Molybdenum oxide/bipyridine hybrid material {[MoO$_3$(bipy)][MoO$_3$(H$_2$O)]}$_n$ as catalyst for the oxidation of secondary amines to nitrones

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ABSTRACT

The inorganic–organic hybrid material {[MoO$_3$(bipy)][MoO$_3$(H$_2$O)]}$_n$ (bipy = 2,2′-bipyridine) can be used as a water-tolerant catalyst for the oxidation of secondary amines under mild conditions using either urea hydrogen peroxide (UHP) or tert-butylhydroperoxide (TBHP) as the oxidant. Under optimized reaction conditions (2 mol % catalyst, 3–4 equiv TBHP, CH$_2$Cl$_2$ as the solvent, 40 °C), the corresponding nitrones were obtained with different efficiency depending on the nature of the cyclic or acyclic amine used.

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The chemistry of Mo^{VI} is very prominent in industrial processes, as proven by the large variety of reactions (oxidation, ammoxidation, metathesis, and hydrocarbon dehydrogenation) which are carried out over Mo^{VI} catalysts.[1] Since the chemistry of Mo^{VI} is largely dominated by complexes containing the cis-dioxomolybdenum(VI) structural unit, a very large number of these complexes have been investigated as catalysts.[2]

Recently, some of us have been developing soft chemistry routes for the synthesis of new molybdenum(VI) oxide inorganic–organic hybrid materials.[3] The exploration of metal oxide-based hybrid materials is of contemporary interest, not only because of their hierarchical structures but also because of their potentially fascinating properties in the fields of catalysis, sorption, electrical conductivity, magnetism, and optics. Many inorganic–organic hybrids combining an optimal trade-off of properties are synthesized by nature using soft synthetic conditions.[4] Therefore, the synthesis of inorganic–organic hybrids by soft chemistry methods is very appealing because it paves the way to the vast field of biological applications.

Last, but not least, soft chemistry routes possess added value in the context of sustainable chemistry.
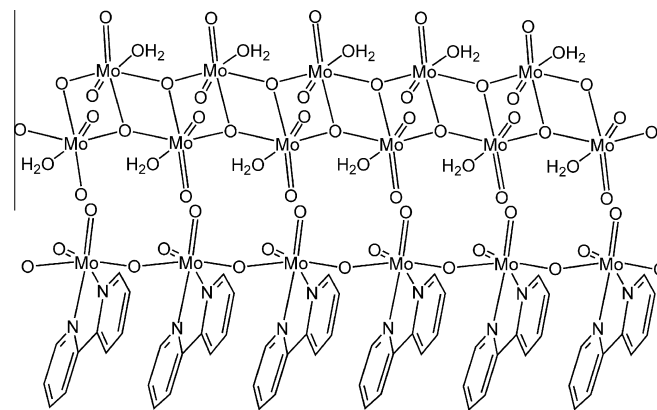

Figure 1. Schematic representation of the structure of **1** containing two one-dimensional polymers formulated as [MoO$_3$(bipy)]$_n$ and [MoO$_3$(H$_2$O)]$_n$, which are interconnected by O–H···O hydrogen bonds (not shown).

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Table 1
Optimization of the reaction conditions
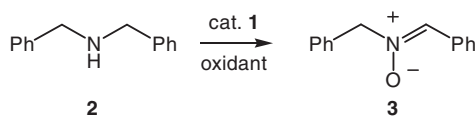
Entry	Solvent	Mol % 1	Oxidant[a]	Temp (°C)	Time (h)	Conv[b] (%)	Yield[c] (%)
1	MeOH	2	UHP	25	8	94	65
2	MeOH	3	UHP	20	8	96	67
3	MeOH	2	UHP	40	6	96	50
4	CH₃CN	2	UHP	40	3	98	46
5	CH₂Cl₂	2	UHP	25	15	98	54
6	CH₂Cl₂	2	TBHP	20	720	>98	61
7	CH₂Cl₂	2	TBHP	40	5	97	64

[a] UHP 3 mol equiv; TBHP 4 mol equiv.
[b] Conversion based on recovered amine after flash chromatography.
[c] Isolated yield.

Our work unraveled that hybrid molybdenum oxide-based materials bearing organonitrogen ligands, like [MoO₃(bipy)]ₙ and {[MoO₃(bipy)][MoO₃(H₂O)]}ₙ (**1**) (Fig. 1), can be synthesized by soft chemistry routes and are potentially interesting catalysts for the epoxidation of nonfunctionalized olefins.[3,5,6] Several other related monometallic molybdenum(VI) oxide based hybrid materials containing organonitrogen ligands directly coordinated to the oxide substructure have been described,[7] but the catalytic potential of these systems has yet to be fully explored. In the present work we have focused on further investigating the catalytic potential of the hybrid material **1** by applying it in the direct oxidation of secondary amines to nitrones.

Nitrones are highly versatile 1,3-dipoles capable of reacting regio- and stereospecifically with a variety of dipolarophiles generating up to three stereocentres in a single reaction step.[8] This reaction allows the access to the important class of isoxazolidine compounds. Nitrones are also of interest because they undergo nucleophilic additions to afford N,N-disubstituted hydroxylamines. One of the reasons for the success of the synthetic application of nitrones is that, contrary to the majority of other 1,3-dipoles, most nitrones are stable compounds that do not require in situ formation. Their utility is well demonstrated in the total synthesis of several natural products including alkaloids, aza-, and amino sugars, in which they are key synthons. Last, but not least, nitrones are used as spin trap agents.[9]

Catalytic oxidation of secondary amines with active oxygen compounds is considered as one of the most attractive methods for the generation of nitrones.[10,11] Quantitative oxidation of secondary amines occurs upon treatment with M^VI polyperoxo complexes (PPC) of general formula [C₅H₅N(CH₂)₁₅CH₃]₃{PO₄[MO(O₂)₂]₄} (M=Mo, W).[12] However, to the best of our knowledge only one catalytic system making use of molybdenum was described in the literature for the oxidation of secondary amines to nitrones. Na₂MoO₄ was successfully used for the direct oxidation of secondary amines in the presence of the oxidant UHP (urea hydrogen peroxide).[10a]

Dibenzylamine (**2**) was used as the model substrate to study the best conditions for the oxidation of secondary amines to nitrones (Table 1). UHP and *tert*-butylhydroperoxide (TBHP) were used as stoichiometric cooxidants together with compound **1**, used in 1–3 mol %. Use of 2 mol % of **1** resulted in the best compromise between reaction time and total yield.

The reactions usually reached a conversion of 96–98% based on the recovery of amine (2–4%) that is observed in a protonated form (deshielded signals of protons adjacent to the nitrogen atom: $\Delta\delta$ = 0.12–0.70 ppm) in the ¹H NMR spectrum of the final crude reaction mixture. Likely, the protonated amine is protected from oxidation by catalyst **1**. Attempts to run the reaction in the presence of a base (Na₂CO₃, K₂CO₃, NaOAc) led to incomplete oxidation and formation of sizable amounts of N-benzylbenzaldimine besides nitrone **3**. The cooxidants, used in moderate excess (3–4 mol equiv), gave similar results. UHP requires polar solvents, such as MeOH or CH₃CN, for its higher content of water. In less polar CH₂Cl₂ longer reaction times are necessary that result in a higher decomposition of the nitrone. TBHP can be used with similar efficiency in CH₂Cl₂ or CHCl₃. Under the same conditions, temperature affects the reaction rate (Table 1, entries 1 and 6 vs 3 and 7, respectively). Small amounts of benzaldehyde, the product of hydrolysis of the nitrone, can be observed in the crude reaction mixture, particularly when UHP is used as the cooxidant. Reactions with TBHP in CH₂Cl₂ are preferred, because these can provide more anhydrous conditions. To test the scope of catalyst **1** in this reaction the oxidation was extended to other acyclic and cyclic secondary amines, using both cooxidants (procedure A and B)[13] whose results are reported in Table 2.

Oxidation of less activated dibutylamine **4** occurred with similar efficiency as dibenzylamine **2** only with TBHP as the cooxidant (Table 2, entries 1 and 2). The same is valid for non-symmetrical ethylbenzylamine **6** (Table 2, entries 3 and 4). With TBHP it gave a mixture of regioisomeric nitrones **7a** and **7b** in 4:1 ratio with the major one deriving from the more favorable oxidation of benzylic methylene (entry 3, Table 2). The catalyst appears to be slightly more selective than other oxidizing systems with the same amine **6**.[14]

In the oxidation of acyclic amines only the Z nitrones were isolated, and the structures assigned on the basis of their NMR signals and comparison with the literature data. In the case of dibutylamine **4** the formation of E-**5** isomer (CD₃OD, δ CH=N–O 7.19 ppm, t, J = 5.9 Hz) was observed in reactions carried out in the NMR tube. Complete isomerization to the Z-**5** isomer (CD₃OD, δ CH=N–O 6.66 ppm, t, J = 5.5 Hz) occurred during the work-up. In the case of the other acyclic nitrones **3** and **7**, the possible formation of the corresponding kinetic E-isomers[15] could not be confirmed by the analysis of NMR spectra of the reaction mixture, because of overlapping aromatic proton signals.

Oxidation of tetrahydroisoquinoline (**8**) affords the expected nitrone **9** besides the aromatized isoquinoline N-oxide **10** with both cooxidants (entries 5 and 6, Table 2). Running the reaction in MeOH with UHP (Procedure B) as the cooxidant at rt gives a higher ratio of **9** versus **10**, likely for the milder reaction conditions. Oxidations of other cyclic amines gave erratic results. 2,6-Dimethylpiperidine **11** (entry 7, Table 2) gave the best results in the oxidation, even on a