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The first example of catalytic *N*-oxidation of tertiary amines by tungstate-exchanged Mg–Al layered double hydroxide in water: a green protocol†

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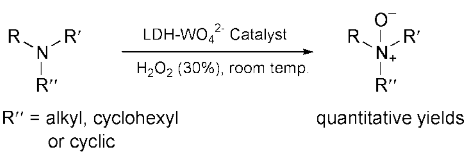
Received (in Cambridge, UK) 31st May 2001, Accepted 23rd July 2001
First published as an Advance Article on the web 28th August 2001

A green process, using a recyclable tungstate-exchanged Mg–Al layered double hydroxide (LDH-WO$_4^{2-}$) heterogenised catalyst and aqueous H_2O_2 oxidant in water, leads to *N*-oxidation of aliphatic *tert*-amines to amine *N*-oxides in quantitative yields, at a high rate at room temperature.

Aliphatic *tert*-amine *N*-oxides are essential and major components for ubiquitously used materials such as hair conditioners, shampoos, toothpaste, laundry detergent powders, fabric softeners, toilet soaps and cosmetics as well as in biomedical applications.[1] Amine oxides are compounds of increasing interest as potential cytoximes which are hypoxia-selective for the treatment of solid tumors.[2] These *N*-oxides are also used as stoichiometric oxidants to accomplish catalytic cycles in important reactions such as osmium catalysed dihydroxylation of olefins,[3a,b] ruthenium catalysed oxidation of alcohols[3c] and Mn–salen catalysed epoxidation of olefins.[3d] Amine *N*-oxides are currently prepared *via* a non-catalytic oxidation of *tert*-amines with H_2O_2 in a slow reaction.[3a,4] Other oxidants employed to hasten the oxidation of *tert*-amines include peracids,[5a] magnesium monophthalamate,[5b] 2-sulfonyloxaziridines,[5c] α-azohydroperoxides[5d] and dioxiranes,[5e] which are not only expensive, but also generate large amounts of effluent during the reaction. The biomimetic oxidation of *tert*-amines is induced by 4a-hydroperoxyflavin in the presence of H_2O_2 as oxidant.[6] This forms the sole example of a catalytic reaction to the best of our knowledge. There is a strong need to develop a '*greener technology*'[7] with higher throughput, and in order to conform to the above, we accordingly designed and developed an eco-compatible process utilising a recyclable heterogeneous catalyst in aqueous medium. We report here, an efficient and heterogeneous tungstate-exchanged layered double hydroxide catalyst (LDH-WO$_4^{2-}$), for the oxidation of aliphatic *tert*-amines in water as solvent using aqueous H_2O_2 as oxidant which leads to excellent yields for the first time (Scheme 1).

Layered double hydroxides (LDHs)[8] have recently received much attention.[9] LDHs consist of alternating cationic M^{II}_{1-x}-$M^{III}_x(OH)_2^{x+}$ and anionic $A^{n-}\cdot zH_2O$ layers. The positively charged layers contain edge-shared metal M^{II} and M^{III} hydroxide octahedra, with charges neutralized by A^{n-} located in interlayer spacings or at edges of the lamellae. Small hexagonal LDH crystals of composition $Mg_{1-x}Al_x(OH)_2Cl_x\cdot 2H_2O$ were synthesized following existing procedures (here $x = 0.25$).[9a] The anionic species tungstate, molybdate and vanadate were exchanged with LDH-Cl to give LDH tungstate, molybdate and vanadate, respectively. The Mg–Al LDH (3 : 1) tungstate (cat **1**) was prepared according to the reported procedure.[9c] 1 g of Mg–Al–Cl LDH was stirred in 100 ml of an aqueous solution of 1.87 mM (0.616 g) sodium tungstate at 293 K for 24 h. The solid catalyst was filtered off, washed with deionised and decarbonated water and lyophilized to dryness. Similarly, the Mg–Al LDH molybdate (cat **2**) and Mg–Al LDH vanadate (cat **3**) were prepared. The preparation of LDH-{$PO_4[WO(O_2)]_4$} (cat **4**) was carried out according to the literature procedure.[10] To a solution of 0.46 mmol of isolated (NBu^n_4){$PO_4[WO(O_2)_2]_4$} in acetone (3 ml) was added 1 ml of H_2O_2 [35% (w/w) aqueous solution] and 1 g of Mg–Al–Cl LDH and the mixture was stirred for 16 h at room temperature. The obtained material (cat **4**) was treated consecutively with water–acetone (1 : 1) and acetone.



Scheme 1 Oxidation of *tert*-amines to amine *N*-oxides catalysed by tungstate-exchanged Mg–Al LDH.

All these catalysts were well characterised by powder-XRD, TGA–DTA and chemical analysis. The X-ray powder diffraction patterns of the LDH and LDH-WO$_4^{2-}$ (cat **1**), LDH-MoO$_4^{2-}$ (cat **2**), LDH-VO$_3^-$ (cat **3**), LDH-{$PO_4[WO(O_2)]_4$} (cat **4**) scarcely differ in the range $2\theta = 3$–65°. These data clearly indicate that the above anions are not intercalated but lie on edge-on positions of LDH in the solid catalyst. Chemical analysis of the catalysts revealed the tungstate (%) content in cat **1** as 11% and cat **4** as 21% while the molybdate content in cat **2** was 9.9%, and vanadate content in cat **3** was 7.8%. The thermogravimetric profiles and the relative derivative curves (TGA and DTA) for the tungstate, molybdate and vanadate exchanged LDH catalysts cat **1–4** show two stages of weight loss associated with two endotherms characteristic of LDHs. These results provide evidence that there is no structural disorder after the ion-exchange.

The exchanged LDH catalysts (cat **1–4**) and their homogeneous analogues were evaluated in oxidation of aliphatic *tert*-amines with H_2O_2 in order to identify the best catalysts (Table 1). The *tert*-amine is oxidised with aqueous hydrogen peroxide (30% w/w) using water as a solvent in the presence of catalyst at room temperature under continuous stirring, while monitoring the progress of the reaction by TLC. The order of activity of

Table 1 Catalytic *N*-oxidation of *N*-methylmorpholine to *N*-methylmorpholine *N*-oxide catalysed using various metal ion-exchanged LDH catalysts and their homogeneous analogues

Entry	Catalyst	Time/h	Yield[c] (%)
1	LDH-WO$_4^{2-}$ (cat **1**)		
	Procedure I[a]	1.0	96
	Procedure II[b]	1.0	96
2	LDH-MoO$_4^{2-}$(cat **2**)	3.5	90
3	LDH-VO$_3^-$ (cat **3**)	3.5	40
4	LDH-{$PO_4[WO(O_2)]_4$} (cat **4**)	3.5	40
5	Na_2WO_4	3.5	75
6	$NaVO_3$	3.5	15
7	Na_2MoO_4	3.5	48
8	None	24.0	25

[a] 2 mmol of substrate, 200 mg of catalyst, 10 ml of water and 6 mmol of aq. H_2O_2 (30% w/w). [b] 6 mg of dodecylbenzenesulfonic acid sodium salt added as surfactant. [c] Isolated yield.

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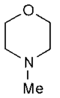
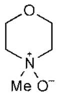
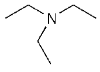
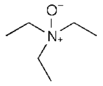
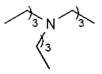
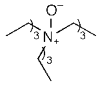
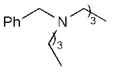
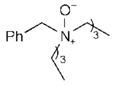
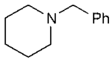
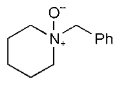
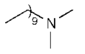
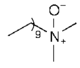
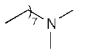
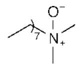
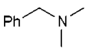
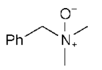
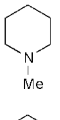
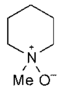
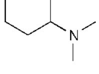
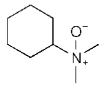
† IICT Communication No: 4804.

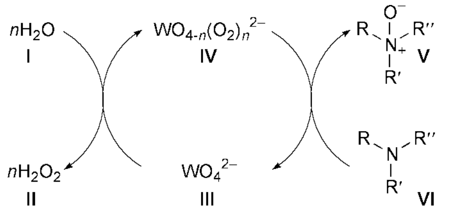
the LDH exchanged catalysts is: cat **1** > cat **2** > cat **3** = cat **4** and thus LDH-WO_4^{2-} (cat **1**) is inferred to be the best catalyst in the oxidation of *tert*-amines. The heterogeneous catalysts provide superior performance over their homogeneous counterparts. The efficacy in increasing the rate of *N*-oxidation is evident from Table 1, in which LDH-WO_4^{2-} affords 96% conversion in 1 h *cf.* 25% in 24 h in the absence of a catalyst.

In an effort to understand the scope of the reaction, several other amines having different R groups attached to the tertiary nitrogen atom were subjected for oxidation using the best catalytic LDH–WO_4^{2-}–H_2O_2 system to give excellent yields and ≅ 100% selectivity (Table 2). No other by-products were observed in these reactions. Water proved to be the best solvent in terms of activity in the *N*-oxidation of *tert*-amines. When the dodecylbenzenesulfonic acid sodium salt is employed as an additive, the rate of the *N*-oxidation reaction is increased 2–3 fold except in the case of *N*-methylmorpholine (Table 2). This may be due to the high hydrophilicity of the latter, when compared with other *tert*-amines used. The present *N*-oxidation reaction takes place under liquid–solid–liquid triphasic conditions, comprising of organic *tert*-amine, solid catalyst and aqueous phase. We assumed that the main role of the surfactant is to increase the contact area of the interface between the aqueous and organic phases and to enhance the transfer of the lipophilic amine from the organic to the aqueous phase. The amine *N*-oxides thus obtained are useful additives for the surfactants,[11,12] for example, the product in Table 2, entry 18 is sold under the trade name *Barlox 10S*.[1a] The benzylic amine *N*-oxides (Table 2, entries 14, 16 and 21) serve as substrates.[13]

Table 2 Oxidation of *tert*-amines catalysed by LDH-WO_4^{2-} (cat **1**)[a]

Entry	Tertiary amine	Procedure	Amine oxide	Time/h	Yield[b] (%)
9		I		1.0	96
10		II		1.0	96
11		I		3.0	96
12		II		1.5	96
13		I		3.0	94
14		I		1.5	96
15		II		1.0	95
16		I		3.0	97
17		II		1.0	97
18		I		2.5	97
19		I		2.5	95
20		II		1.0	95
21		I		1.5	95
22		II		1.0	96
23		I		3.5	95(94)[c]
24		II		1.0	95
25		I		3.0	96
26		II		1.0	95

[a] Reaction conditions as in Table 1 (footnotes *a* and *b*). [b] Isolated yields (all the products were characterized by ^1H NMR and mass spectrometry). [c] Yield after sixth cycle.



Scheme 2 Plausible catalytic cycle for the *N*-oxidation of *tert*-amines to amine *N*-oxides by tungstate-exchanged Mg–Al LDH.

Furthermore cat **1** can be reused for six cycles (see Table 2, entry 23) without loss of activity and selectivity. The reaction did not proceed when conducted with the resulting filtrate after separation of the solid catalyst from the previous batch. This indicates that the active ingredient has not leached out of the solid catalyst during the reaction.

A plausible catalytic cycle in the oxidation of amines to amine oxides as described in Scheme 2 involves formation of peroxotungstate, **IV** on interaction of tungstate LDH **III** with hydrogen peroxide **II**.[9c] A shift of λ_{max} 250 (LDH **III**) to 325 nm (**IV**) according to UV-DRS confirms the formation of peroxotungstate species. The peroxotungstate **IV** species transfers its electrophilic oxygen to an amine **VI** forming the amine *N*-oxide **V** with regeneration of the active catalyst **III**.

In conclusion, the present process represents the sole example for synthesis of *N*-oxides wherein the heterogenised tungstate-based Mg–Al LDH is used as a catalyst. The potential for its commercial application is strengthened by the high throughput of the product, lower process inventories and use of an aqueous phase reaction system.

B. B. and Ch. V. R. thank CSIR, India for SRF.

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