Selective Oxidation of Sulfides to Sulfoxides Using Modified Keggin Heteropolyacids as Catalyst

Valeria Palermo[a], Ángel G. Sathicq[a], Patricia G. Vázquez[a] & Gustavo P. Romanelli[a]

[a] Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. Ronco" (CINDECA-CCT-CONICET), Universidad Nacional de La Plata. Calle 47 N° 257, B1900AJK La Plata, Argentina
Accepted author version posted online: 13 Mar 2014.Published online: 21 Aug 2014.

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis
Taylor & Francis Group

SELECTIVE OXIDATION OF SULFIDES TO SULFOXIDES USING MODIFIED KEGGIN HETEROPOLYACIDS AS CATALYST

Valeria Palermo, Ángel G. Sathicq, Patricia G. Vázquez, and Gustavo P. Romanelli

Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. Ronco" (CINDECA-CCT-CONICET), Universidad Nacional de La Plata. Calle 47 N° 257, B1900AJK La Plata, Argentina

GRAPHICAL ABSTRACT
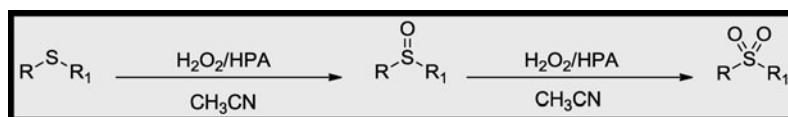
R = R$_1$ = alkyl or aryl
HPA= PMo, PMoV, PMoAl

13 examples = 95%–79 % sulfoxide
using PMoV at 25 °C

Abstract *The use of modified Keggin phosphomolybdic heteropolyacids (HPA) (V and Al) as catalysts in the selective oxidation of sulfides to the corresponding sulfoxides is reported. Excellent yields were obtained (13 examples: 79%–95%), using 35% (w/v) aqueous hydrogen peroxide as oxidant, and acetonitrile as solvent at 25°C. The relationship between the electron densities of the sulfur atoms, which was estimated by molecular theoretical calculations, and the oxidative relativities of the sulfur-containing compounds was also investigated. The results indicate that the time for 100% conversion decreases with an increase in electron density.*

R, R$_1$ = Alkyl and Aryl

HPA = PMo, PMoV, PMoAl
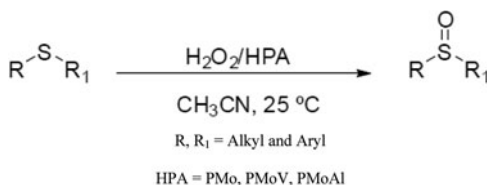
Keywords Modified Keggin heteropolyacids; Catalyst; Sulfide oxidation; Sulfoxides

INTRODUCTION

The oxidation of organic substrates with aqueous hydrogen peroxide is very attractive from the viewpoint of industrial technology and synthetic organic chemistry since aqueous hydrogen peroxide is very cheap, environmentally clean and easy to handle.[1–8]

The development of efficient catalytic systems for the oxidation of sulfides to sulfoxides and sulfones has attracted attention because they are essential intermediates for the synthesis of many drugs and natural products, such as ligands in asymmetric catalysis and reagents for oxygen transfer.[9] The increased interest in the sulfoxides has been due to their importance as synthetic intermediates for the production of a wide range of chemically and biologically active molecules.[7] They often perform a major function as therapeutic agents such as antiulcer,[10] antihypertensive,[11] cardiotonic agents,[12] psychotronics,[13] vasodilators,[14] antibacterial, and antifungal.[15]

There are many reagents available for the oxidation of sulfides such as halogen compounds, nitrates, transition metal oxides, hydrogen peroxide, and oxygen. Most of these reagents are not satisfactory for sulfoxide synthesis, for different reasons such as low content of effective oxygen, overoxidation, formation of environmentally unfavorable byproducts, and cost effectiveness.[16] Recently methods include the use of different catalyst in heterogeneous or solvent free-condition for example: DABCO tribromide immobilized on magnetic nanoparticle under metal-free conditions, or graphene-γ-Fe2O3 magnetic nano-composites.[17,18]

Heteropolyacids (HPA) with Keggin structures show activity as both acid and redox catalysts. Due to their complex structure and reactive properties, they give ample opportunity for novel scientific study.[19–21] Vanadium heteropolycompounds have recently been studied due to their importance as catalysts in different oxidation reactions,[17,22,23] as well as benzyl alcohol,[24] phenols,[25] and amine oxidation[26] and the selective oxidation of sulfides to sulfoxides and sulfones using hydrogen peroxide.[17,23,27]

We studied the use of modified Keggin HPA (V and Al) as catalyst in the selective oxidation of sulfides to the corresponding sulfoxides, using 35% (w/v) aqueous hydrogen peroxide as oxidant, and acetonitrile as solvent (Scheme 1). The three catalysts used were $H_3PMo_{12}O_{40}$ (PMo), $H_6PMo_{11}AlO_{40}$ (PMoAl), and $H_4PMo_{11}VO_{40}$ (PMoV). Excellent yields were obtained (13 examples: 79%–95%) using 35% (w/v) aqueous hydrogen peroxide as oxidant, 1 mmol% of PMoV and acetonitrile as solvent at 25°C. The relationship between the electron densities of the sulfur atoms, which was estimated by theoretical calculations, and the oxidative relativities of the sulfur-containing compounds was also investigated.

R, R$_1$ = Alkyl and Aryl

HPA = PMo, PMoV, PMoAl
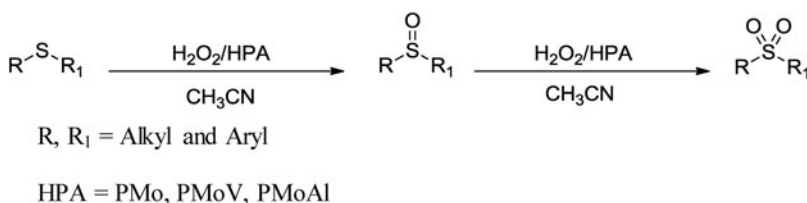
Scheme 1 Selective oxidation of sulfides using HPA as catalyst.

Table 1 Oxidation of diphenylsulfide using HPA-H_2O_2 system in acetonitrile[a]

Entry	Catalyst	H_2O_2 amount (mmol)	Temperature (°C)	Time (min)	Conversion (%)	Selectivity sulfoxide (%)	Selectivity sulfone (%)
1	None	3	25	300	—	—	—
2	PMo	3	25	300	65	98	2
3	PMoAl	3	25	300	52	100	—
4	PMoV	3	25	300	98	98	2
5[a]		3	25	300	98	99	1
6		1	25	300	92	98	2
7		10	25	300	100	97	3
8		30	25	300	100	95	5
9		30	40	300	100	41	59
10		30	70	300	100	10	90
11		30	70	420	100	—	100

[a]Using a mixture acetonitrile: *t*-butanol 4:1.

RESULTS AND DISCUSSION

The reaction conditions were first optimized using diphenylsulfide as substrate at 25°C (Scheme 1). The results of the study of the oxidation reaction of diphenylsulfide with the use of the three different HPAs (PMo, PMoAl, and PMoV) are summarized in Table 1. No conversion was obtained in the absence of the catalyst at 25°C, in a time period of 300 min using 3 mmol of 35% (w/v) hydrogen peroxide (Table 1, entry 1), but when HPA is added, the reaction takes place efficiently.
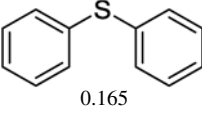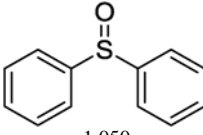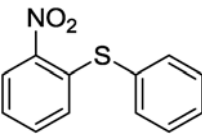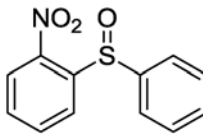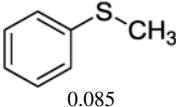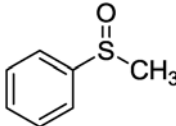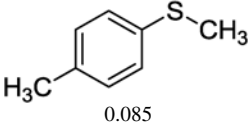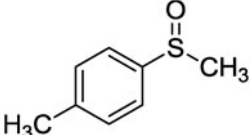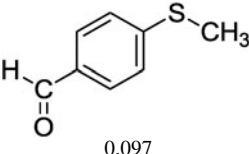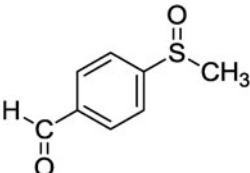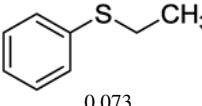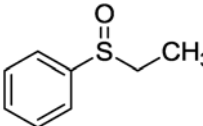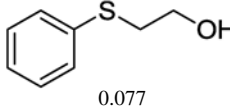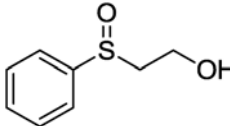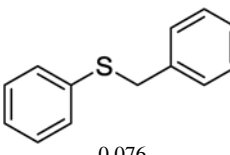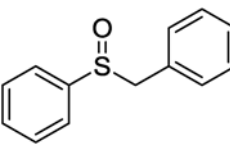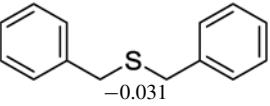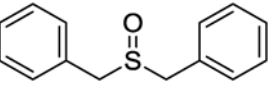
When PMo is used (Table 1, entry 2), a conversion of 65% is observed at 300 min, with a 98% of selectivity of the corresponding sulfoxide. Although PMoAl is less active than PMo (52%, 300 min) it is more selective (100%), (Table 1, entry 3).

However, when vanadium is incorporated into the PMo structure, a marked increase in the activity is observed, which produces 98% of conversion of diphenylsulfide, and a sulfoxide selectivity of 98%, in the same time period (Table 1, entry 4).

The PMoV catalyst shows unique catalytic features for oxidation due to its bifunctional character, which arises because of the redox nature of vanadium and the oxidation/acidic character of the molybdophosphoric acid.[28] As reported by Song et al.,[29] the metal substitution may be modifying the energy and composition of the lowest unoccupied molecular orbital (LUMO) and consequently, its redox properties. The substitution of vanadium ions into the molybdenum framework stabilizes the LUMOs because these orbitals derive in part from vanadium *d*-orbitals, which have been assumed to be more stable than those of molybdenum.
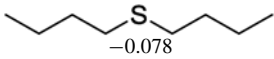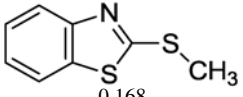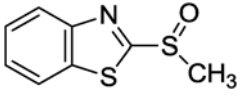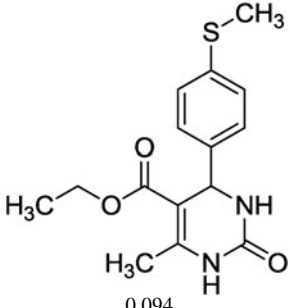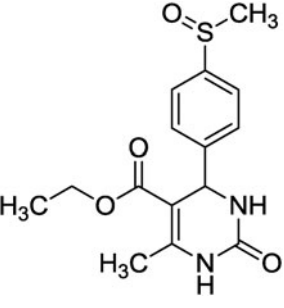
Several researchers have investigated vanadium incorporated molybdophosphoric acid catalysts by replacing 1, 2, and 3 molybdenum atoms with the corresponding number of vanadium atoms. The acidic, redox, and thermal stability properties of the vanadium catalysts are influenced by the degree of vanadium substitution.[24] In solutions, the reduction potentials of heteropolyanions containing Mo and V are high as these ions are easily reduced. Oxidative ability decreases generally in the order: V- > Mo- > W- containing heteropolyanions, which means that the vanadium-containing heteropoly compounds are the strongest oxidants.[26]

Table 2 Oxidation of sulfides to sulfoxides using PMoV-H$_2$O$_2$ catalyst

Entry	Substrate/atomic charge on S atom (Qs)	Product	Time (min)	Yields (%)
1	0.165	1.050	300	95
2	0.220		350	82
3	0.085		60	92
4	0.085		60	93
5	0.097		80	83
6	0.073		50	94
7	0.077		55	88
8	0.076		55	91
9	−0.031		35	83

(Continued on next page)

Table 2 Oxidation of sulfides to sulfoxides using PMoV-H_2O_2 catalyst *(Continued)*

Entry	Substrate/atomic charge on S atom (Qs)	Product	Time (min)	Yields (%)
10	−0.078		30	88
11	−0.047		40	83
12	0.168		300	85
13	0.094		75	79

As PMoV was much more active, it was used in the next reaction optimization essays. The effect of H_2O_2 amount on conversion and selectivity was studied, and four different H_2O_2/substrate molar ratios were used: 1, 3, 10, and 30 (Table 1, entries 4, 6–8). No significant effect on conversion was obtained and diphenylsufoxide selectivity was excellent (between 95%–98%).

In order to continue with the study of the reaction optimization, the effect of temperature on the conversion and selectivity of diphenylsulfide was analyzed using H_2O_2 in excess (H_2O_2/substrate ratio: 30:1) (Table 1, entries 8–11). As can be observed, at 25°C, the reaction reaches 100% of diphenylsulfide conversion and is selective to sulfoxide (95%). On increasing the reaction temperature, a higher selectivity to sulfone results. For example, at 70°C and for 420 min, 100% selectivity to diphenylsulfone is achieved (Table 1, entry 11).

In order to explore a possible reaction mechanism, an additional experiment was performed using a radical inhibitor such as *t*-butanol. The experimental conditions were: 1 mmol% of the PMoV catalyst, 1 mmol of diphenylsulfide, 3 mmol of 35% (w/v) H_2O_2, 4 mL of acetonitrile, and 1 mL of *t*-butanol; reaction for 300 min at 25°C. In these conditions, a similar conversion of diphenylsulfide (98%) and selectivity of the corresponding sulfoxide (99%) were obtained, compared to the initial experiment without the radical inhibitor (Table 1, entries 5 and 4, respectively). This result demonstrates that the reaction mechanism is not via a free radical oxidation.

Once the reaction condition for the selective oxidation of sulfides to sulfoxides and sulfones had been optimized, the reaction was extended to other starting substrates. Diaryl
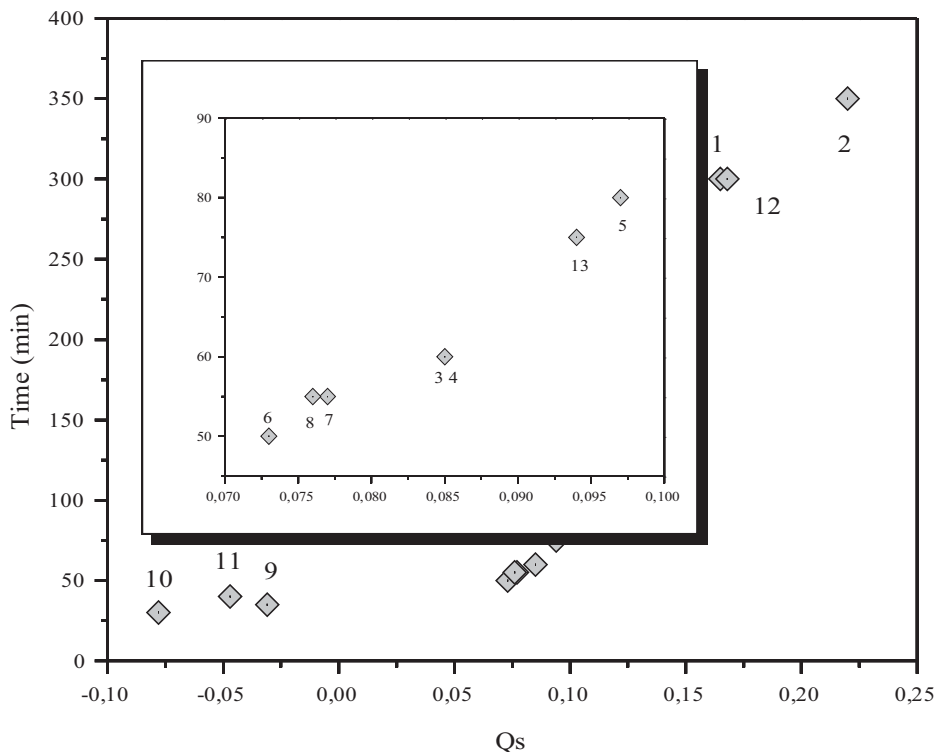
Figure 1 Reaction time for 100% conversion of sulfide vs. Q_s (charge on sulfur atom in the corresponding sulfide)[a]. [a]Number 1–13 corresponding to the different sulfides (see Table 1).

(Table 2, entries 1–2), aryl-alkyl (Table 2, entries 3–8), dialkyl (Table 2, entries 9–11), and more sophisticated compounds (Table 2, entries 12–13) were used as starting materials.

Table 2 lists the results for the selective oxidation of these sulfides to the corresponding sulfoxides. All the reactions were run within a reasonable reaction time and the sulfoxides were obtained in excellent yields (79%–95%), and only traces of sulfones and other secondary products were detected. Therefore, the reaction condition is selective to the transformation of sulfides to sulfoxides. For example, in Table 2, entry 5, it can be seen that the formyl group was not affected by the reaction condition. Similarly, the hydroxyl group (Table 2, entry 7) was not affected under the same reaction condition and the other group present in the sulfides remained unchanged.

The reactivity of the different sulfur-containing compounds was investigated for 13 examples using computational methods. The relationship between the electron densities of the sulfur atoms, which were estimated by Hyperchem 5, and the oxidative relativities of the sulfur-containing compounds was also investigated. The electron densities on the sulfur atom of the 13 sulfides, which varied between -0.078 and 0.168, are shown in Table 2.

Figure 1 shows a relationship between the substrate reactivity, evaluated as the reaction time for a 100% conversion of sulfide and the electron densities on the sulfur atom. From the results obtained, it could be observed that dialkyl sulfides (-0.031, -0.047,

and −0.078) are more reactive than alkyl-aryl sulfides (0.076–0.097) and alkyl-aryl sulfides are more reactive than diaryl sulfides (0.165 and 0.220). This different reactivity is associated with the electronic density on the sulfur, since a higher electronic density on this atom facilitates the attack on the electrophilic form of the hydrogen peroxide-catalyst system.

A plausible mechanism of this reaction involves the formation of peroxo-heteroatom (Mo, V, Al) species and the subsequent nucleophilic attack of the sulfur atom in the sulfide on the peroxo species. Indeed, it is known that sulfides are oxidized to sulfoxides by electrophilic oxidants. Mechanistically, it is believed that the electrophilicity of the peroxide oxygen in H_2O_2 is increased by an oxometal group (M=Od) in the HPA (Scheme 2).[30]
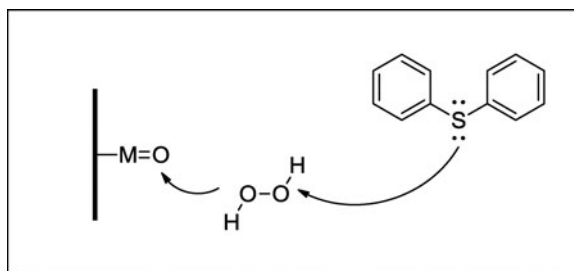
Scheme 2 Plausible hydrogen peroxide activation with the heteropolyacid and electrophilic attack to diphenylsulfoxide.

The overoxidation of sulfoxide to sulfone requires the presence of an oxidant with nucleophilic character. To verify this asseveration, we performed an additional experiment using diphenylsulfoxide as substrate and the standard reaction conditions. The experimental conditions were: 1 mmol% of the PMoV catalyst, 1 mmol of diphenylsulfoxide, 3 mmol of 35% (w/v) H_2O_2, and 5 mL of acetonitrile; reaction for 300 min at 25°C. In these conditions, the conversion of diphenylsulfoxide was only 4%, which means that the electrophilic oxidant-catalyst system is not efficient to oxidize sulfur with a high positive electronic density (1.050).

CONCLUSIONS

In conclusion, in this research, we found a convenient and selective procedure for oxidizing sulfides to sulfoxides, using 35% (w/v) aqueous hydrogen peroxide and a catalytic amount of HPA. The yields were excellent, and all reagents are cheap and the catalyst preparation is easy. The reaction for the sulfoxide preparation was carried out at room temperature (25°C), in a reasonable reaction time. The incorporation of V into the structure of PMo increases the catalytic activity. The PMoV catalyst shows unique catalytic features for oxidation due to its bifunctional character, which arises because of the redox nature of vanadium and the oxidation/acidic character of the molybdophosphoric acid. The different reactivity of sulfides is associated with the electronic density on the sulfur atom, since a higher electronic density on this atom facilitates the attack by the electrophilic form of the hydrogen peroxide/catalyst system.

EXPERIMENTAL SECTION

General Remarks

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. The products were characterized by spectroscopy data (^{1}H and ^{13}C NMR). The NMR spectra were recorded on a 200 MHz Bruker spectrometer. The NMR spectra were measured in $CDCl_3$ relative to TMS (0.00 ppm). The organic phase was dried on anhydrous Na_2SO_4 and filtered for its analysis by gas chromatography using Varian Scan 3400 cx equipment. The product distribution was quantified by a Shimadzu C-R34 instrument. Reactions were monitored by thin layer chromatography (TLC) analyses.

Catalytic Preparation

$H_3PMo_{12}O_{40}$ (PMo) was purchased from Aldrich and used without further purification. The other HPA, doped with Al and V, were prepared as in previous work[31] and were labeled $H_4PMo_{11}VO_{40}.12H_2O$ (PMoV) and $H_6PMo_{11}AlO_{40}.12H_2O$ (PMoAl), respectively.

General Procedure for the Oxidation of Sulfide

A solution of sulfide (1 mmol) and catalyst (0.01 mmol), in acetonitrile, was added to 35% (w/v) H_2O_2 (2 mmol). The mixture was stirred at 25°C for a time period (see Tables 1 and 2). The solvent was evaporated and then H_2O (5 mL) was added. The substrate was extracted with toluene (2 × mL) and dried with anhydrous Na_2SO_4; filtration and evaporation afforded the corresponding crude sulfoxides. The solids were purified by recrystallization to afford the pure sulfoxides. The products were confirmed by ^{1}H NMR and ^{13}C NMR analyses.

Sample Analysis

Samples were withdrawn from the organic phase at 15-min intervals. Each volume sample was approximately 20 μL and it was diluted with 1–2 mL of acetonitrile, the concentrations were calculated with an internal standard method. Conversions were obtained with GC analysis performed with a Varian GC 3400 instrument. The capillary column was a 30 m Chromopack CP Sil 8 CB, 0.32 mm in diameter. The identification of products was performed with GC–MS (detector HP 5971) for comparison with GC–MS authentic samples. Detailed characterization data for previously known samples are presented in the Supplemental Materials.

Electronic Densities of Sulfur Atom Determination

The densities of the sulfur atoms in the sulfide were determined after optimization of their conformation. The conformations of the compounds were drawn by means of the "model build" modulus available in HyperChem 5.0.[32] Each molecular structure was firstly preoptimized with the Molecular Mechanics Force Field (MM+) procedure and the resulting geometry was further refined by means of the semiempirical method PM3 (Parametric Method-3). A gradient norm limit of 0.01 kcal Å^{-1} was chosen.

ACKNOWLEDGMENTS

SUPPLEMENTAL MATERIAL

Supplementary data for this article can be accessed on the publisher's website, www.tandfonline.com/gpss

REFERENCES

1. Ishii, Y.; Yamawaki, K.; Ura, T.; Yamada, H.; Yoshida, T.; Ogawa, M. *J. Org. Chem.* **1988**, 53, 3587-3593.
2. Kaczorowska, K.; Kolarska, Z.; Mitka, K.; Kowalsky, P. *Tetrahedron* **2005,** 61, 8315-8327.
3. He, Y.; Ma, X.; Lu, M. *Arkivok* **2012,** viii, 187-197.
4. Sato, K.; Hyodo, M.; Takagi, J.; Aoki, M.; Noyori, R. *Tetrahedron Lett.* **2000,** 41, 1439-1442.
5. Hasan, K.; Brown, N.; Kozak, C. *Green Chem.* **2011,** 13, 1230-1237.
6. Bach, R.; Su, M.; Bernhard Schlegel, H. *J. Am. Chem. Soc.* **1994,** 116, 5379-5391.
7. Golchoubian, H.; Hosseinpoor, F. *Molecules* **2007,** 12, 304-311.
8. Yube, K.; Furuta, M.; Mae, K. *Catal. Today* **2007,** 125, 56-63.
9. Yamaura, T.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *Catal. Today* **2013,** 203, 76-80, and references cited herein.
10. Lai, S.; Lam, K.; Chu, K.; Wong, B.; Hui, W.; Hu, W.; Lau, G.; Wong, W.; Yuen, M.; Chan, A.; Lai, C.; Wong, J. *New Engl. J. Med.* **2002,** 346, 2033-2038.
11. Kotelanski, B.; Grozmann, R.; Cohn, J. *Pharmacol. Ther.* **1973,** 14, 427-433.
12. Schmied, R.; Wang, G.; Korth, M. *Circ. Res.* **1991,** 68, 597-604.
13. Nieves, A.; Lang, A. *Clin. Neuropharmacol.* **2002,** 25, 111-114.
14. Padmanabhan, S.; Lavin, R.; Durant, G. *Tetrahedron: Asymmetr.* **2000,** 11, 3455-3645.
15. Sovova, M.; Sova, P. *Ceska Slov. Farm.* **2003,** 52, 82-87.
16. Hussain, S.; Talukdar, D.; Bharadwaj, S.; Chadhuri, M. *Tetrahedron Lett.* **2012,** 53, 6512-6515, and references cited herein.
17. Rostami, A.; Navasi, Y.; Moradi, D.; Ghorbani-Choghamarani, A. *Catal. Commun.* **2014,** 43, 16-20.
18. Salam, N.; Sinha, A.; Mondal, P.; Roy, A.; Jana, N.; Islam, S. *RSC Advances* **2013,** 3, 18087-18098.
19. Romanelli, G.; Vázquez, P.; Pizzio, L.; Cáceres, C.; Blanco, M.; Autino, J. *Synth. Commun.* **2003,** 33(8), 1359-1365.
20. Romanelli, G.; Autino, J.; Blanco, M.; Pizzio, L. *Appl. Catal. A: Gen.* **2005,** 295, 209-215.
21. Bennardi, D.; Romanelli, G.; Sathicq, Á.; Autino, J.; Baronetti, G.; Thomas, H. J. *Appl. Catal. A: Gen.* **2011,** 404(1–2), 68-73.
22. Tundo, P.; Romanelli, G.; Vázquez, P.; Aricò, F. *Catal. Commun.* **2010,** 11, 1181-1184.
23. Palermo, V.; Sathicq, A.; Vázquez, P.; Thomas, H.; Romanelli, G. *React. Kinet. Mech. Catal.* **2011,** 104, 181-195.
24. Rao, P. S. N.; Venkateswara Rao, K. T.; Sai Prasad, P. S.; Lingaiah, N. *Catal. Commun.* **2010,** 11, 547-550.
25. Kende, A. S.; Ebertino, F. H. *Tetrahedron Lett.* **1984,** 25, 923-926.
26. Villabrille, P.; Romanelli, G.; Gassa, L.; Vázquez, P.; Cáceres, C. *Appl. Catal. A: Gen.* **2007,** 324(1–2), 69-76.
27. Romanelli, G.; Villabrille, P.; Cáceres, C.; Vázquez, P.; Tundo, P. *Catal. Commun.* **2011,** 12, 726-730.

28. Casarini, D.; Centi, G.; Jiro, P.; Lena, V.; Tvaruzkova, Z. *J. Catal.* **2003,** 143, 325-344.

29. Park, D.; Park, P.; Bang, Y.; Song, I. *Appl. Catal. A: Gen.* **2010,** 373, 201-207.

30. Maciuca, A.; Ciocan, C.; Dumitriu, E.; Fajula, F.; Hulea, V. *Catal. Today* **2008,** 138, 33-37.

31. Romanelli, G.; Bennardi, D.; Palermo, V.; Vázquez, P.; Tundo, P. *Lett. Org. Chem.* **2007**, 544–549.

32. *Hyperchem version 5.0*; Hypercube, Inc.: Gainesville, **1996**.