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Catalytic alcoholysis of epoxides using metal-free cucurbituril-based solids†

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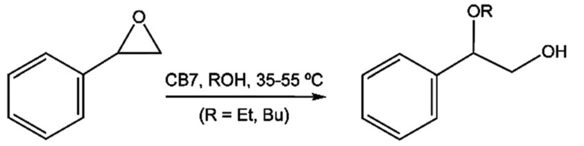
Metal-free cucurbit[7]uril (CB7) solid-state assemblies promote acid-catalysed alcoholysis of aliphatic and aromatic epoxides under mild conditions to give β-alkoxy alcohols, which are important intermediates for the synthesis of a vast range of compounds such as bioactive pharmaceuticals. The catalytic process is heterogeneous and the catalyst can be reused in consecutive runs without any reactivation treatment. The acid species responsible for the catalytic activity of CB7 may be entrapped hydronium ions.

Cucurbit[*n*]urils (CB*n*, *n* = 5–8, 10, 14) are a family of macrocyclic compounds comprising *n* glycoluril units linked by methylene bridges.[1] CB*n* can be readily prepared on a large scale by one-pot synthesis from cheap starting materials, glycoluril and formaldehyde. The unique properties of CBs, notably their rigid structure, two highly polar carbonyl-lined portals, a hydrophobic non-polarisable inner cavity, and high binding affinities, have prompted numerous studies within the fields of host–guest chemistry,[2a] supramolecular catalysis,[1c,2b] drug delivery,[2c] molecular machines and electronics, amongst others.[1d] Catalytic applications are still waiting to be extensively explored. Although CB-mediated catalysis has made important contributions to organic synthesis, the virtual lack of solubility of CBs in common organic solvents has restricted the reaction scope to transformations involving aqueous solutions, *e.g.* acid hydrolysis,[3a,b] oxidation of alcohols,[3c] desilylation,[3d] and photodimerisation.[3e] One exception is the use of an oxovanadium(IV)–CB6 complex as a heterogeneous catalyst for hydrocarbon oxidation.[3f]

An interesting feature of CB*n* assemblies in the solid-state is the existence of both intrinsic (from the cavity) and extrinsic (from inefficient molecular packing) porosities. The extrinsic porosity may comprise interstitial voids in amorphous solids[4a] or channels in crystalline materials.[4b–e] In addition to water molecules, the channels or voids may be filled with acid molecules, which has led to studies of proton conductivity and to the suggestion that CB materials could have potential as acid catalysts.[5] However, to the best of our knowledge, the use of CB assemblies as acid catalysts has hardly been explored.

Herein, we report that the unfunctionalised CB7, used in its as-prepared form, is a highly efficient metal-free catalyst for the heterogeneous alcoholysis of styrene oxide (StyOx) under mild conditions (Table 1). The acid-catalysed opening of epoxides with alcohols is an important transformation in the synthesis of β-alkoxy alcohols, which are useful intermediates for the synthesis of α-alkoxy ketones, α-alkoxy acids, enol ethers, and a range of bioactive natural and synthetic products.[6] In the production of drugs, high product purity is a crucial requirement for commercialisation, and the use of mild

Table 1 Catalytic performance of CB7 in StyOx alcoholysis[a]



Solvent	Cat. load (g_{cat} L^{-1})	*T* (°C)	*t* (min)	Conversion (%)
EtOH	10	35	1/10/30/60	17/61/94/100
EtOH (CT/35)[b]	10	35	1/10/30/60	13/63/97/100
EtOH	10	55	1/10/30	39/96/100
EtOH (CT/55)[b]	10	55	1/10	40/100
EtOH	5	55	1/10/30	13/67/100
BuOH	10	55	1/30/60/120/240	0/23/44/69/100
EtOH[c]	10	35	1/10/30/60	18/54/92/100
EtOH[d]	10	35	240/360	40/95

[a] The only product was the corresponding 2-alkoxy-2-phenylethanol (100% selectivity). [b] Catalytic runs using the solids recovered from the contact tests at 35 (CT/35) or 55 °C (CT/55). [c] In-house synthesized CB6 was used instead of CB7. [d] A commercial CB7 sample (Sigma-Aldrich) was used instead of in-house synthesized CB7.

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† Electronic supplementary information (ESI) available: Synthetic protocol and characterisation data for CB6 and CB7, and experimental details for the alcoholysis reactions. See DOI: 10.1039/c6ob00512h

synthesis conditions helps to avoid the decomposition of relatively unstable polyfunctionalised products. Hence, the use of metal-free catalysts capable of promoting the chemical reactions with excellent selectivity, under mild conditions, is highly desirable. To date, most of the homogeneous and heterogeneous catalysts that have been investigated for the alcoholysis of epoxides contain metals and/or metalloids. Only a few examples of metal-free heterogeneous acid catalysts have been reported, *e.g.* graphene oxide,[7a] mesoporous carbon,[7b] and the commercial ion-exchange resin Amberlyst™-15.[7c]

In the ethanolysis of StyOx, the alcohol serves as both a solvent and a reactant. As a catalyst, CB7 was highly active and selective, giving 2-ethoxy-2-phenylethanol (StyOEt) with 100% selectivity at 100% conversion, which was reached within 1 h of reaction at approximately room temperature (35 °C, Table 1). Increasing the reaction temperature from 35 to 55 °C led to an extremely fast alcoholysis reaction (96% conversion at 10 min) without affecting product selectivity (100%). At this reaction temperature, the catalyst loading could be reduced from 10 to 5 g_{cat} L^{-1} while still maintaining very good results (100% conversion within 30 min, Table 1). The catalytic role of CB7 was confirmed by the fact that the reaction of StyOx was negligible in the absence of cucurbituril (*e.g.*, conversion was only 1% after 4 h of reaction at 55 °C).

The use of *n*-butanol as a reacting solvent instead of ethanol led to excellent selectivity towards the corresponding β-alkoxy alcohol product: 100% 2-butoxy-2-phenylethanol (StyOBu) yield at 4 h reaction (Table 1). The slower kinetics with *n*-butanol than with ethanol may be partly due to more important steric effects in the former case.

To check whether the catalytic reaction occurred in the homogeneous or heterogeneous phase, two tests were performed for CB7 (as described in detail in the ESI†): (i) contact test (CT), in which CB7 was treated with ethanol, followed by separation and use of the liquid phase for the reaction of StyOx, and (ii) filtration test (FT), in which the catalytic reaction was interrupted at an initial stage by separating (at the reaction temperature) the solid from the reaction solution, which was then allowed to react further. The solution obtained from the CT led to less than 5% StyOx conversion after 4 h at 55 °C, which is negligible compared to that observed for a typical catalytic batch run with CB7. Similarly, for the CT and FT at 35 °C, the liquid phases led to no catalytic reaction. Hence, the catalytic reaction occurred in the heterogeneous phase.

The solids obtained from the CTs at 35 and 55 °C (denoted CT/35 and CT/55, respectively) were tested in the reaction of StyOx, and led to comparable catalytic results to those observed for the original catalyst, under similar reaction conditions (Table 1). Hence, CB7 seems to be fairly stable. The catalyst stability was further studied in terms of recyclability by carrying out three consecutive batch runs at 35 °C; between runs, the solid catalyst was separated from the reaction mixture, washed and dried. StyOx conversion reached 100% at 1 h for the three runs, and StyOEt selectivity was always 100%. The FT-IR spectrum of the reused catalyst was similar to that of the original catalyst (Fig. 1), and SEM indicated no significant morphological changes (Fig. 2), suggesting that the physico-chemical integrity of CB7 was essentially preserved during the catalytic process.

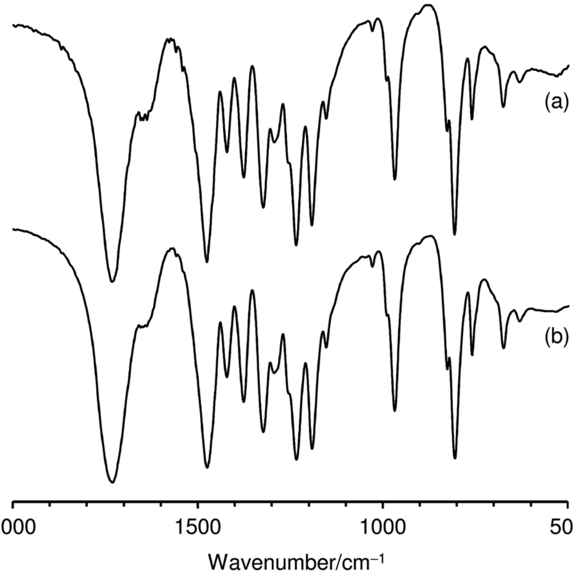


Fig. 1 FT-IR spectra of (a) CB7 and (b) CB7-reused.

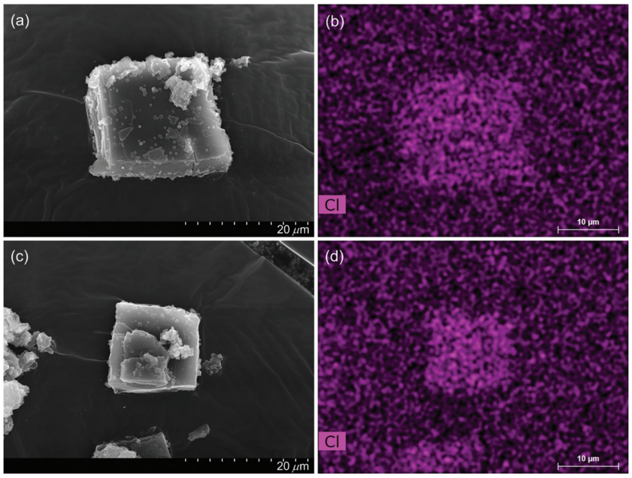


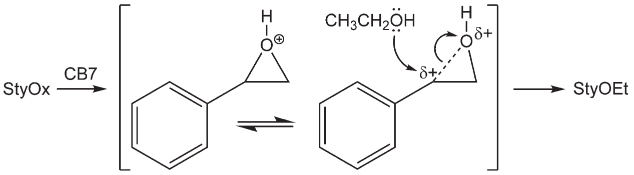
Fig. 2 SEM and the corresponding EDS Cl mapping images of CB7 (a, b) and CB7-reused (c, d).

Acid–base titration for the fresh and used catalysts (performed with ethanol as the solvent) indicated a similar acid content of *ca.* 34 μeq H^+ g_{solid}^{-1} for the two solids. A value of *ca.* 63 μeq H^+ g_{solid}^{-1} was obtained when the titrations were performed in water. Similar chloride contents (corresponding to HCl) of *ca.* 74 μeq H^+ g_{solid}^{-1} were determined by ion chromatography (IC) for the fresh and used catalysts. Accordingly, EDS elemental mapping for Cl indicated that no significant depletion of Cl had occurred during the catalytic reaction (Fig. 2). These results are consistent with the fairly good

Table 2 Literature data for catalytic alcoholysis of StyOx performed in the presence of metal-free heterogeneous catalysts

Catalyst	Cat. load (g_{cat} L^{-1})	$[StyOx]_0$ (M)	*T* (°C)	*t* (min)	Conv. (%)	Ref.
CB7	10	0.40	35	60	100[a]	t.w.[b]
Amberlyst™-15	10	0.40	35	30	100[a]	t.w.[b]
Amberlyst™-15	20	0.20	24–28	30	100[c]	7*c*
Mesoporous carbon	32	0.47	a.t.[d]	30	99[e]	7*b*
Graphene oxide	0.45	0.80	a.t.[d]	60	99[f]	7*a*

[a] StyOEt was formed with 100% selectivity. [b] This work. [c] Isolated StyOEt yield was 95%. [d] Ambient temperature. [e] StyOEt was formed with 97% selectivity. [f] StyOMe was formed with 93% selectivity.



Scheme 1 StyOx reaction mechanism in the presence of CB7.

catalyst stability results discussed above. The initial catalytic activities (or turnover frequencies) expressed per mass of catalyst (or per eqH^+, based on the titration results in ethanol) are 0.41 mol g_{cat}^{-1} h^{-1} (12 000 mol mol_{H+}^{-1} h^{-1}) at 35 °C, and 0.94 mol g_{cat}^{-1} h^{-1} (27 500 mol mol_{H+}^{-1} h^{-1}) at 55 °C.

The catalytic performance of CB7 was compared to that of HCl, chosen as a liquid acid catalyst and used in an amount equivalent to the acid content for 10 g_{CB7} L^{-1}, at 35 °C. The ethanolysis of StyOx in the presence of HCl was much slower (<10% conversion at 24 h reaction) than for CB7. In a second comparison, the commercially available sulfonic acid ion-exchange resin Amberlyst™-15 (which possesses a much higher acid content of 4300 μeq H^+ g_{solid}^{-1}) was chosen as a benchmark solid acid catalyst (the mass of the solid catalyst was the same for the different catalysts). Amberlyst™-15 led to 100% conversion at 30 min reaction and 100% StyOEt selectivity (Table 2), and initial catalytic activity was 1.52 mol g_{cat}^{-1} h^{-1} (353 mol mol_{H+}^{-1} h^{-1}). While, for the same mass of the catalyst, the ion-exchange resin led to a faster reaction, the intrinsic activity of the acid sites was higher for CB7. Hence, CB7 seems to possess distinct acid properties. The catalytic performance of CB7 compares favourably with the limited literature data available for metal-free solid acid catalysts tested in the same reaction (Table 2).[7]

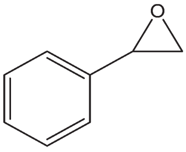
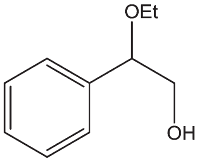
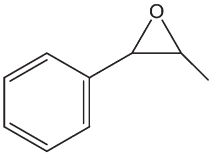
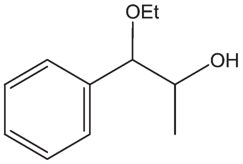
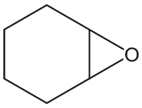
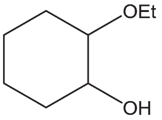
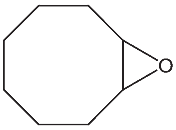
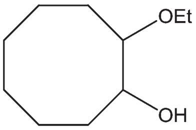
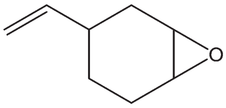
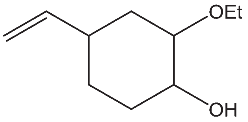
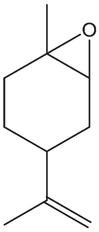
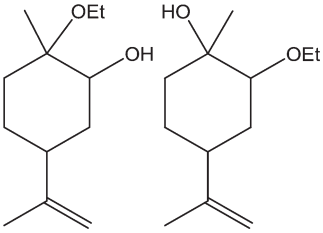
CBs such as CB7 have been shown to promote acid hydrolysis of amides, carbamates and oximes under homogeneous conditions.[3a] The CBs were proposed to serve as unconventional "acid substitutes" by virtue of complexation-induced pK_a shifts, thereby facilitating the protonation of the substrates. Similar effects are difficult to investigate for heterogeneous catalytic processes which, besides chemical reactions, involve physical phenomena (*e.g.* adsorption, internal diffusion) that do not apply for homogeneous catalysts.

The acid sites responsible for the catalytic activity of CB7 may be stabilised by hydronium ions associated with the co-crystallised acid molecules, which are very difficult to remove.[4e] The results of various tests supported this hypothesis. In one test performed at 35 °C with 10 g_{CB7} L^{-1}, Brønsted acid species in the CB7 sample were neutralised by the initial addition of NaOH (in an amount equivalent to 34 μmol g_{CB7}^{-1}). The subsequent reaction led to 21% conversion at 2 h, whereas a typical batch run with the as-prepared CB7 gave 100% conversion at 1 h (no reaction occurred with NaOH and without CB7 up to 24 h). In another test, a commercially available CB7 sample (Sigma-Aldrich) led to 40%/95% StyOx conversions at 4 h/6 h and 35 °C, which are lower than those observed for the as-prepared (in-house) CB7, under similar reaction conditions (Table 1). The lower activity for the commercial sample correlates with its lower acid content of *ca.* 14 μeq H^+ g_{solid}^{-1} determined by acid–base titration in ethanol. The activity of the in-house synthesised CB7 was found to be comparable with that of a CB6 sample (isolated from the same synthesis batch used to obtain CB7) possessing a similar acid content of *ca.* 38 μeq H^+ g_{solid}^{-1}, under identical reaction conditions (10 g_{solid} L^{-1}, 35 °C), *i.e.*, similar kinetic results (Table 1) correlate with similar acid contents of the two catalysts. Overall, the catalytic reaction seems to be essentially governed by hydronium ions. The StyOx reaction mechanism may involve protonation of the oxygen atom of the oxirane ring, thereby favouring the nucleophilic attack of the alcohol reagent at the more substituted carbon atom of the epoxide group, leading selectively to the β-alkoxy alcohol product (Scheme 1).[8]

As mentioned above, water, hydronium ions and anions such as chloride play an important role in the assembly and packing patterns of CB molecules in the solid state. Extensive hydrogen-bonding networks are present both within voids or channels and between neighbouring CB molecules. Strong interactions between hydronium ions and the carbonyl groups located at the CB7 portals have been studied by DFT calculations[9] and proposed to be the driving force for the unusual hydrogel formation observed under acidic conditions.[4c] On the basis of these structural studies and the results of the catalytic tests performed in the present work, we propose that the ethanolysis of StyOx is promoted by hydronium species that are directly interacting with CB7 molecules and/or located in the void spaces of the solid-state structure; the relative contributions of the differently located acid species may depend on their accessibility towards the reactants.

The catalytic performance of CB7 was further investigated for the ethanolysis of aliphatic epoxides, namely cyclohexene oxide (Cy6Ox), cyclooctene oxide (Cy8Ox) and cyclododecene oxide (Cy12Ox), at 35 °C (Table 3). The reaction of Cy6Ox was fast, giving 2-ethoxycyclohexanol in 93% yield at 96% conversion (6 h reaction; cyclohexane-1,2-diol was formed as a by-product in 3% yield). The reaction of Cy8Ox was very sluggish (7% conversion at 96 h), and that of Cy12Ox did not occur. For the three aliphatic cyclic epoxide substrates, using HCl (in an amount equivalent to the acid content for 10 g_{CB7} L^{-1}) instead

Table 3 Reaction of different epoxides in the presence of CB7

Substrate	Conv. (%)	*t* (h)	Alkoxy alcohol product yields (%)
	100	1	100 
	87	6	87 
	96	6	93 
	7	96	4 
	96	24	62 
	95	24	73 

Reaction conditions: $[\text{substrate}]_0 = 0.40$ M, 10 g_{CB7} L^{-1}, 35 °C.

of CB7 led to negligible conversion, which parallels that observed for StyOx as a substrate. The trend in the reaction rate for the substrates with increasing ring dimension may be partly due to steric hindrance and/or reduced accessibility to active sites.

The CB7 catalyst was further investigated for the ethanolysis of substituted aliphatic and aromatic C6-membered ring substrates, namely (1*R*,2*R*)-phenylpropylene oxide (Me-StyOx), 4-vinylcyclohexene oxide (vinyl-Cy6Ox) and the renewable epoxide *R*-limonene oxide (LimOx). With Me-StyOx as a substrate, 87% conversion was reached at 6 h and 1-ethoxy-1-phenyl-2-propanol was the only product (100% selectivity). With vinyl-Cy6Ox as a substrate, 96% conversion was reached at 24 h to give a 62% total yield (65% total selectivity) of the *cis*/*trans* alkoxy alcohols; other products were 1,2-diethoxy-3-vinyl-cyclohexane formed in 25% yield (26% selectivity), and 7% yield (7% selectivity) of vinyl cyclohexane-1,2-diol. The ethanolysis of LimOx led to 95% conversion at 24 h, giving 73% total yield (77% total selectivity) of alkoxy alcohol isomers, namely 2-ethoxy-2-methyl-5-(prop-1-en-2-yl)cyclohexanol and 2-ethoxy-1-methyl-4-(prop-1-en-2-yl)cyclohexanol (Table 3); 1-methyl-4-(prop-1-en-2-yl)-cyclohexane-1,2-diol was formed with 10% yield (11% selectivity). The slower conversion of the more substituted substrate Me-StyOx when compared with that for StyOx (and also for vinyl-Cy6Ox and LimOx *vs.* Cy6Ox) may be partly due to steric hindrance.

In summary, cucurbit[7]uril has been demonstrated to be an efficient heterogeneous metal-free catalyst for the alcoholysis of aliphatic and aromatic epoxides under mild conditions. The catalytic potential of CBs may be extended to different acid-catalysed reactions in future studies, and advanced solid-state molecular-level characterisation may help gain deeper insights into structure–activity relationships.

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References

1 (*a*) L. Isaacs, *Chem. Commun.*, 2009, 619; (*b*) E. Masson, X. Ling, R. Joseph, L. Kyeremeh-Mensah and X. Lu, *RSC Adv.*, 2012, **2**, 1213; (*c*) K. I. Assaf and W. M. Nau, *Chem. Soc. Rev.*, 2015, **44**, 394; (*d*) G. Parvari, O. Reany and E. Keinan, *Isr. J. Chem.*, 2011, **51**, 646.

2 (*a*) Y. H. Ko, I. Hwang, D.-W. Lee and K. Kim, *Isr. J. Chem.*, 2011, **51**, 506; (*b*) B. C. Pemberton, R. Raghunathan, S. Volla and J. Sivaguru, *Chem. – Eur. J.*, 2012, **18**, 12178; (*c*) S. Walker, R. Oun, F. J. McInnes and N. J. Wheate, *Isr. J. Chem.*, 2011, **51**, 616.

3 (*a*) C. Klöck, R. N. Dsouza and W. M. Nau, *Org. Lett.*, 2009, **11**, 2595; (*b*) N. Basilio, L. García-Río, J. A. Moreira and M. Pessêgo, *J. Org. Chem.*, 2010, **75**, 848; (*c*) Y.-H. Wang, H. Cong, F.-F. Zhao, S.-F. Xue, Z. Tao, Q.-J. Zhu and G. Wei, *Catal. Commun.*, 2011, **12**, 1127; (*d*) X. Lu and E. Masson, *Org. Lett.*, 2010, **12**, 2310; (*e*) B. C. Pemberton, R. K. Singh, A. C. Johnson, S. Jockusch, J. P. Da Silva, A. Ugrinov, N. J. Turro, D. K. Srivastava and J. Sivaguru, *Chem. Commun.*, 2011, **47**, 6323; (*f*) S. M. de Lima, J. A. Gómez, V. P. Barros, G. de S. Vertuan, M. D. Assis, C. F. O. Graeff and G. J.-F. Demets, *Polyhedron*, 2010, **29**, 3008.

4 (*a*) J. Tian, S. Ma, P. K. Thallapally, D. Fowler, B. P. McGrail and J. L. Atwood, *Chem. Commun.*, 2011, **47**, 7626; (*b*) S. Lim, H. Kim, N. Selvapalam, K.-J. Kim, S. J. Cho, G. Seo and K. Kim, *Angew. Chem., Int. Ed.*, 2008, **47**, 3352; (*c*) I. Hwang, W. S. Jeon, H.-J. Kim, D. Kim, H. Kim, N. Selvapalam, N. Fujita, S. Shinkai and K. Kim, *Angew. Chem., Int. Ed.*, 2007, **46**, 210; (*d*) D. Bardelang, K. A. Udachin, D. M. Leek and J. A. Ripmeester, *CrystEngComm*, 2007, **9**, 973; (*e*) D. Bardelang, K. A. Udachin, D. M. Leek, J. C. Margeson, G. Chan, C. I. Ratcliffe and J. A. Ripmeester, *Cryst. Growth Des.*, 2011, **11**, 5598.

5 M. Yoon, K. Suh, H. Kim, Y. Kim, N. Selvapalam and K. Kim, *Angew. Chem., Int. Ed.*, 2011, **50**, 7870.

6 (*a*) Y.-X. Zhou, Y.-Z. Chen, Y. Hu, G. Huang, S.-H. Yu and H.-L. Jiang, *Chem. – Eur. J.*, 2014, **20**, 14976; (*b*) S. S. Kahandal, S. R. Kale, S. T. Disale and R. V. Jayaram, *Catal. Sci. Technol.*, 2012, **2**, 1493; (*c*) T. Weil, M. Kotke, C. M. Kleiner and P. R. Schreiner, *Org. Lett.*, 2008, **10**, 1513; (*d*) D. Bhuyan, L. Saikia and D. K. Dutta, *Appl. Catal., A*, 2014, **487**, 195; (*e*) M. L. Kantam, K. Aziz, K. Jeyalakshmi and P. R. Likhar, *Catal. Lett.*, 2003, **89**, 95; (*f*) J. Otera and Y. Niibo, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3977; (*g*) C. Baylon, G. Prestat, M.-P. Heck and C. Mioskowski, *Tetrahedron Lett.*, 2000, **41**, 3833.

7 (*a*) A. Dhakshinamoorthy, M. Alvaro, P. Concepción, V. Fornésand and H. Garcia, *Chem. Commun.*, 2012, **48**, 5443; (*b*) I. Matos, P. D. Neves, J. E. Castanheiro, E. Perez-Mayoral, R. Martin-Aranda, C. Duran-Valle, J. Vital, A. M. Botelho do Rego and I. M. Fonseca, *Appl. Catal., A*, 2012, **439–440**, 24; (*c*) Y.-H. Liu, Q.-S. Liu and Z.-H. Zhang, *J. Mol. Catal. A: Chem.*, 2008, **296**, 42.

8 (*a*) A. Dhakshinamoorthy, M. Alvaro and H. Garcia, *Chem. – Eur. J.*, 2010, **16**, 8530; (*b*) G. Kumar, A. P. Singh and R. Gupta, *Eur. J. Inorg. Chem.*, 2010, 5103; (*c*) R. F. Mendes, P. Silva, M. M. Antunes, A. A. Valente and F. A. A. Paz, *Chem. Commun.*, 2015, **51**, 10807.

9 E. Makrlík, P. Toman and P. Vaňura, *Acta Chim. Slov.*, 2013, **60**, 416.