ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 4489–4493

Tetrahedron Letters

Catalytic investigations of calix[4]arene scaffold based phase transfer catalyst

Pallavi Srivastava and Rajendra Srivastava*

Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Republic of Korea

Received 20 March 2007; revised 26 April 2007; accepted 1 May 2007
Available online 5 May 2007

Abstract—Calix[4]arene scaffold based quaternary ammonium salts as multi-site phase transfer catalysts were prepared and their catalytic activities were investigated for Darzens condensation, O/N-alkylation reactions and ethyl benzene oxidation. These calix[4]arene based multi-site phase transfer catalysts showed significant high catalytic activity as compared to single-site phase transfer catalysts.

© 2007 Elsevier Ltd. All rights reserved.

The reaction between two reactants present in two separate phases is often inhibited because of inability of the reagents to interact with each other. The rate of such reactions can be enhanced by using a catalyst known as a phase transfer catalyst. The phase-transfer catalysis is a well-known concept, in which, a reactant (organic-soluble component) and an anionic reactant (aqueous soluble reactant) are brought together by the use of a small quantity of catalyst which transports one reactant across the interface into the other phase to enhance the reaction rate.[1] Quaternary ammonium salt has unique capability to dissolve in both organic and aqueous solution and hence widely used as a phase-transfer catalyst.[2] Phase transfer catalytic processes are industrially important and environmentally friendly since they produce less industrial waste and consume less energy than traditional processes.[3,4] Recently, efforts have been made to develop more eco-friendly phase transfer catalysts by immobilizing on the polymer or solid supports.[5]

The potential value of the quaternary ammonium catalyst was exploited in various organic transformations.[6] The application of phase-transfer catalysis to the Williamson synthesis of ethers has been widely investigated and is far superior to any classical method for the synthesis of aliphatic ethers.[7] The drawback of the existing process is that it requires a large amount of quaternary ammonium salt as a phase-transfer catalyst. Hence, it is very important to develop new phase-transfer catalysts (PTCs) that can be used in smaller proportions. In order to overcome this problem novel multi-site PTCs have been developed.[8] Multi-site PTCs were applied in small proportion to obtain a catalytic effect. Syntheses of the multi-site PTCs have been less explored than the single-site PTCs. The objective of this work is to develop an efficient multi-site quaternary ammonium salt as PTC and investigate its catalytic efficiency in various organic transformations.

In the present study, calix[4]arene based multi-site PTCs were synthesized. Multi-site PTCs **I** and **II** (Scheme 1) were prepared as per the reported procedure.[9] For comparison, single-site PTCs (**III** and **IV**) were also prepared using *p*-methoxy benzylchloride and trialkylamine. All the compounds were well characterized by ^{1}H NMR, elemental analysis, melting point and were confirmed with the reported value in the literature.

In the present study, the catalytic activity of calix[4]arene based quaternary ammonium salts was investigated for the Darzens condensation, O/N-alkylation reactions and ethylbenzene oxidation. The Darzens condensation is one of the most potential synthetic tool available to organic chemists for the preparation of α,β-epoxy carbonyl compounds (Scheme 2).[10] Various attempts have been made for the phase transfer catalyzed Darzens condensation of chloroketones and sulfones.[11]

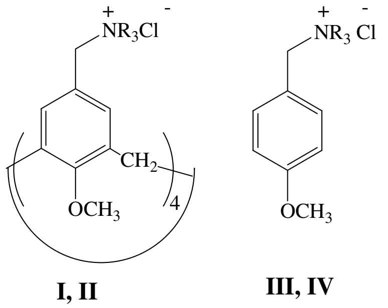
First set of experiments were designed to obtain the optimum reaction condition. Solvents and bases have strong influence on the reaction. Among the bases and solvent

---

Keywords: Calixarenes; Phase transfer catalysts; Quaternary ammonium salts.

* Corresponding author. Tel.: +82 42 869 5830; e-mail: chemi_rajendra@yahoo.co.in

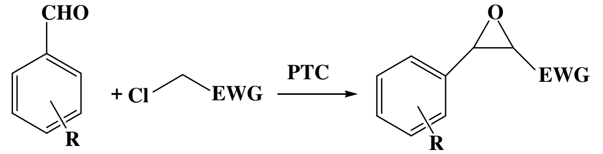
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.001



I, II **III, IV**

I, III = R = CH_3
II, IV = R = $CH_2CH_2CH_2CH_3$

Scheme 1. Multi-site and single-site phase transfer catalysts.



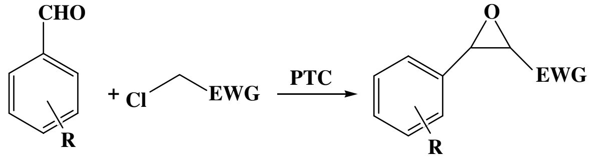
Scheme 2. Darzens condensation of benzaldehyde derivatives with α-chloroester and nitrile.

studied, KOH and THF were found to be the best (Table 1). Having found the optimum reaction condition, various phase transfer catalysts were examined for the reaction. A very low yield of product was obtained when the reaction was performed without catalyst (Table 1, entry 1). Single-site phase transfer catalyst such as **III** and **IV** were found to be weakly active for this reaction, whereas calix[4]arene derived multi-site phase transfer catalyst **I** and **II** were highly active (Table 1, entries 2–5). The chain length of the alkyl group in the multi-site phase transfer catalysts influenced the catalytic activity. The long aliphatic chain (*tert*-butyl) substituted salts were found to be more active than the short alkyl chain (*tert*-methyl) substituted salts. However, diastereoselectivity was similar for all the phase transfer catalysts investigated in the present study. Aromatic aldehydes having an electron donating group such as $-CH_3$ offered higher yields (Table 1, compare entries 11 and 12), whereas an electron withdrawing group such as $-NO_2$ offered lower yields for Darzens adduct (Table 1, compare entries 11 and 13). However, the product yield can be improved by carrying out the reaction for a longer time. The aromatic aldehydes reactivity is faster with α-chloroacetonitrile than with ethyl chloroacetate (Table 1, compare entries 13 and 15).

The catalytic activity of calix[4]arene based quaternary ammonium salt was investigated for O-alkylation of phenol and N-alkylation of pyrrole (Scheme 3). First set of experiments were carried out between sodium phenolate and benzylbromide at 298 K in 1,2-dichloromethane solvent. In this case also, single-site quaternary ammonium salts were found to be less active than the calix[4]arene based multi-site catalysts (Table 2). Since, the pyrrole being more reactive than phenol, a high yield of the product was obtained in a short reaction time (5 min instead of 30 min in case of phenol). Similar to Darzens condensation, the long aliphatic chain (*tert*-butyl) substituted salts were found to be more active than the short alkyl chain (*tert*-methyl) substituted salts (Table 2).

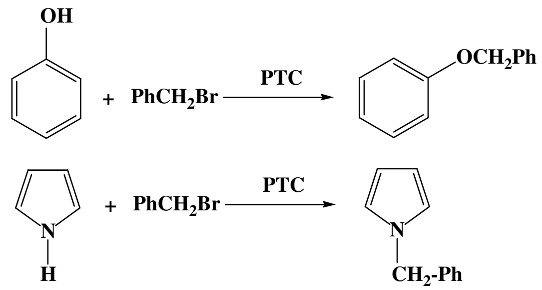
The slow atmospheric oxidation of a C–H bond to a C–O–O–H group (hydroperoxide) is called autoxidation.

Table 1. Catalytic investigation of multi-site PTCs in Darzens condensation



Entry	R	EWG	Solvent	Base	Catalyst	Yield[a] (%)	Cis/trans
1	H	–COOEt	THF	KOH	None	9.0	8:1
2	H	–COOEt	THF	KOH	**I**	43.9	8:1
3	H	–COOEt	THF	KOH	**II**	72.0	7:1
4	H	–COOEt	THF	KOH	**III**	8.7	7.9:1
5	H	–COOEt	THF	KOH	**IV**	12.3	7.5:1
6	H	–COOEt	THF	NaOH	**II**	65.2	7.5:1
7	H	–COOEt	THF	LiOH	**II**	35.9	14:1
8	H	–COOEt	CH_2Cl_2	KOH	**II**	39.5	4.5:1
9	H	–COOEt	$(C_2H_5)_2O$	KOH	**II**	59.2	6.7:1
10	H	–COOEt	C_6H_6	KOH	**II**	54.2	6.4:1
11	H	–COOEt	THF	KOH	**II**	35.8[b]	6.5:1[b]
12	4-CH_3	–COOEt	THF	KOH	**II**	42.0[b]	1:1[b]
13	4-NO_2	–COOEt	THF	KOH	**II**	10.5[b] (29.3)[a]	3:1[b] (2.9:1)[a]
14	4-NO_2	–COOEt	THF	KOH	**IV**	No reaction	—
15	4-NO_2	–CN	THF	KOH	**II**	24.0[b]	3.5:1[b]

[a] Reaction condition: aldehyde (5 mmol), α-chloroester or α-chloroacetonitrile (6.0 mmol), base (6.0 mmol), catalyst (2.0 mol %), solvent (10 ml), reaction temperature (298 K), run time (24 h).
[b] Reactions were carried out for 8 h.



Scheme 3. O/N-Alkylation reaction of phenol and pyrrole over phase transfer catalysts.

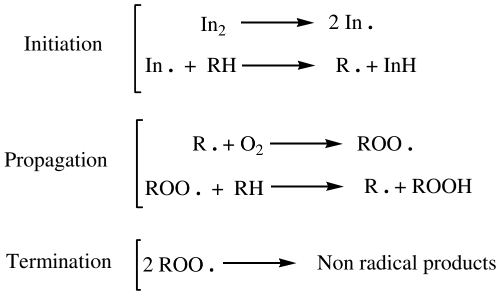
Table 2. Catalytic investigation of multi-site PTCs in O/N-alkylation reaction

Entry	Substrate	Alkylating reagents	Catalyst	Run time (min)	Yield (%)
1	Phenol	Benzylbromide	**I**	30	70.0
2			**II**	30	98.0
3			**III**	30	10.0
4			**IV**	30	18.0
5	Pyrrole	Benzylbromide	**I**	5	77.0
6			**II**	5	96.0
7			**III**	5	16.0
8			**IV**	5	24.0

Reaction condition: phenol/pyrrole (5 mmol), benzylbromide (5.0 mmol), NaOH (6.0 mmol), catalyst (2.0 mol %), CH_2Cl_2 (10 ml), reaction temperature (298 K).

Oxygen itself is very unreactive, which can abstract the proton. However, if a trace amount of free radicals are produced by some initiating processes, then they react with oxygen to give R–O–O$^\bullet$ and thereby the radical chain reaction propagates (Scheme 4). Hydrocarbon oxidation by O_2 is highly dependent on the concentration of hydrocarbon peroxides because these hydrocarbon peroxides are radical initiators for the formation of oxidized products. Various surfactants[12] and onium salts[13] were reported to accelerate the hydrocarbon oxidation. The mechanism of onium salts catalyzed hydrocarbon oxidation is well documented.[14]

The role of multi-site phase transfer catalysts was also investigated in the oxidation of ethylbenzene (EB) using molecular oxygen. Three products, that is, ethylbenzene hydroperoxide (EBHP), acetophenone (ACP) and 1-phenylethanol (PE) were formed during the oxidation reaction of ethylbenzene. Under the reaction condition, 1.0 wt % of ethylbenzene hydroperoxide was added as a radical initiator. A blank experiment was performed under the same reaction conditions without adding PTCs. The oxidation of ethylbenzene at 403 K in the presence of 1.0 wt % of ethylbenzene hydroperoxide is a typical autocatalytic chain reaction. At this temperature, the decomposition of the EBHP to produce free radicals (Scheme 4) is one of the key steps in the oxidation reaction because it leads to an increase in the chain initiation rate and hence in the overall reaction rate. Because of this reason, a small amount of hydroperoxides were added in liquid-phase hydrocarbon oxidations, which act as a radical initiator and remove the induction period just at the beginning of the reaction with molecular oxygen. With this low concentration of EBHP, the amount of radicals in the reaction medium are enough to maintain the reaction rate at an almost constant level from the very beginning with no detectable induction period. Figure 1a shows that the single-site PTCs **III** and **IV** do not catalyze the EB oxidation as efficiently as multi-site PTCs **I** and **II**. It may be noted that EBHP form autocatalytic under the reaction condition, but its rate can be influenced by the addition of PTCs. The activity of catalysts and the selectivity of EBHP formation are highly dependent on the chain length of quaternary ammonium salts. The long alkyl chain (*tert*-butyl) substituted salt such as compound **II** hinders interaction and favours interaction of Cl^- with the EBHP, leading to its decomposition (Eq. 1). Whereas the short alkyl chain (*tert*-methyl) substituted PTC such as compound **I** seems to be more appropriate and allow the interaction with EBHP and favours the formation of ethylbenzyl and hydroperoxy radicals which are the active species in the propagation step (Scheme 4) in which EBHP is formed.



Scheme 4. Auto-oxidation of organic compounds.

$$[\text{R–OOH} + \text{Cl}^- \rightarrow \text{R–O}^\bullet + \text{OH}^- + \text{Cl}^\bullet] \qquad (1)$$

In addition, the hydroxyl group generated in reaction 1 is responsible to produce radicals that drive the reaction towards the formation of oxidized products (ACP and PE). Figure 1b shows the result obtained after 6 h of the reaction. EB oxidation is highly dependent on the EBHP concentration. After 6 h, a large amount of EBHP remained in the reaction medium when compound **I** was used in the reaction. The low concentration of EBHP in the reaction medium in case of compound **II** indicates that EBHP was utilized in the formation of oxidized products. Hence, it can be concluded that compound **II** is the promoter in EB oxidation, whereas compound **I** is the inhibitor. From Figure 1b it is inferred that compound **II** reacts with the formed EBHP, until compound **II** is completely consumed. After this, the formed EBHP is stable in the reaction medium. These observations are in keeping with the previous studies addressing the decomposition of organic hydroperoxides with quaternary ammonium salts.[14,15]

In summary, calix[4]arene based multi-site quaternary ammonium salts were prepared and used as phase transfer catalysts. The catalytic activity of calix[4]arene based phase transfer catalysts was investigated for Darzens condensation, O/N-alkylation reactions and ethylbenzene oxidation. For comparison, single-site phase

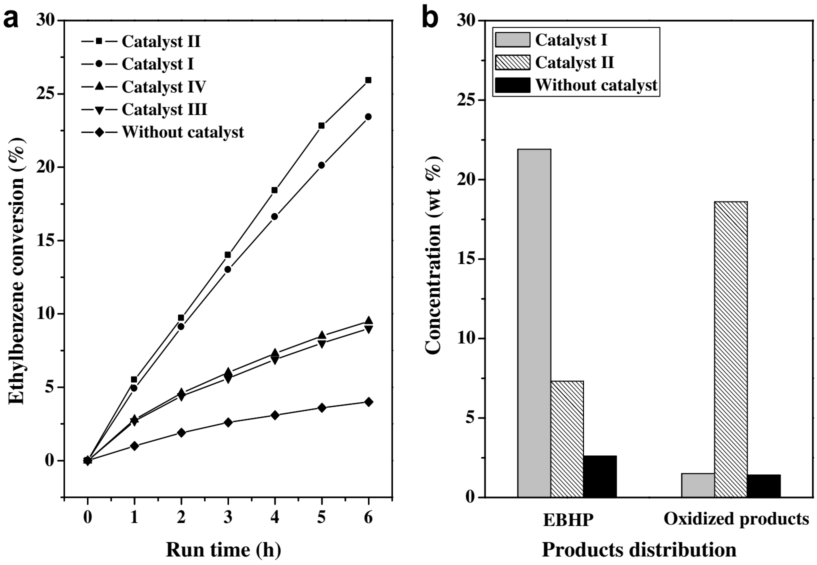


Figure 1. Ethylbenzene oxidation at 403 K over various catalysts: (a) ethylbenzene conversion plot verses reaction time and (b) products distribution after 6 h.

transfer catalysts were also prepared. The multi-site phase transfer catalyst showed significant high catalytic activity as compared to the single-site phase transfer catalyst. The chain length of the alkyl group present in the PTCs also influences the catalytic activity. Long chain (*tert*-butyl) substituted quaternary salt was found to be more active.

Experimental

Phase transfer catalysts preparation and characterization

Catalysts were prepared by the reported procedure.[9] All the compounds were well characterized by ^{1}H NMR, elemental analysis, melting point and they matched well with the reported values in the literature. ^{1}H NMR (300 MHz) and elemental analysis results of calix[4]-arene based multi-site PTCs (**I** and **II**) and single-site PTCs (**III** and **IV**) are given below.

5,11,17,23-tetrakis(trimethylammoniomethyl)-25,26,27,28-tetramethoxycalix[4]arene tetracholoride (**I**): 7.3 (ArH, S, 2H), 4.37 ($PhCH_2Ph$, s, 2H), 3.88 (N^+CH_2, S, 2H), 3.67 (OCH_3, S, 3H), 2.98 (N^+CH_3, S, 9H). Anal. Calcd for $(C_{12}H_{18}NOCl)_4$: C, 63.29; H, 7.97; N, 6.15. Found: C, 62.81; H, 7.76; N, 6.35.

5,11,17,23-tetrakis(tributylammoniomethyl)-25,26,27,28-tetramethoxycalix[4]arene tetracholoride (**II**): 7.3 (ArH, S, 2H), 4.37 ($PhCH_2Ph$, s, 2H), 3.88 (N^+CH_2, S, 2H), 3.67 (OCH_3, S, 3H), 2.93 (N^+CH_2, t, 6H), 1.61 ($N^+CH_2–CH_2$, m, 6H), 1.38 ($N^+CH_2–CH_2–CH_2$, m, 6H), 0.86 ($N^+CH_2–CH_2–CH_2–CH_3$, t, 9H). Anal. Calcd for $(C_{21}H_{36}NOCl)_4$: C, 71.29; H, 10.18; N, 3.96. Found: C, 72.01; H, 10.06; N, 4.11.

p-Methoxy-(tri-methylammonio)-benzylcholoride (**III**): 7.27 (ArH, d, 2H), 6.90 (ArH, d, 2H), 3.86 (N^+CH_2, S, 2H), 3.66 (OCH_3, S, 3H), 2.96 (N^+CH_3, S, 9H). Anal. Calcd for $(C_{11}H_{18}NOCl)_4$: C, 61.25; H, 8.21; N, 6.49. Found: C, 61.01; H, 7.96; N, 6.75.

p-Methoxy-(tri-butylammonio)-benzylcholoride (**IV**): 7.25 (ArH, d, 2H), 6.90 (ArH, d, 2H), 3.86 (N^+CH_2, S, 2H), 3.65 (OCH_3, S, 3H), 2.90 (N^+CH_2, t, 6H), 1.58 ($N^+CH_2–CH_2$, m, 6H), 1.36 ($N^+CH_2–CH_2–CH_2$, m, 6H), 0.88 ($N^+CH_2–CH_2–CH_2–CH_3$, t, 9H). Anal. Calcd for $(C_{20}H_{36}NOCl)$: C, 70.25; H, 10.61; N, 4.10. Found: C, 70.01; H, 10.36; N, 4.41.

Catalytic measurements

Darzens condensation. In a typical Darzens condensation, a mixture of aldehyde (5.0 mmol), α-chloroester (6.0 mmol) and catalyst (2 mol %) was suspended in a solvent (10 ml) and stirred for 30 min. Base (6.0 mmol) was added to the above reaction mixture. After stirring for a stipulated period of time at room temperature, the reaction was quenched with water and was extracted with ethyl acetate (15 ml × 3). The combined organic layer was washed with brine and solvent, dried with anhydrous sodium sulfate and concentrated under reduced pressure. Following purification by a flash column chromatography, the isolated yield was obtained.

O/N-Alkylation. Typical alkylation reaction was conducted by mixing benzyl bromide (5 mmol) in 10 ml of CH_2Cl_2 and phenol/pyrrol (5 mmol) and NaOH (5.2 mmol) in 10 ml of water. Catalyst (2 mol %) was added and the reaction was conducted for a stipulated time period (Table 2) at 298 K. Reaction mixture was quenched with dilute HCl solution and extracted with CH_2Cl_2 (15 ml × 3). The combined organic layer was washed with brine and solvent, dried with anhydrous sodium sulfate and concentrated under reduced pressure. Following purification by a flash column chromatography, the isolated yield was obtained.

Ethylbenzene oxidation. A 150 ml thermostatted glass cylindrical vessel attached with a glass stirrer (800 rpm) and a gas inlet system, a thermocouple and a reflux condenser cooled with water were used for the experiments. Gases were fed to the reactor through mass flow controllers. In a typical oxidation reaction, 30 g of ethylbenzene containing 1.0 wt % of ethylbenzene hydroperoxide was used. The reactions were performed at 403 K. Once the temperature had reached at a constant value, 2 mmol of catalyst was added into the reactor and an air flow of 200 ml/min was set and kept constant during the experiment. The concentration of EBHP was measured by standard iodometric titration. The remaining organic compounds were analyzed by a gas chromatography (Hewlett-Packard 5890 Series II gas chromatograph equipped with a flame ionization detector and a packed column with 10% SE-30).

References and notes

1. Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.
2. Jones, R. A. *Quaternary Ammonium Salts: Their Use in Phase Transfer Catalyzed Reactions*; Academic Press: UK, 2001.
3. Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*; Chapman and Hall: New York, USA, 1994.
4. Manroka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
5. (a) Tundo, P.; Venturello, P. *J. Am. Chem. Soc.* **1981**, *103*, 856; (b) Wang, Z.; Xu, L.; Mu, Z.; Xia, C.; Wang, H. *J. Mol. Catal. A: Chem.* **2004**, *218*, 157.
6. (a) *Handbook of Phase Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic and Professional: London, UK, 1997; (b) Grushin, V. V.; Alper, H. *J. Org. Chem.* **1992**, *57*, 2188; (c) Starks, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 3613; (d) Jonczyk, A.; Michalski, K. *Synlett* **2002**, 1703; (e) Li, Z.; Wang, X. C. *Synth. Commun.* **2002**, *32*, 3087; (f) Bujok, R.; Makosza, M. *Synlett* **2002**, 1285; (g) Landini, D.; Maia, A. *J. Mol. Catal. A: Chem.* **2003**, *204*, 235; (h) Yadav, G. D.; Jadhav, Y. B.; Senguptas, S. *J. Mol. Catal. A: Chem.* **2003**, *200*, 117.
7. Freedman, H. H.; Dubois, R. A. *Tetrahedron Lett.* **1975**, *16*, 3251.
8. (a) Lissel, M.; Feldman, D.; Nir, M.; Rabinovitz, M. *Tetrahedron Lett.* **1989**, *30*, 1683; (b) Balakrishnan, T.; Jayachandran, J. P. *Synth. Commun.* **1995**, *25*, 3821; (c) Alvarez-Builla, J.; Vaquero, J. J.; Navio, J. L. G.; Cabello, J. F.; Sunkel, C.; Gasa-Juana, M. F. D.; Dorrego, F.; Santos, L. *Tetrahedron* **1990**, *46*, 967.
9. (a) Nagasaki, T.; Sisido, K.; Arimura, T.; Shinkai, S. *Tetrahedron* **1992**, *48*, 797; (b) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.
10. (a) Ballester, M. *Chem. Rev.* **1955**, *55*, 283; (b) Rosen, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 409.
11. (a) Peschke, B.; Bundgaard, J. G.; Breinholt, J. *Tetrahedron Lett.* **2001**, *42*, 5127; (b) Arai, S.; Suzuki, Y.; Tokumara, K.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 833; (c) Jayachandran, J. P.; Balakrishnan, T.; Wang, M. L. *J. Mol. Cat. A: Chem.* **2000**, *152*, 91.
12. (a) Alcántara, R.; Canoira, L.; Guilherme-Joao, P.; Santos, J. M.; Vázquez, I. *Appl. Catal. A: Gen.* **2000**, *203*, 259; (b) Alcántara, R.; Canoira, L.; Guilherme-Joao, P.; Pérez-Mendo, J. P. *Appl. Catal. A: Gen.* **2001**, *218*, 269.
13. (a) Barrio, L.; Toribio, P. P.; Campos-Martin, J. M.; Fierro, J. L. G. *Tetrahedron* **2004**, *60*, 11527; (b) Fukui, K.; Ohkubo, K.; Yamabe, T. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 312.
14. Csányi, L. J.; Jáky, K.; Palinko, I.; Rockenbauer, A.; Korecz, L. *Phys. Chem. Chem. Phys.* **2000**, *2*, 3801.
15. Ohkubo, K.; Yamabe, T.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2200.