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Selective reductive amination of aldehydes from nitro compounds catalyzed by molybdenum sulfide clusters

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Secondary amines are selectively obtained from low value starting materials using hydrogen and a non-noble metal based catalyst. Reductive amination of aldehydes from nitroarenes or nitroalkanes is efficiently catalyzed by a well-defined diamino molybdenum sulfide cluster in a one-pot homogeneous reaction. The integrity of the molecular cluster catalyst is preserved along the process.

Introduction

Amines are the most important building blocks employed in modern medicinal chemistry.[1] Secondary amines are regularly prepared by alkylation or reductive amination of the parent amines through transition metal, typically precious metals, catalyzed reactions.[2,3] In the last years, the catalytic alkylation of amines with alcohols under hydrogen-borrowing conditions[4] as well as the catalytic reductive amination of carbonyl compounds using hydrogen as reductant have been proposed as environmentally friendly procedures to produce *N*-substituted amines.[5]

An actual challenge in catalysis research is to take low value starting materials and convert them to high value products using non-toxic earth abundant materials through an atom efficient procedure. Nitro compounds are an economic feedstock to provide primary amines and their use in reductive amination processes is highly attractive since it does not require prior isolation of the amine. Our groups have recently shown that well-defined Mo_3S_4 cuboidal clusters are efficient catalysts for the chemoselective reduction of nitroarenes to anilines using different reducing agents.[6–8] Interestingly, the diamino cluster of formula $[Mo_3S_4Cl_3(dmen)_3]^+$ (dmen = *N,N'*-dimethylethylenediamine), depicted in Figure 1, performs this transformation under mild conditions and using molecular hydrogen, the most "green" and least expensive reducing agent.[6] On this basis, we became interested in its use as catalyst for the related reductive amination of aldehydes with nitroarenes and nitroalkanes to generate secondary amines in a straightforward manner.

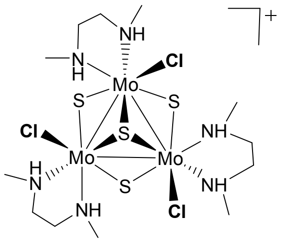

Figure 1. Structure of the $[Mo_3S_4Cl_3(dmen)_3]^+$ cluster catalyst.

Domino catalytic transformations starting from nitroarenes and carbonyl compounds directed towards the preparation of *N*-alkylated aryl amines are not so common and they are usually done in heterogeneous phase using palladium, platinum, rhodium or gold nanocatalysts.[9–16] *N*-alkylation of nitroarenes with aldehydes catalyzed by palladium operates under ambient hydrogen pressure at room temperature when alcohols are used as solvents. However, formation of byproducts such as benzylalcohol and toluene derivatives limits the selectivity of the process. Several cost effective carbon-supported catalysts based on nanostructured Fe_2O_3 and Co-Co_3O_4 partially encapsulated by nitrogen-enriched graphene layers (Fe_2O_3/NGr@C and Co-Co_3O_4/NGr@C, respectively) have also been recently developed by some of us for the tandem reductive amination between nitro compounds and carbonyl compounds using hydrogen as reductant.[17–19] In general, these heterogeneous processes employing non-noble metals require

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more demanding conditions (110-170 ^{o}C and 50-70 bar H_2) and contrary to general assumption that anhydrous conditions favor reductive aminations, water has a positive influence on the reaction. Lanthanide Metal Organic Frameworks have also proved to be active catalysts for the tandem reductive amination of nitrobenzene with heptanal to produce *N*-heptylaniline in moderate yields.[20]

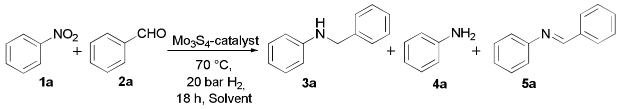
Although heterogeneous catalysts are usually preferred for most industrial applications, molecularly defined complexes are still an attractive approach in catalysis due to their higher selectivity and easy modification. To our knowledge, the only examples of homogeneous catalysts capable to afford secondary amines from nitroarenes and aldehydes in the presence of hydrogen in a tandem fashion were reported by Corma's group. The complex IrLCl (L = (E)-2-*tert*-Butyliminomethyl)-6-diisopropylaminomethyl-pyridine) is able to produce *N*-benzylaniline in 66% yield after full conversion of nitrobenzene under 6 bar of H_2 pressure and 100 ^{0}C, while a trialkoxysilyl derivative of the pincer-type complex [RuHClCO((NHC)NN)] ((NHC)NN = (*S*)-1-((6-((3-aryl-2,3-dihydro-1*H*-imidazol-1-yl)methyl)pyridin-2-yl)methyl) affords 86% conversion and 25% yield under similar conditions (80 ^{0}C and 5 bar H_2).[21,22] Remarkably, immobilization of these molecular complexes in MOF architectures or mesoporous silica combines the catalytic power of the iridium or ruthenium complex with that of the support enhancing both conversion and selectivity.

Homogeneous catalysis by well-defined metal cluster complexes offers the possibility of performing transformations similar to those observed in heterogeneous phase, which are known to be difficult to trace and control. Herein, we report the first homogeneous catalyst based on non-noble metals for the clean and atom efficient *N*-alkylation of amines starting from nitro compounds and aldehydes using molecular hydrogen as a benign reducing agent. The catalyst, a diamino cuboidal molybdenum sulfide cluster, is highly selective and preserves its integrity during the process.

Results and discussion

An initial evaluation of the $[Mo_3S_4Cl_3(dmen)_3]^+$ catalyst performance on the model reaction of nitrobenzene (**1a**) with benzaldehyde (**2a**) was realized using different solvents motivated by the already established solvent influence on the reactants conversion and products selectivity.[17,19] For this study, we have tentatively chosen the optimum reaction conditions used for the hydrogenation of nitroarenes to anilines applying this molybdenum-based complex (18 h at 70 °C under 20 bar H_2 and 5 mol% of catalyst) and 1.2 equivalents of **2a** have been added to the reaction mixture.[6] While methanol appears as an optimum solvent for the hydrogenation of nitroarenes, the best yield towards the formation of the *N*-benzylaniline (**3a**) has been obtained in THF (Table 1, entries 1-3). When molecular sieves are added to remove water from the reaction mixture and tentatively shift the equilibrium towards the in situ generated imine, conversion of **1a** halved and no secondary amine **3a** is formed (Table 1, entry 4). Surprisingly, similar reactivity is observed in THF-H_2O mixtures (Table1, entries 5 and 6). Thus, traces of water, approximately between 150 and 1500 ppm, are needed to achieve a quantitative formation of **3a**, while an excess of water has a detrimental effect on the reaction outcome (Table 1, entry 4). These results suggest a direct implication of the water molecules in the reaction mechanism. The beneficial effect of controlled amount of water in the reductive *N*-alkylation of amines is not unprecedented.[23] In contrast, larger amounts of water, up to 50%, are tolerated in the tandem reactions of nitro compounds to secondary amines catalyzed by Co-Co_3O_4/NGr@C and Fe_2O_3/NGr@C catalysts in THF.[17–19] In this last case, water addition is believed to promote hydrophobic association of aldehydes and amines as well as suppress catalysts poisoning.[24]

Table 1. Influence of the solvent in the reductive amination of nitrobenzene with benzaldehyde.



Entry [a]	Solvent	Conv. [%][b]	Yield [%][b]		
			3a	**4a**	**5a**
1	1,4-Dioxane	31	0	7	22
2	CH_3OH	99	74	23	0
3	THF (150-1500 ppm of H_2O)	>99	99	0	0
4	THF (molecular sieves)	50	0	18	30
5	THF-H_2O (10:1)	47	0	36	11
6	THF-H_2O (5:1)	14	0	11	2

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), H_2 (20 bar), catalyst (5 mol %), solvent (2 mL), 18 h, 70 ºC. [b] Determined by GC analysis using hexadecane as an internal standard.

Next, optimization of the temperature, hydrogen pressure and catalyst loading was addressed (Tables SI1, SI2 and SI3). Full conversion of **1a** with a quantitative yield of **3a** (>99%) occurs at 70 ^{0}C, 20 bar of hydrogen pressure and 5 mol% of catalyst loading within 18 hours. In contrast, partial conversion of **1a** (48%) with only scarce formation of **4a** (7% yield) and **5a** (38% yield) is achieved after 4 h. Then, longer reaction times are needed for the reduction of the imine intermediate, which is in good agreement with the general tendency that imine hydrogenation is regarded as the rate-determining step in the reductive amination sequence. It shoud be noted that when aldehydes were replaced by ketones, the reaction stopped at the aniline formation stage and no traces of the iminium ion or the secondary amine could be detected.

Our recent works on the catalytic reduction of nitroarenes to aniline derivatives mediated by Mo_3S_4-based clusters decorated with diphosphino, diamino or diimino ligands show no fragmentation of the cluster core during the first stage of this tandem process.[6–8] Here, a color change, from green to brown, occurs during the catalytic process due to the basicity increase caused by the amine

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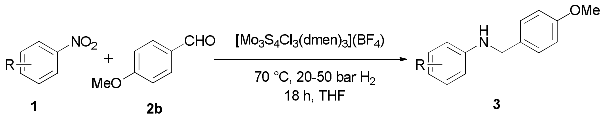
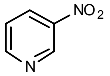
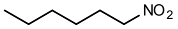
generation. However, analysis of the reaction mixture by electrospray ionization mass spectrometry (ESI-MS), shows a single peak at m/z = 786.9, associated to the pseudomolecular $[Mo_3S_4Cl_3(dmen)_3]^+$ ion on the basis of the m/z value and its characteristic isotopic pattern (Figure SI1). Additionally, cluster integrity was further confirmed by ^1H NMR spectroscopy (Figure SI2). Therefore, the integrity of the cluster core is also preserved during the reductive amination stage. In addition, catalyst recycling in the model reaction after recovering the catalyst by evaporating, washing and drying the reaction mixture, shows full conversion and an excellent yield of **3a** (90%) in the second run (Figure SI3). In a third run, conversion decreased to 67% and only traces of the secondary amine **3a** were formed together with *N*-benzylideneaniline (**5a**) as a major product (46%) and aniline (**4a**) in 16% yield.

To prove the general applicability of the Mo_3S_4-based catalytic system, the reaction between various functionalized nitro compounds and aldehydes was investigated. More specifically, different nitro compounds were reacted with *p*-anisaldehyde (**2b**) (Table 2), and as shown in Table 3, the reductive amination of diverse structure aldehydes was carried out with *p*-chloronitrobenzene (**1b**). To our delight, the corresponding secondary amines were afforded in good to excellent yields. As a general trend, when both the aldehyde and nitroarene are funtionalized with electron-donating groups, such as alkyl, alkoxy or thiomethyl groups, the one-pot reductive amination reaction proceeds smothly towards the formation of the secondary amines. However, the presence of electron-withdrawing groups on the aromatic ring had a high impact on the reductive amination activity since an increased hydrogen pressure (up to 50 bar H_2) is required to avoid accumulation of the imine intermediate.

Gratifyingly, both halogen-substituted nitroarenes and aldehydes react to give the corresponding halogenated-amines without any dehalogenation processes affording the corresponding halogenated secondary amines in moderate to excellent yields. Notably, reductive amination of *p*-fluorobenzaldehyde with **1b** affords a quantitative yield of the expected alkylated amine (Table 3, entry 5). However, reaction with the *ortho*-isomer requires an increased hydrogen pressure (50 bar H_2) to get a moderate yield of the corresponding secondary amine (Table 3, entry 6). Hence, it seems that reactivity could be affected by both electronic and steric effects.

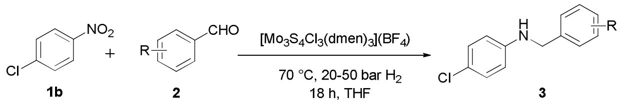
Table 2. Hydrogenation of different nitroarenes (entries 1-9) and 1-nitrohexane with *p*-anisaldehyde.

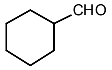


Entry[a]	Substrate	P (bar)	Conv. [%][b]	Yield amine **3** [%][b]
1	R = H	20	>99	(98)
2[c]	R = 3-Me	20	>99	91
3[d]	R = 3-CF_3	50	>99	(97)
4	R = 4-F	20	>99	>99
5[d]	R = 4-Cl	20	>99	(91)
6	R = 4-I	20	>99	(90)
7[d,e]	R = 4-CN	50	>99	(82)
8[d,e]	R = 4-COOMe	50	>99	(85)
9[d, f]		50	>99	(81)
10[c, d, g]		50	>99	61

[a] Reaction conditions: **1** (0.25 mmol), **2b** (0.3 mmol), catalyst (6 mol % related to nitroarene), solvent (2 mL). [b] Determined by GC analysis using hexadecane as an internal standard; yields of isolated products given in parentheses. [c] Traces of aniline as byproduct. [d] Traces of imine as byproduct. [e] 24 h. [f] 100 ºC of temperature. [g] 150 ºC of temperature; Yield based on ^1H NMR using 2,4,6-trimethylphenol as internal standard.

Table 3. Hydrogenation of diverse benzaldehydes (entries 1-8) and cyclohexanecarboxaldehyde with 1-chloro-4-nitrobenzene.



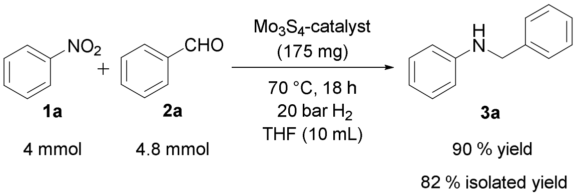
Entry[a]	Substrate	P (bar)	Conv. [%][b]	Yield amine **3** [%][b]
1	R = H	40	>99	(95)
2[c]	R = 4-*i*Pr	20	>99	(90)
3	R = 3-OMe; 4-OEt	20	>99	(97)
4	R = 4-SMe	20	>99	(95)
5	R = 4-F	20	>99	>99
6[c,d]	R = 2-F	50	>99	(68)
7[c,d]	R = 4-Br	50	>99	(77)
8[d]	R = 3-$CHCH_2$	40	>99	(85)
9[c,d]		50	>99	88 (79)

[a] Reaction conditions: **1b** (0.25 mmol), **2** (0.3 mmol), catalyst (6 mol % related to nitroarene), solvent (2 mL). [b] Determined by GC analysis using hexadecane as an internal standard; yields of isolated products given in parentheses. [c] 24 h. [d] Traces of imine as byproduct.

From a synthetic point of view, substrates bearing reducible functionalities are highly attractive. In this respect, we tested some substrates functionalized with nitriles, esters or olefines. To our delight, these moieties were well tolerated, thus furnishing the expected amines in 82-85% isolated yields (Table 2, entries 7 and 8; Table 3, entry 8). In addition, a nitro-substituted heteroarene was tested and the corresponding N-heterocyclic amine was isolated in 81% yield (Table 2, entry 9).

Nowadays, the reductive amination of aldehydes with aliphatic nitrocompounds remains as an important challenge. Interestingly, in the presence of our Mo_3S_4-based catalyst reaction between **2b** and 1-nitrohexane leads to the formation of the secondary amine in 61% yield (Table 2, entry 10). Moreover, our catalytic system also works with cyclic aliphatic aldehydes. Reductive amination of cyclohexanecarboxaldehyde with **1b** affords a moderate yield (60%) of the desired amine (Table 3, entry 9).

Finally, the preparative value of this protocol was further demonstrated upscaling the model reaction of nitrobenzene (**1a**) with benzaldehyde (**2a**) by a factor of 40 and using a considerable higher concentration of reactants. As shown Scheme 1, *N*-benzylaniline (**3a**) was obtained in 90 % yield after purification by column chromatography.



Scheme 1. Up-scaled preparation of N-benzylaniline (**3a**)

Conclusions

In conclusion, we have developed an atom-efficient catalytic protocol for the synthesis of secondary amines through a one-pot reductive amination reaction from easily available nitroarenes and aldehydes using hydrogen as reducing agent. The use of a well-defined diamino molecular Mo_3S_4 cluster as catalyst allows for successful reductive amination of aldehydes with the in situ generated primary amines selectively affording a variety of secondary amines in good to excellent yields. Remarkably, this procedure applies for aromatic as well as for aliphatic nitro compounds or aldehydes. Spectrometric and spectroscopic techniques show no changes in cluster composition or evidences of cluster fragmentation during the catalytic reaction. Mechanistic investigations on the catalytic process which combine theory with experiment are in progress.

Experimental section

Synthesis of the catalyst: The catalyst $[Mo_3S_4C_{l3}(dmen)_3](BF_4)$ was prepared starting from the $[Mo_3S_4(tu)_8(H_2O)]Cl_4{\cdot}4H_2O$ thiourea precursor according to the literature.[6]

General procedure for the one-pot reductive amination: A 8 mL glass vial containing a stirring bar was sequentially charged with the molybdenum catalyst (4.4 mg, 0.005 mmol of $[Mo_3S_4Cl_3(dmen)_3](BF_4)$), nitrobenzene (10 µL, 0.097 mmol), benzaldehyde (12 µL, 0.12 mmol), *n*-hexadecane (15 µL; added as an internal standard) and 2 mL of THF. Afterwards, the reaction vial was capped with a septum equipped with a needle and set in the alloy plate, which was then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30 bar of hydrogen, then pressurized to 20 bar and placed into an aluminum block, which was preheated at 70 °C. After 18 h, the autoclave was cooled to room temperature and the hydrogen was released. Ethyl acetate (2 mL) was then added, and a sample was taken to be analyzed by GC. To determine the isolated yields of the anilines, the general procedure was scaled up by the factor of 2.5, and no internal standard was added. After completion of the reaction, the mixture was purified by silica column chromatography (n-heptane/ethyl acetate mixtures) to give the corresponding anilines. In the case of the nitroalkane, 2,4,6-trimehtylphenol was added as internal standard and the yield was calculated based on ^{1}H NMR.

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COMMUNICATION

One-pot selective synthesis of secondary amines catalyzed by a well-defined Mo_3S_4 cluster using hydrogen as benign reductant.