterns of the as-prepared catalysts performed to further elucidate the structure of the catalysts (see Fig. S3). The CuAlOx samples show diffraction peaks at 36.7°, 43.3°, 50.6°, 74.1° and 89.9°, which can be ascribed to the diffraction peaks of $Cu_2O(111)$, Cu(111), (200), (220) and (311). From the analysis of the XRD diffraction patterns, both CuAlOx (2:8) and CuAlOx (3:7) samples display broad peaks of Cu(111), which suggest the amorphous nature of these catalysts. However, with the increasing of Cu : Al ratios in the catalysts, sharper diffraction peaks of Cu(111) and Cu(200) were observed in CuAlOx (5 : 5), CuAlOx (7 : 3), and CuAlOx (8 : 2). CuAlOx catalysts were further characterized by TEM and HR-TEM, Fig. 3. The HR-TEM image confirmed the observations from the XRD diffraction patterns in Fig. S3. The crystal lattices of Cu(111) and Cu₂O(111) can be observed clearly. The catalyst sample used three times was also characterized by XPS and the formation of Cu₂O on the catalyst surface was observed, but no Cu₂O diffraction peak was seen from XRD diffraction patterns. Considering that this is a reductive reaction and according to the analytical results, we suppose that metallic copper might be the active species for this reaction. The Fourier transform (FT) of Cu K-edge EXAFS spectra of different catalyst samples also support this perspective. Although some

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CuOx species were observed by XRD and XPS characterizations from sample CuAlOx (5 : 5), almost no Cu-O coordination peak can be observed from the Cu K-edge EXAFS spectra. Therefore, only small amount of CuOx was formed in CuAlOx (5 : 5), and the main copper species is metallic copper.

Next, the N-monomethylation reaction of aniline with paraformaldehyde and H₂ was chosen as the model reaction to test the performance of these catalysts (Table 2, entries 1-5). Clearly, with the increasing of Cu : Al ratios in the catalysts, the reactivity and the selectivity for N-methylaniline were improved and 94% conversion of aniline with 97% Nmethylaniline selectivity was achieved when CuAlOx (5 : 5) was used as the catalyst (entry 3). However, both the conversion of aniline and the selectivity for N-methyl aniline were slightly decreased if the Cu : Al ratio was further increased. The impact of the solvent over the reactivity and selectivity of this reaction was further investigated, and it was discovered that THF remained the optimal choice (see Table S1). Furthermore, if the amount of CuAlOx (5 : 5) was reduced to 20 mg, it still maintained good catalytic performance (entries 6-9). Finally, 97% aniline conversion and 93% N-methylaniline selectivity were obtained when reducing the H₂ pressure to 0.5 Mpa and prolonging the reaction time to 9 h (entry 12). Unfortunately, both conversion and selectivity were decreased if the reaction temperature was decreased (see Table S1). Noteworthy, this catalyst is easily recoverable by simple filtration, and it can be reused directly without further treatment. To our delight, 98% conversion of aniline with 91% N-methylaniline selectivity was maintained when it was used at the 3rd run thus this catalyst exhibits nice reusability.



Entry	$CuAlOx (m \cdot n)$	$Conv^{b}(\%)$	501. (78)					
LIILIY		COIN. (70)	3a	4a	5a	6a	7a	
1	(2 : 8), 50 mg	80	76	10	13			-
2	(3 : 7), 50 mg	78	87	1	10	2		
3	(5 : 5), 50 mg	94	97	3				
4	(7 : 3), 50 mg	90	91	9				
5	(8 : 2), 50 mg	90	91	8		1		
6	(5 : 5), 30 mg	91	98	2				
7	(5 : 5), 20 mg	96	96	4				
8	(5 : 5), 10 mg	94	89	3	3	3	2	
9	(5 : 5), 5 mg	93	77	2	13	6	2	
10^{d}	(5 : 5), 20 mg	89	94	1	2	2	2	
11^e	(5 : 5), 20 mg	83	95		3	1		
12 ^f	(5 : 5), 20 mg	97(98 ^g)	93(91 ⁹)	7(9 ^g)				

^{*a*}1a (1.0 mmol), paraformaldehyde (1.2 mmol), CuAlOx (x mg), H₂ (1.0 Mpa), THF (3.0 mL), 120 °C, 5 h. ^{*b*}Determined by GC-MS. ^{*c*}Determined by GC-MS. ^{*d*} H₂ (0.5 Mpa). ^{*e*} H₂ (0.2 Mpa). ^{*f*} H₂ (0.5 Mpa), 9 h. ^{*g*} The catalyst was reused at the 3^{*rd*} run.

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Table 3 Results of the N-monomethylation of primary amines ^a						
Entry	Substrate	Product	Yield(%) ^b			
1	NH ₂ 1a	H N 3a	89			
2	Me NH ₂	Me 3b	85			
3	Me NH ₂ 1c	Me H N 3c	84			
4	Me NH ₂ Me 1d	Me Me Me 3d	83			
5	But NH ₂ 1e	But 3e	80			
6 ^c	Meo NH ₂	MeO 3f	76			
7 ^c	F NH ₂	F 3g	70			
8 ^c	CI NH2 1h	CI H 3h	74			
9 ^c	Br NH ₂ 1i	Br 3i	69			
10 ^c	EtO ₂ C NH ₂	EtO ₂ C 3j	79			
11 ^c	NC NH ₂ 1k	NC 3k	61			
12 ^c	NH ₂ 11	J J	81			
13 ^{<i>d</i>}	NH2 1m	H 3m	73			
14 ^e	NH ₂ 1n	⊖ ^H 3n	64			
15 ^e	✓ ^{NH} ² 10	J ^H 30	66			

^{*a*}amine (1.0 mmol), paraformaldehyde (1.2 mmol), CuAlOx (5 : 5) (20 mg), H₂ (0.5 MPa), THF (3.0 mL), 120 °C, 9 h. ^{*b*}Isolated yields. ^{*c*}Amine (1.5 mmol), paraformaldehyde (1.0 mmol), 140 °C. ^{*d*}GC-FID yield. ^{*e*}NMR yield.

With the optimized conditions in hand, the scope of this CuAlOx catalyzed selective N-monomethylation of different primary amines was further investigated. As shown in Table 3, the anilines with both electron-withdrawing and -donating groups on the phenyl ring were well tolerated the current conditions. Reductive amination of electron-rich methyl-, *tert*-

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butyl-, and methoxy-substituted anilines proceeded smoothly to provide the corresponding products in 76-89% yields (Table 3, entries 1-6). The anilines bearing electron-deficient groups, such as halogen, ester, and cyano groups, provided the corresponding products in 61-79% yields (entries 7-10). The halogen groups in the products are useful handles for further synthetic elaborations. As expected, 2-naphthalene amine also underwent the N-monomethylation to give the desired product in 81% yield (entries 12). It should be noted that selective N-monomethylation of aliphatic primary amines remains a challenge in this field. After improving the reaction conditions, benzylamine, cyclohexylamine and cyclopentylamine underwent successful N-monomethylation to afford the aim products in 64-73% yields (entries 13-15).

Fable 4 Results of the N-methylation of secondary amines ^a				
Entry	Substrate	Product	Yield(%) ^b	
1 ^c	o√ 1p	S → 3p	79	
2	NH 1q	~ ^N 3q	99	
3 ^c	₩ ₇ ^H , 1r	₩ ₇ ^N ₩ ₇ 3r	88	
4 ^{<i>c</i>}	Ph~ ^H ~ ^{Ph} 1s	Ph~ N~ ^{Ph} 3s	75	
5		N J 3t	99	
6	∩_ _N 1u	N J 3u	99	
7 ^c	الله الله الله الله الله الله الله الله	I N Sv	67	

 a amine (1.0 mmol), paraformaldehyde (1.5 mmol), CuAlOx (5 : 5) (20 mg), H₂ (0.5 MPa), THF (3.0 mL), 120 °C, 9 h. ^bIsolated yields. ^c140 °C.

Next, we further investigated the N-methylation of different secondary amines. Cyclic secondary amines, such as morpholine and piperazine, were converted into desired products in 79% and 99% yields, respectively (Table 4, entries 1-2). In addition, dialkylamines were also compatible with this catalyst system, affording the corresponding products in good to excellent yields, too (entries 3-6). Furthermore, Nmethylaniline can also be transformed into N.Ndimethylaniline with good yield (entry 7).

In conclusion, we have developed a simple CuAlOx catalyst system for the selective N-monomethylation reaction of primary amines with paraformaldehyde and H₂. This work offers a clean and economic methodology for the selective synthesis of N-monomethyl amines. Further investigation of selective N-monomethylation of the long-chain primary alkyl amines is underway in our laboratory.

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