Oxidation of *N*,*N*-Disubstituted Hydroxylamines to Nitrones with Hydrogen Peroxide Catalyzed by Polymer-Supported Methylrhenium Trioxide Systems

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Abstract: Poly(4-vinylpyridine)/methylrhenium trioxide (MTO) compounds **I**–**III** and microencapsulated polystyrene/MTO systems **IV**–**V** are efficient catalysts for the oxidation of secondary hydroxylamines to the corresponding nitrones with H_2O_2. Complete conversions of substrates and quantitative yields of products are obtained under environmentally friendly experimental conditions and with the use of simple work-up procedures. Symmetrically substituted hydroxylamines, and non-symmetrical 3-substituted and 2-substituted hydroxypyrrolidines, precursors of nitrones applied in the synthesis of alkaloids and biologically active congeners, have been considered as substrates. The heterogeneous catalysts are stable under the reaction conditions and can be recovered and recycled for at least five times without any appreciable loss in efficiency.

Keywords: green chemistry; hydrogen peroxide; methylrhenium trioxide; nitrones; oxidation; supported catalysts

Introduction

Nitrones are very useful building blocks for the synthesis of biologically active nitrogen-containing compounds. They have been widely employed either as 1,3-dipoles in [3+2] cycloaddition reactions with alkenes[1] or as electrophilic acceptors towards organometallic reagents.[2] In addition, nitrones are widely used as spin trap reagents in biological systems.[3]

Nitrones can be synthesized by a variety of methods, among which the two most general consist in the condensation of *N*-monosubstituted hydroxylamines with carbonyl compounds and in the oxidation of suitable precursors.[4] In this latter case, *N*,*N*-disubstituted hydroxylamines or secondary amines have been used as the starting materials. Procedures employing the latter substrates, generally readily available, are usually more useful, particularly the catalytic ones developed by Murahashi and others.[5] However, some of us have recently accessed a variety of enantiopure five-membered cyclic nitrones by oxidation of the corresponding hydroxylamines.[6] In this particular case, *N*-hydroxypyrrolidines are much better precursors and more easily available substrates than the corresponding amines. Although several oxidants, such as metal salts or oxides (copper, lead, silver) or complex organic oxidants (oxaziridines and quinones), are available for this transformation, they are not satisfactory, since they have to be used at least in stoichiometric amounts and often lack in generality.[4,7] Oxidations of hydroxylamines catalyzed by palladium,[8] tetrapropylammonium perruthenate[9] or Jacobsen (salen)Mn(III) catalyst[10] have been found to be effective. These catalytic procedures certainly have many advantages (use of inexpensive and less dangerous stoichiometric oxidants, if any, and simple work-up procedures), but low yields for water-soluble nitrones and low regioselectivities with non-symmetrically substituted dialkylhydroxylamines have been reported.

Methylrhenium trioxide (CH_3ReO_3, MTO),[11] in combination with hydrogen peroxide, has become in recent years an important catalyst for a variety of synthetic transformations, such as oxidation of olefins,[12] alkynes,[13] aromatic derivatives,[14] sulfur compounds,[15] phosphines,[16] Bayer–Villiger rearrangement,[17] and oxygen insertion into C–H bonds.[18] MTO has also been recently applied to the oxidation of nitrogen containing organic compounds.[5f–i,19] We first reported the oxidation of secondary amines to nitrones, replacing hydrogen peroxide with the complex urea-H_2O_2 (UHP),[5f]

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which simplifies the work-up procedures and allows the use of non-aqueous solvents and safe reagents. This methodology has been scaled-up and optimized[5g] and has already found application for the synthesis of cyclic nitrones.[20] Others have independently reported the oxidation of secondary amines to nitrones employing the MTO/H_2O_2 system.[5h, i] The results reported in the literature suggest that hydroxylamines are the intermediates in the MTO-catalyzed oxidations of secondary amines to nitrones, since the use of 1 equivalent of H_2O_2 with respect to the amine gave the hydroxylamine as the main product, while the use of an excess of H_2O_2 led to nitrones predominantly.[19b] The oxidation of *N*,*N*-disubstituted hydroxylamines to nitrones with H_2O_2 catalyzed by MTO has been subsequently studied concerning its kinetic and mechanistic aspects.[21]

Recently, with the aim of developing clean oxidation processes, we described the preparation of novel heterogeneous rhenium compounds of the general formula $(polymer)_f/(MTO)_g$ (the f/g quotient expresses the ratio by weight of the two components) by heterogenization of MTO on poly(4-vinylpyridine) or polystyrene,[22] applying an extension of the "mediator" concept,[23] and of the microencapsulation technique,[24] respectively. All the new MTO compounds were characterized by FT-IR, scanning electron microscopy (SEM), and wide-angle X-ray diffraction (WAXS).[22] To the best of our knowledge, apart from silica supported MTO complexes,[25] the NaY zeolite/MTO supercage system,[26] and a niobia supported MTO compound,[27] no further data are available in the literature about heterogeneous MTO catalysts. Polymer/MTO catalysts have already proved to be efficient and selective systems for the epoxidation of simple olefins,[22] and for the oxidation of substituted phenol and anisole derivatives.[28]

In this paper we report on the applicability of polymer/MTO systems to the selective oxidation of a series of hydroxylamines with H_2O_2, including simple acyclic hydroxylamines and *N*-hydroxypyrrolidines, to the corresponding nitrones. Among the latter substrates, protected hydroxylated *N*-hydroxypyrrolidines and enantiomerically pure hydroxypyrrolidines, precursors of nitrones applied in the synthesis of alkaloids and biologically active congeners, have been considered. The issue of regioselectivity, relevant for synthetic purposes, has also been addressed, either with 3-substituted and 2-substituted hydroxypyrrolidines. The structures of poly(4-vinylpyridine)/MTO and polystyrene/MTO catalysts **I**–**V** employed, namely poly(4-vinylpyridine) 2% and 25% cross-linked (with divinylbenzene)/MTO (PVP-2%/MTO, **I** and PVP-25%/MTO, **II**, respectively), poly(4-vinylpyridine-*N*-oxide) 2% cross-linked/MTO (PVPN-2%/MTO, **III**), microencapsulated polystyrene 2% cross-linked/MTO (PS-2%/MTO, **IV**), and microencapsulated polystyrene/poly(4-vinylpyridine) 2% cross-linked/MTO (PS-2%/PVP-2%/MTO, **V**), are schematically represented in Figure 1.

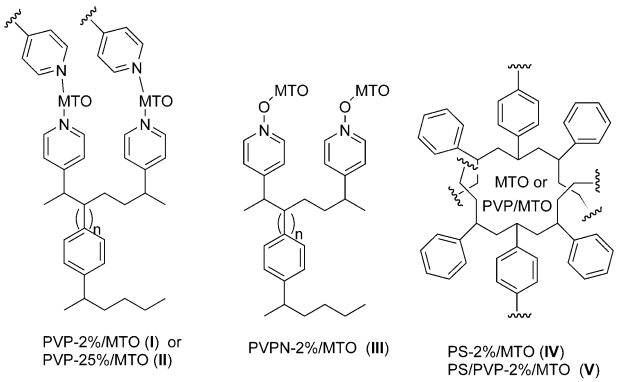


Figure 1. Structures of poly(4-vinylpyridine)/MTO and polystyrene/MTO catalysts **I**–**V**.

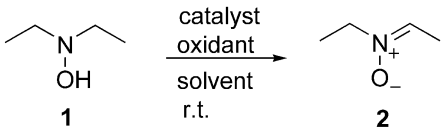
Results and Discussion

The oxidation of hydroxylamines with poly(4-vinylpyridine)/MTO systems **I**–**III**, and microencapsulated polystyrene/MTO systems **IV** and **V** were studied using *N*,*N*-diethylhydroxylamine (**1**), *N*,*N*-dibenzylhydroxylamine (**3**), *N*-hydroxypyrrolidine (**5**), and 3,4-isopropylidenedioxy-*N*-hydroxypyrrolidine (**7**) as representative model compounds of symmetrically substituted acyclic and cyclic hydroxylamines (Schemes 1–4). As a general procedure, the hydroxylamine (1.0 mmol) to be oxidized and H_2O_2 (35% water solution) were added to a suspension of freshly prepared catalysts **I**–**V** (loading factor 0.5) in EtOH (1.0 mL), and the mixture was stirred at 25 °C. The oxidation results are summarized in Tables 1–4, entries 2–6 of each Table. For comparison, the reactions with MTO under homogeneous conditions were carried out and their results are reported in entries 1. In the absence of the catalyst, less than 5% conversion of substrate took place under otherwise identical conditions. Under the appropriate experimental conditions, all of the catalysts were effective in accomplishing the oxidation of hydroxylamine **1** to the corresponding nitrone **2** with complete conversion of substrate and quantitative yield of product (Table 1). The efficient oxidation of **1**, under relatively mild experimental conditions, may be attributed to the retained reactivity of the monoperoxometal $[MeRe(O)_2(O_2)]$ and the bisperoxometal $[MeRe(O)(O_2)_2]$ intermediate species[29] even in the presence of the polymeric supports. On the other hand, heterogeneous MTO systems showed a lower reactivity with respect to MTO, probably because of the presence of a kinetic barrier to the approach of hydroxylamine **1** to polymeric catalysts (Table 1, entries 2–4 *vs.* 1). Among the poly(4-vinylpyridine)/MTO systems **I**–**III**, compound **II**, characterized by a high value of reticulation grade of the matrix, was the best catalyst, giving the nitrone **2** faster than compounds **I** and **III** (Table 1, entries 3 *vs.* 2 and 4). These data are in agreement with our results on the selective epoxidation of olefins with polymer-supported methylrhenium trioxide systems.[22]

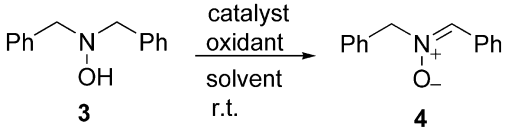
Compound **III**, which is characterized by a pyridine *N*-oxide moiety as anchorage site for the rhenium atom showed the lowest reactivity, and more oxidant was required to complete the oxidation (Table 1, entry 4). Microencapsulated polystyrene/MTO systems **IV** and **V** were the most active catalysts among the heterogeneous compounds used (Table 1, entries 5 and 6).

A quantitative conversion of substrate, and excellent yield of nitrone, was also obtained in the oxidation of *N,N*-dibenzylhydroxylamine (**3**) either with MTO and compounds **I**–**V** (Table 2, Scheme 2). As shown in Table 2, hydroxylamine **3** was less reactive than **1** under similar experimental conditions (compare reaction times for **1** and **3** in Tables 1 and 2). This reactivity pattern is in good agreement with the kinetic trends previously described for the oxidation of hydroxylamines with MTO, in which cases steric effects play a relevant role on the rate constants of the oxidation.[21] However, it should be noted that an opposite trend is shown by the reaction carried out under homogeneous conditions; this result is not consistent with the data previously reported. Microencapsulated polystyrene/MTO systems **IV** and **V** were the most reactive catalysts also for the oxidation of hydroxylamine **3** (Table 2, entries 5 and 6). Again, compound **II** was the best catalyst in the poly(4-vinylpyridine)/MTO series (Table 2, entry 3 *vs.* 2 and 4).

Cyclic hydroxylamines **5** and **7** behaved in a similar way and were efficiently oxidized to give the corresponding nitrones **6** and **8** with high conversions and quantitative yields (>98% for all of the cases studied, Tables 3 and 4, Schemes 3 and 4). Again, microencapsulated polystyrene/MTO systems **IV** and **V** were more reactive than catalysts based on poly(4-vinylpyridine). Even if we have not studied in detail the mechanism of the reaction, data previously collected on the oxidation of cardanol derivatives showed a significant difference in reactivity, depending on the nature of the matrix used for the heterogenization process of MTO.[28b] Thus, while poly(4-vinylpyridine)/MTO systems gave selectively *ortho*- and *para*-benzoquinones, microencapsulated polystyrene/MTO catalysts showed a pro-



Scheme 1.



Scheme 2.

Table 1. Oxidation of *N,N*-diethylhydroxylamine (**1**) with poly(4-vinylpyridine)/MTO systems **I**–**III**, and microencapsulated polystyrene/MTO systems **IV** and **V**.

Entry	Catalyst	H_2O_2 (equivs.)	Solvent	Conversion (%)[a]	Yield (%)[a]	Reaction time
1	MTO 2%[b]	1.5	EtOH	>98	>98	45 min
2	PVP-2%/MTO (**I**)	2.0	EtOH	>98	>98	7 h
3	PVP-25%/MTO (**II**)	2.0	EtOH	>98	>98	4 h
4	PVPN-2%/MTO (**III**)	5.0	EtOH	>98	>98	9 h
5	PS-2%/MTO (**IV**)	1.5	EtOH	>98	>98	2 h
6	PS-2%/PVPy-2%/MTO (**V**)	1.5	EtOH	>98	>98	2 h

[a] Calculated by integration of the ^{1}H NMR of the crude mixture.
[b] 10% molar amount of pyridine added.

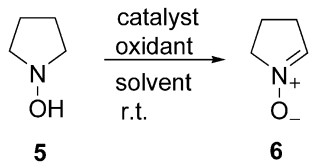
Table 2. Oxidation of *N,N*-dibenzylhydroxylamine (**3**) with poly(4-vinylpyridine)/MTO systems **I**–**III**, and microencapsulated polystyrene/MTO systems **IV** and **V**.

Entry	Catalyst	H_2O_2 (equivs.)	Solvent	Conversion (%)[a]	Yield (%)[b]	Reaction time
1	MTO 2%[b]	1.5	EtOH	>98	93	15 min
2	PVP-2%/MTO (**I**)	4.0	EtOH	>98	>98	10 h
3	PVP-25%/MTO (**II**)	3.0	EtOH	>98	>98	6 h
4	PVPN-2%/MTO (**III**)	4.0	EtOH	>98	>98	12 h
5	PS-2%/MTO (**IV**)	1.5	EtOH	>98	>98	3 h
6	PS-2%/PVPy-2%/MTO (**V**)	1.5	EtOH	>98	>98	5 h

[a] Calculated by integration of the ^{1}H NMR of the crude mixture.
[b] 10% molar amount of pyridine added.

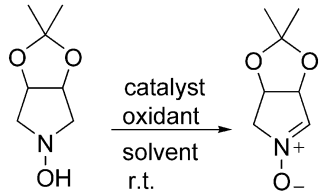
nounced reactivity affording an unprecedented γ-lactone, a product of oxidative aromatic ring degradation and subsequent rearrangement.[28b]

Some experiments were then performed to evaluate the leaching and stability of the catalysts, using compounds **II** and **IV** as representative models. In a test for checking the leaching of **II** and **IV**, the oxidation of hydroxylamine **1** was stopped at *ca.* 50% conversion. After centrifugation, the obtained solutions were colorless and lost their catalytic activity, indicating that no appreciable amount of MTO had been removed from the matrixes. In the tests for recyclability of the catalyst, the reaction mixture was filtered after the hydroxylamine **1** had completely oxidized. The remaining solid was washed with EtOH, dried and used in successive oxidations of the same substrate. Table 5 shows that catalysts **II** and **IV** are stable enough to perform at least five recycling experiments maintaining essentially the same efficiency in terms of conversion and selectivity.



5 **6**

Scheme 3.



7 **8**

Scheme 4.

Next, we addressed the issue of regioselectivity with the oxidation of non symmetric hydroxylamines. Although in some cases good selectivities have been observed,[6b,d,30] regioselective oxidation of non-symmetrical hydroxylamines (or secondary amines) still remains a problem which needs a general solution. A tricky regioselective formation of nitrones has been reported by means of a decarboxylative oxidation of α-amino acids.[31] *N*-Hydroxypyrrolidines **9** and **12**, possessing a substituent at C-3 and C-2, respectively, were considered and were reacted under similar experimental conditions (Tables 6 and 7, Schemes 5 and 6). Non-symmetrical hydroxylamines gave rise to a couple of isomeric nitrones, since the elimination reaction can involve the abstraction of hydrogen at either the α or the α' carbon atom. The ratios of the two nitrones were determined by ^{1}H NMR and are reported in Tables 6 and 7.

The oxidation of the protected 3-hydroxypyrrolidine **9** with catalysts **I**–**V** under the previously described experimental conditions gave a mixture of nitrones **10** and **11** with quantitative conversion of substrate and yield of products (Scheme 5, Table 6). On the basis of the results

Table 3. Oxidation of *N*-hydroxypyrrolidine (**5**) with poly(4-vinylpyridine)/MTO systems **I**–**III**, and microencapsulated polystyrene/MTO systems **IV** and **V**.

Entry	Catalyst	H_2O_2 (equivs.)	Solvent	Conversion (%)[a]	Yield (%)[a]	Reaction time
1	MTO 2%[b]	1.5	EtOH	>98	>98	10 min
2	PVP-2%/MTO (**I**)	5.0	EtOH	>98	>98	11 h
3	PVP-25%/MTO (**II**)	2.0	EtOH	>98	>98	8 h
4	PVPN-2%/MTO (**III**)	6.0	EtOH	>98	>98	14 h
5	PS-2%/MTO (**IV**)	2.0	EtOH	>98	>98	6 h
6	PS-2%/PVPy-2%/MTO (**V**)	2.0	EtOH	>98	>98	6 h

[a] Calculated by integration of the ^{1}H NMR of the crude mixture.
[b] 10% molar amount of pyridine added.

Table 4. Oxidation of 3,4-isopropylidenedioxy-*N*-hydroxypyrrolidine (**7**) with poly(4-vinylpyridine)/MTO systems **I**–**III**, and microencapsulated polystyrene/MTO systems **IV** and **V**.

Entry	Catalyst	H_2O_2 (equivs.)	Solvent	Conversion (%)[a]	Yield (%)[a]	Reaction Time
1	MTO 2%[b]	1.5	EtOH	>98	>98	15 min
2	PVP-2%/MTO (**I**)	9.0	EtOH	>98	>98	22 h
3	PVP-25%/MTO (**II**)	2.0	EtOH	>98	>98	4 h
4	PVPN-2%/MTO (**III**)	9.0	EtOH	>98	>98	21 h
5	PS-2%/MTO (**IV**)	1.0	EtOH	>98	>98	1.5 h
6	PS-2%/PVPy-2%/MTO (**V**)	3.0	EtOH	>98	>98	3 h

[a] Calculated by integration of the ^{1}H NMR of the crude mixture.
[b] 10% molar amount of pyridine added.

Table 5. Stability of polymer-supported MTO catalysts **II** and **IV** in the oxidation of hydroxylamine **1**.

Catalyst[a]	Conversion (%)[b]				
	Run No. 1	Run No. 2	Run No. 3	Run No. 4	Run No. 5
II	>98 (>98)[a]	>98 (>98)	>98 (95)	>98 (97)	>98 (97)
IV	>98 (>98)	>98 (>98)	>98 (>98)	>98 (96)	>98 (>98)

[a] Catalyst: PVP-25%/MTO, **II**, PS-2%/MTO, **IV**.
[b] Values of nitrone **2** yields are given in parentheses. Reaction time: 4 h for **II**, 2 h for **IV**.

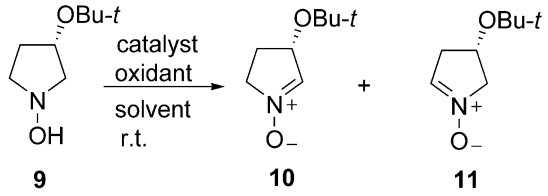
Table 6. Oxidation of 3(*S*)-*tert*-butoxy-*N*-hydroxypyrrolidine (**9**) with poly(4-vinylpyridine)/MTO systems **I**–**III**, and microencapsulated polystyrene/MTO systems **IV** and **V**.

Entry	Catalyst	H_2O_2 (equivs.)	Solvent	Conversion (%)[a]	Yield (%)[a]	**10**:**11** Ratio[a]	Reaction time
1	MTO 2%[b]	1.5	EtOH	>98	>98	1.40	20 min
2	PVP-2%/MTO (**I**)	1.5	EtOH	>98	>98	1.77	8 h
3	PVP-25%/MTO (**II**)	2.0	EtOH	>98	>98	2.57	9 h
4	PVPN-2%/MTO (**III**)	1.5	EtOH	>98	>98	2.45	7 h
5	PS-2%/MTO (**IV**)	3.0	EtOH	>98	>98	1.50	11 h
6	PS-2%/PVPy-2%/MTO (**V**)	1.5	EtOH	>98	>98	1.77	8 h

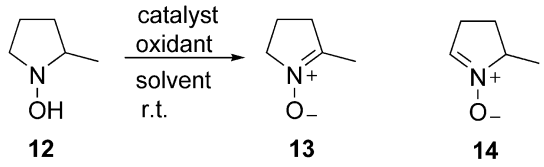
[a] Calculated by integration of the ^{1}H NMR of the crude mixture.
[b] 10% molar amount of pyridine added.

reported in Table 6, all catalysts **I**–**V** were found to be more selective than MTO, giving the nitrone **10** in higher yields (entries 2–6 *vs.* 1). The observed regioselectivity is in qualitative agreement, albeit poorer, with that obtained in the stoichiometric oxidation of **9** with HgO, in which case the electronegative substituent at C-3 enhanced the rate of the adjacent C–H bond cleavage by stabilizing the incipient negative charge at C-2.[6b,d] Compound **II** was the best catalyst system for the synthesis of nitrone **10** concerning the selectivity of the oxidation (Table 6, entry 3). It is interesting to note that in this case microencapsulated polystyrene/MTO systems and poly(4-vinylpyridine)/MTO compounds showed a similar reactivity.

As expected for reagents with electrophilic properties, the more electron-rich 2-methyl-*N*-hydroxypyrrolidine (**12**) showed with all catalysts a higher reactivity with respect to all the previous substrates (Table 7, Scheme 6). However, the difference in reactivity for the heterogen-



Scheme 5.



Scheme 6.

Table 7. Oxidation of 2-methyl-*N*-hydroxypyrrolidine (**12**) with poly(4-vinylpyridine)/MTO systems **I**–**III**, and microencapsulated polystyrene/MTO systems **IV** and **V**.

Entry	Catalyst	H_2O_2 (equivs.)	Solvent	Conversion (%)[a]	Yield (%)[a]	**13**:**14** Ratio[a]	Reaction time
1	MTO 2%[b]	1.5	EtOH	>98	46	1.6	<15 min
2	PVP-2%/MTO (**I**)	1.0	EtOH	>98	>98	1.4	10 min
3	PVP-25%/MTO (**II**)	1.0	EtOH	>98	>98	2.0	5 min
4	PVPN-2%/MTO (**III**)	1.0	EtOH	>98	>98	2.2	15 min
5	PS-2%/MTO (**IV**)	2.0	EtOH	>98	>98	>98	10 min
6	PS-2%/PVPy-2%/MTO (**V**)	1.0	EtOH	>98	>98	4	10 min

[a] Calculated by integration of the ^{1}H NMR of the crude mixture.
[b] 0% molar amount of pyridine added.

ized catalysts is striking and the observed reaction times must be considered abnormal for reactions occurring under heterogeneous conditions. In this case, MTO and polymer-supported MTO systems showed a similar behavior giving a quantitative conversion of substrate with a reaction time that ranged from 5 min (PVP-25%/MTO, Table 7, entry 3) to 15 min (PVPN-2%/MTO, Table 7, entry 4). The more stable keto nitrone **13** was obtained as the major product, prevailing over its aldonitrone isomer **14** in all oxidations. This behavior is in agreement with results obtained with different oxidants.[7,30] It must be stressed that a remarkably high selectivity, compared to the other catalysts used, was obtained in the case of microencapsulated PS-2%/MTO. In this case, nitrone **13** was the only recovered product (Table 7, entry 5), which result is unprecedented and paves the way to a possible selective access to ketonitrones from the corresponding 2-substituted cyclic hydroxylamines.

Conclusion

Poly(4-vinylpyridine)/MTO compounds **I**–**III** and microencapsulated polystyrene/MTO systems **IV** and **V** were efficient and selective catalysts for the oxidation of *N*,*N*-disubstituted hydroxylamines to the corresponding nitrones, affording quantitative conversion of substrates and yield of products, under environmental friendly conditions and employing simple work-up procedures. It is worth noting that these oxidations occur at room temperature in ethanol, thus avoiding the use of chlorinated organic solvents or of glacial acetic acid often used in MTO-catalyzed oxidations. Symmetrically substituted hydroxylamines, and non-symmetrical 3-substituted and 2-substituted *N*-hydroxypyrrolidines, precursors of nitrones applied in the synthesis of alkaloids and biologically active congeners, have been considered. Presumably, the high catalyst activity observed for all the heterogeneous MTO systems is to be ascribed to the formation of the known MTO peroxo intermediates $[MeRe(O)_2(O_2)]$ and $[MeRe(O)(O_2)_2]$ even in the presence of the polymeric support. Irrespective from the catalyst used in the oxidation, values of the loading factor of the catalyst higher than 0.5 did not give an appreciable increase of the reactivity. As in the case of olefin epoxidation,[22] polymer-supported MTO systems **II** and **IV** were stable enough to perform at least five recycling experiments with similar conversion and selectivity. The reticulation grade of the polymer appears to be a crucial variable for the reactivity of poly(4-vinylpyridine)/MTO compounds. Thus, the most reticulated PVP-25%/MTO, **II**, that is characterized by particles with a regular spherical shape,[22] was the best catalyst. On the other hand, the microencapsulated polystyrene derivatives **IV** and **V** were, in general, more reactive than poly(4-vinylpyridine)/MTO compounds. In accord with these data it is reasonable to suggest that the coordination of the rhenium atom by pyridine ligands in poly(4-vinylpyridine)/MTO compounds partially decreases the reactivity of the peroxorhenium intermediate toward hydroxylamines, even if the possibility of a concentration process of the substrates inside the low polar microenvironment of polystyrene microcapsules cannot be completely ruled out. From the practical point of view, all the supported catalysts perform well and are equally simple in use. However, on the basis of the reported experimental results, the polystyrene/MTO system is to be preferred for the shorter reaction times. In the case of 3-substituted and 2-substituted *N*-hydroxypyrrolidines, oxidation at C-2 prevailed, to afford the α-substituted nitrone and the most stable ketonitrone, respectively, as the major products, although the selectivity is generally poor. However, the completely selective ketonitrone formation from 2-methyl-*N*-hydroxypyrrolidine in the presence of the microencapsulated polystyrene system **IV** is particularly remarkable from the synthetic point of view. It constitutes one more, strong reason for choosing the polystyrene resin in the oxidation of α-substituted hydroxylamines. Polymer-supported MTO compounds, which can be easily recovered by filtration from the reaction mixture and used for successive transformations, confirm their high versatility and broaden their use as catalysts for the oxidation of organic compounds.

Experimental Section

General Remarks

N,*N*-Diethylhydroxylamine (**1**), *N*,*N*-dibenzylhydroxylamine (**3**), 35% hydrogen peroxide, methylrhenium trioxide, poly(4-vinylpyridine) 2% and 25% cross-linked with divinylbenzene, polystyrene 2% cross-linked with divinylbenzene, and analytical reagent grade organic solvents were purchased (Aldrich) and used without any further purification. *N*-Hydroxypyrrolidine (**5**),[32] 3,4-isopropylidenedioxy-*N*-hydroxypyrrolidine (**7**),[6e] 3(*S*)-*tert*-butoxy-*N*-hydroxypyrrolidine (**9**),[6d] and 2-methyl-*N*-hydroxypyrrolidine (**12**)[30a] were prepared according to the literature methods. NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer (^1H, 200 MHz).

Preparation of Heterogeneous MTO Catalysts

Poly(4-vinylpyridine)/MTO [PVP-2%/MTO (**I**), PVP-25%/MTO (**II**), and PVPN-2%/MTO (**III**)] and polystyrene/MTO [PS-2%/MTO (**IV**), and PS/PVP-2%/MTO (**V**)] catalysts were prepared as previously reported.[22] In summary, MTO (77 mg, 0.3 mmol) was added to a suspension of the appropriate resin (600 mg) in ethanol (4 mL), or tetrahydrofuran in the case of polystyrene. The mixture was stirred for 1 h using a magnetic stirrer. Coacervates were found to envelop the solid core dispersed in the medium and hexane (5 mL) was added to harden the capsule walls. The solvent was removed by filtra-

tion, and the solid residue was washed with ethyl acetate and finally dried under high vacuum. In every case, MTO was completely included into the polymer. This result was confirmed by spectroscopic analysis of the residue obtained after evaporation of the organic layers. The catalysts were used without any further purification.

Oxidation of Hydroxylamines; General Procedures

Homogeneous oxidation; general procedure: A 5-mL reaction flask was charged sequentially with MTO (0.01 mmol), ethanol (0.5 mL), pyridine (4 μL, 0.05 mmol)[33] and H_2O_2 (35% aqueous solution, 0.75 mmol, 73 μL). The stirred solution became yellow due to the formation of peroxo species and, after having been cooled to 0 °C with an ice bath, a solution of the hydroxylamine (0.5 mmol) in ethanol (0.5 mL) was added dropwise. The mixture was stirred at room temperature until no more starting material could be detected on TLC, after which H_2O (5 mL) was added. The mixture was extracted with AcOEt (3×15 mL), dried over Na_2SO_4, and then concentrated, furnishing pure nitrones by ^{1}H NMR analysis. The nitrones obtained from hydroxylamines **1**, **5**, **7** and **11** are highly soluble in water; therefore, the mixture was directly evaporated under reduced pressure when no more starting material could be detected on TLC.

Heterogeneous oxidation; general procedure: To the solution/suspension of the hydroxylamine (1.0 mmol) in EtOH (1 mL) were added the appropriate heterogeneous catalyst (23 mg, 0.01 mmol of MTO, loading factor 0.5) and H_2O_2 (35% aqueous solution, amount indicated in the Tables) as primary oxidant. The mixture was stirred at room temperature until no more starting material could be detected on TLC (see Tables). The suspension was filtered off, and the recovered catalyst washed with ethyl acetate. After drying under high vacuum, some of the catalysts were used for further reactions to evaluate their stability. The organic solution was dried over Na_2SO_4 and the solvent removed under reduced pressure. The nitrones were identified by ^{1}H NMR, ^{13}C NMR, and by comparison with authentic samples. Hydroxylamines **9** and **12** produced two nitrones. Their ratios were determined by integrating their NMR signals; triplicate determinations on independent samples were made.

Characterization of Nitrones

All of the synthesized nitrones have been reported previously.[34] Representative NMR spectroscopic data are reported below.

Nitrone **2**: ^{1}H NMR: δ = 6.80 (q, 1H, *J* = 5.8 Hz, CH), 3.75 (q, 2H, *J* = 7.2 Hz, CH_2), 1.93 (d, 3H, J = 5.8 Hz, CH_3), 1.35 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR: δ = 134.6 (CH), 59.8 (CH_2), 13.2 (CH_3), 2.7 (CH_3); MS (EI): *m/z* = 87.

Nitrone **4**: ^{1}H NMR: δ = 8.12 (m, 2H, Ar-H), 7.35–7.45 (m, 9H, ArH + CH=N), 5.10 (s, 2H, CH_2); ^{13}C NMR: δ = 134.1 (N=CH), 133.3 (C), 130.5 (CH), 130.3 (CH), 131.4 (C), 129.2 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 71.3 (CH_2); MS (EI): *m/z* = 211.

Nitrone **6**: ^{1}H NMR: δ = 6.90 (m, 1H, CH), 4.00 (m, 2H, CH_2), 2.75 (m, 2H, CH_2), 2.25 (m, 2H, CH_2); ^{13}C NMR: δ = 135.6 (N=CH), 62.4 (CH_2), 29.0 (CH_2), 19.4 (CH_2); MS (EI): *m/z* = 85.

Nitrone **8**: ^{1}H NMR: δ = 6.89 (m, 1H, CH), 5.25 (d, 1H, *J* = 6.3 Hz, CH), 4.86 (ddd, 1H, *J* = 5.7, 5.1, 1.5 Hz, CH), 3.95–4.18 (m, 2H, CH_2), 1.40 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR: δ = 132.6 (N=CH), 112.1 (C), 79.8 (CH), 73.6 (CH), 67.9 (CH_2), 25.6, 27.1 (CH_3); MS (EI): *m/z* = 157.

Nitrone **10**: ^{1}H NMR: δ = 6.90 (m, 1H, CH), 4.75 (m, 1H, CH), 4.10–3.70 (m, 2H, CH_2), 2.50–2.00 (m, 2H, CH_2), 1.18 (s, 9H); ^{13}C NMR: δ = 135.6 (N=CH), 74.5 (CH), 71.2 (C), 61.0 (CH_2), 29.1 (CH_2), 28.0 (CH_3); MS (EI): *m/z* = 157.

Nitrone **11**: ^{1}H NMR: δ = 6.90 (m, 1H, CH), 4.40 (m, 1H, CH), 4.10–3.70 (m, 2H, CH_2), 3.00–2.50 (m, 2H, CH_2), 1.17 (s, 9H); ^{13}C NMR: δ = 133.4 (N=CH), 71.7 (C), 69.1 (CH_2), 65.3 (CH), 38.9 (CH_2), 27.7 (CH_3); MS (EI): *m/z* = 157.

Nitrone **13**: ^{1}H NMR: δ = 3.80 (m, 2H, CH_2), 2.80 (m, 2H, CH), 2.10 (m, 2H, CH_2), 2.00 (s, 3H, CH_3); ^{13}C NMR: δ = 143.6 (N=C), 60.6 (CH_2), 31.4 (CH_2), 15.0 (CH_2), 10.8 (CH_3); MS (EI): *m/z* = 99.

Nitrone **14**: ^{1}H NMR: δ = 6.82 (m, 1H, CH), 4.01 (m, 1H, CH), 2.62 (m, 2H, CH_2), 1.85 (m, 2H, CH_2), 1.46 (d, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR: δ = 142.3 (N=CH), 71.86 (CH), 31.02 (CH_2), 27.41 (CH_2), 14.38 (CH_3); MS (EI): *m/z* = 99.

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