

Catalysis

Metal-Free Epoxidation of Internal and Terminal Alkenes with *tert*-Butyl Hydroperoxide/Isobutyraldehyde/Oxygen SystemMei Hong,* Jie Min, and Shifa Wang^[a]

The epoxidation of several alkenes was studied using oxygen as green oxidant, isobutyraldehyde (IBA) as co-reagent and *tert*-butyl hydroperoxide (TBHP) as radical initiator at mild conditions (60 °C, atmospheric pressure with an oxygen balloon). TBHP could accelerate the production of carbonyl radical and its peroxidation, without using a metal catalyst. The factors influencing the conversion of the substrates and selectivity of the epoxides have been well investigated. Under optimized reaction conditions, the epoxidation of linear terminal, cyclic and aromatic alkenes was evaluated. Most performed reactions were high selectivity for production of the corresponding epoxides.

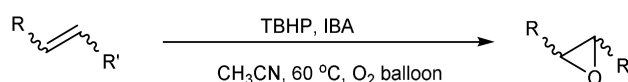
Epoxides are precious precursors in organic synthesis. They are easily obtained from alkenes using either strong organic oxidants (e.g. *m*-CPBA, NaClO),^[1] or mild oxidants (e.g. TBHP, H₂O₂),^[2] with the assistance of metal-based catalysts (Fe, Mn, Co, Ni, Mo, V, Ti, Cu and W).^[3] Taking account of environmental, safety and economic concerns, the utilization of O₂ the oxidant is one of the attractive developments. However, its direct utilization needs activation processes owing to the restriction of Wigner spin conservation rule^[4] in its triplet ground state structure. As a result, some metal-containing catalysts (Ru,^[5] Co,^[6] Cu,^[7] etc.) have been explored to catalyze molecular oxygen for the epoxidation. From the standpoint of so-called green and sustainable chemistry, the development of metal-free catalytic systems for epoxidation is needed. Burgeoning metal-free organocatalytic strategies have attracted much attention in recent years in many oxidation processes with molecular oxygen,^[8] which have outstanding performances and other undeniable advantages in green chemistry^[9] from long-term considerations, as compared to metallic or organometallic catalysis. Minisci and co-workers disclosed an organocatalyzed epoxidation of olefins by aerobic oxidation using *N*-hydroxyphthalimide (NHPI) as catalyst.^[10] However this method suffers from long reaction times (24–48 h). Itoh^[11] reported metal-free

oxidation protocol of alkenes under visible light irradiation of fluorescent lamp. The development of efficient and inexpensive methods for the epoxidation of alkenes is still a challenge.

Epoxyethylbenzene is an important raw material for the manufacturing of phenethyl alcohol, tetramisole, levamisole and phenylacetaldehyde, which have found extensive applications in the petrochemical industry, fine chemicals, medicines, perfumery and polymers. Traditionally, epoxyethylbenzene was obtained by the epoxidation of styrene with oxyhalides (or alternatively from chlorohydrins and bromohydrins via dehalogenation/dehydration under basic conditions),^[12] however, these procedures produce a vast amount of environmentally undesirable waste. It is highly preferential to develop an environmentally benign procedure by using green oxidants such as molecular oxygen. Styrene epoxidation bear low or non-selectivity (0–47%) due to the uncontrolled over-oxidation of the initially formed epoxide to phenylacetaldehyde and benzaldehyde.^[13] Yang et al. reported that Yolke-shell nanospheres confined with ultra-small Au nanoparticles catalyzed styrene oxidation with oxygen at ambient pressure affording styrene oxide with 62.2% of selectivity at 100 °C in 15 h.^[14] The key challenge is to develop efficient protocols for the epoxidation of styrene with molecular oxygen as oxidant on metal-free under mild conditions.

In this work, we report a facile and efficient method for the selective epoxidation of alkenes using molecular oxygen as the oxidant with an oxygen balloon, TBHP as initiator at moderate temperature (60 °C) in the presence of isobutyraldehyde (IBA) (Scheme 1). The product formation could be completed in a few hours, whereas the uncatalyzed reaction with O₂/aldehyde takes a day or more to reach the maximum conversion.^[15]

Styrene was selected as a model substrate to optimize the reaction parameters and conditions directly under oxygen atmosphere by using an O₂ balloon. To study the effectiveness of TBHP, experiments were carried out on the epoxidation of styrene under 60 °C for 5 h and these results are presented in Table 1. In the set of experiments, the TBHP and the aldehyde could react with oxygen for 30 min at 35 °C before the addition



Scheme 1. Metal free aerobic epoxidation of alkenes.

[a] Dr. M. Hong, J. Min, Prof. S. Wang

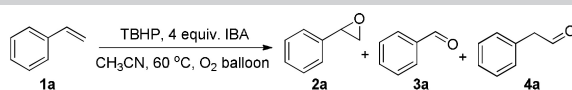
Jiangsu Key Laboratory of Biomass-based Green Fuels and Chemicals, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China

E-mail: hongmei-613@njfu.edu.cn



Supporting information for this article is available on the WWW under <https://doi.org/10.1002/slct.201800378>

Table 1. Variation of the amount of TBHP.^[a]



Entry	Equiv. of TBHP	Conv. ^[b] (%)	Sel. ^[b] (%)		
			2a	3a	4a
1	0	2	9	68	23
2 ^[c]	0	85	50	33	17
3	0.16	47	56	21	23
4	0.30	100	63	15	23
5	0.50	100	63	16	21
6	1.00	100	58	24	18

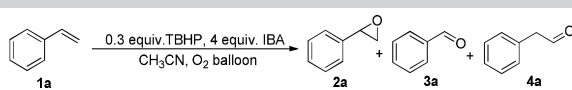
[a] Reaction conditions: Styrene 1 mmol, IBA 4 mmol, Acetonitrile 3 mL, Temperature 60 °C, Reaction time 5 h, O₂ balloon. [b] Determined by GC-MS. [c] Reaction time 24 h.

of the alkene. After 5 h of reaction time, the conversion of styrene was 100%. However, the reaction time of the process was more than 24 h without the initiator. Only 2% of styrene was oxidized without the addition of TBHP (Table 1, entry 1). Furthermore, when the reaction was performed for 24 h, only 85% of conversion was achieved with 50% of selectivity for the epoxyethylbenzene (Table 1, entry 2). Comparing these two results, we can infer that TBHP accelerates the autoxidation rate, possibly by contributing to the formation of the corresponding acyl radical. It is clear that when the molar ratio of TBHP to styrene is 0.3, the selectivity towards styrene oxide reaches 63% at full conversion of styrene, which was higher than that with the ratio of 0.16 (56% selectivity and 47% conversion) (Table 1, entries 3 and 4). Upon increasing the amount of TBHP (> 0.3 mmol), the selectivity almost remains constant (Table 1, entries 5 and 6).

In order to study the effect of the temperature on the epoxidation process, the reaction was evaluated in a temperature range from 40 to 70 °C. The results are shown in Table 2. The conversion of styrene decreased up to 55% at lower temperatures than 50 °C whereas the selectivity of the epoxide showed no change. As a result, 60 °C was selected for further studies.

It was found that the aldehyde acted as a sacrificial co-reductant.^[16] Two different aldehydes were chosen based on the precedent described in the literatures,^[17a,17] the effects of

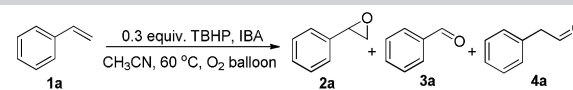
Table 2. Variation of temperature.^[a]



Entry	Temp. [°C]	Conv. ^[b] [%]	Sel. ^[b] (%)		
			2a	3a	4a
1	40	55	60	16	24
2	50	55	53	31	16
3	60	100	63	16	21
4	70	100	63	13	24

[a] Reaction conditions: Styrene 1 mmol, TBHP 0.3 mmol, IBA 4 mmol, Acetonitrile 3 mL, Reaction time 5 h, O₂ balloon. [b] Determined by GC-MS.

Table 3. Variation of the number of equivalents of isobutyraldehyde.^[a]



Entry	Equiv. of IBA	Conv. ^[b] (%)	Sel. ^[b] (%)		
			2a	3a	4a
1	0	-	-	-	-
2	2	74	51	31	18
3 ^[c]	2	52	44	37	19
4	3	80	56	26	18
5	4	100	63	16	21
6	5	100	62	15	23
7	6	100	68	8	24
8	7	100	61	23	16
9	8	100	60	23	16

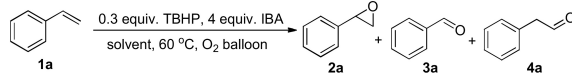
[a] Reaction conditions: Styrene 1 mmol, TBHP 0.3 mmol, Acetonitrile 3 mL, Temperature 60 °C, Reaction time 5 h, O₂ balloon. [b] Determined by GC-MS. [c] Trimethylacetaldehyde instead of IBA.

trimethylacetaldehyde and isobutyraldehyde were studied in the epoxidation of styrene. The isobutyraldehyde was more suitable because of the better epoxidation effect (Table 3, entries 2 and 3). The effectiveness of isobutyraldehyde was studied in epoxidation of styrene under 60 °C using an oxygen balloon for 5 h. The results are presented in Table 3. It was pointed out that there was no reaction in the absence of isobutyraldehyde, which indicated that the aldehyde was an essential additive for the epoxidation. The conversion increased with a higher molar ratio of isobutyraldehyde and reached 100% when the molar ratio was 4 (Table 3, entry 5). An improvement in selectivity to epoxidized styrene was also obtained by increasing the molar ratio from 2 to 6 (Table 3, entries 2 and 4–6). However, the selectivity decreased slightly with 6 equiv. of isobutyraldehyde (Table 3, entries 7–9). This reduction is observed due to the self-polymerization of the isobutyraldehyde during the epoxidation process and therefore lead to a decrease of its peroxidation abilities. The dimer of isobutyric acid was detected by GC-MS measurements. Therefore, the optimal molar ratio of isobutyraldehyde towards styrene in the epoxidation process was 4.

The solvent could offer an ideal autoxidation environment for the aldehyde in this epoxidation process. However, epoxide may easily undergo isomerisation in polar solvents.^[18] To study the solvent effect, the epoxidation of styrene was carried out in aprotic solvents, such as acetonitrile, 1,4-dioxane and 1,2-dichloroethane. The results are presented in Table 4. Among the solvents studied, acetonitrile was found to be the most suitable solvent, followed by 1,2-dichloroethane and 1,4-dioxane.

The polarity of acetonitrile is higher than 1,2-dichloroethane and 1,4-dioxane. Probably, the polarity and aprotic nature of acetonitrile plays a key role in improving the conversion and selectivity of epoxidation of styrene. The effect of the concentration of styrene on the epoxidation of styrene was also studied and the results are also presented in Table 4. Results shown, under relatively mild conditions, the most significant solvent effect is that the product distribution is

Table 4. Variation of solvents.^[a]



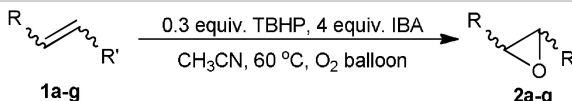
Solvent	Styrene Conc. [M]	Conv. ^[b] [%]	2 a	3 a	4 a
Acetonitrile	1	94	48	36	16
Acetonitrile	0.3	100	63	16	21
Acetonitrile	0.2	100	61	18	21
1,4-dioxane	0.3	70	54	31	14
1,2-dichloroethane	0.3	92	59	18	22









[a] Reaction conditions: Styrene 1 mmol, TBHP 0.3 mmol, IBA 4 mmol, Reaction time 5 h, Temperature 60 °C, O₂ balloon. [b] Determined by GC-MS.

dependent on the concentration of reactant. The selectivity towards styrene oxide is increased with the dilution of the reaction, from 1 M to 0.3 M. A further increase of the dilution to 0.2 M doesn't significantly influence the catalytic reaction.

To explore the role of the oxygen concentration, the epoxidation of styrene was carried out in an open vessel, and it still showed good results (Table 5, entry 2). The conversion of styrene was lower in comparison to when the O₂ balloon was used, which is due to the low concentration of molecular oxygen in the air. However, the selectivity towards the epoxide

Table 5. Scope of the epoxidation reaction.^[a]



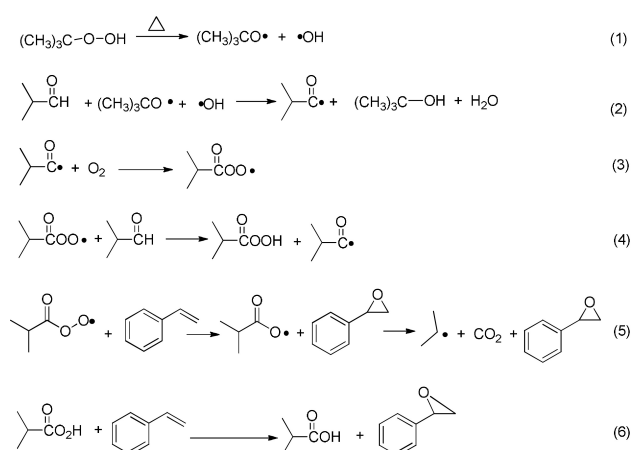
Entry	Sub.	t [h]	Conv. ^[b] [%]	Epoxide Sel. ^[b] [%]	Epoxide Yield ^[b] [%]
1		5	100	63	63
2 ^[c]		5	51	63	32
3		5	88	37	33
4		7	92	80	74
5		8	89	92	82
6		10	100	100	100
7		8	73	100	73
8		8	64	100	64

[a] Reaction conditions: Substrate 1 mmol, TBHP 0.3 mmol, IBA 4 mmol, Acetonitrile 3 mL, Temperature 60 °C, O₂ balloon. [b] Determined by GC-MS. [c] In an open vessel without balloon.

remained completely the same (63%). The oxidation reaction in the air makes the developed method much more convenient and economical. Encouraged by the obtained results, the scope of this catalytic system was further investigated in the epoxidation of other alkenes such as trans- β -methylstyrene, α -methylstyrene, cyclohexene, cyclooctene, 1-octene and 1-decene under the optimized epoxidation conditions. As seen in Table 5, endocyclic alkenes such as cyclooctene and cyclohexene participated well in this epoxidation reaction. Full conversion of cyclooctene was achieved in 10 h without any byproduct (Table 5, entry 6). Cyclohexene shows 89% conversion to form cyclohexene oxide as the major product with 92% selectivity. In addition, 2-cyclohexen-1-ol was generated, owing to allylic C–H oxidation.

Furthermore, terminal linear alkenes are generally considered as inert olefins towards epoxidation.^[19] Interestingly, they were also oxidized in good yields and with excellent selectivities (Table 5, entries 7 and 8). In case of terminal olefin α -methylstyrene (1 b) the selectivity was not encouraging. Both steric and electronic factors affect the conversion and the time of the epoxidation. For instance, the electron-rich substrates such as α -methylstyrene (1 b), trans- β -methylstyrene (1 c) and styrene (1 a) are more reactive than cyclohexene (1 d) and cyclooctene (1 e) for the epoxidation by the system. Moreover, 1-octene (1 f) and 1-decene (1 g) as linear terminal, mono-substituted alkenes with low π -electron density displays lower activity in this alkene series.

As reported previously, the mechanism of oxidation by molecular oxygen in the presence of aldehyde was usually considered as a free radical reaction.^[20] In order to assess whether the mechanism of this oxidation by molecular oxygen in the presence of TBHP takes place via a free radical pathway, some control experiments were performed. A free radical inhibitor 2,6-di-tert-butyl-4-methylphenol, was added to the TBHP/IBA/oxygen oxidation systems. After 5 h no reaction was detected according to the GC-MS analysis. These observations demonstrated the epoxidation in the presence of aldehyde takes place via a concerted radical mechanism. With styrene for example, a plausible mechanism is proposed (Scheme 2) based



Scheme 2. The mechanism of styrene epoxidation with TBHP/IBA/O₂.

on the precedent described in the literature^[21] and the above discussions. The t-butoxyl (t-BuO) and OH radicals formed from the homolytic cleavage of TBHP, which acts as radical initiator, preferentially abstract hydrogens to give the acyl radical (Scheme 2, eqs 1 and 2).^[22] As shown in eq 3, the corresponding acyl radical could react to molecular oxygen, affording the acylperoxy radical which is responsible for the transfer of oxygen from its molecular form in the gas phase to the products of olefin oxidation. The acylperoxy radical might directly react to the olefin double bond, which subsequently decomposes to produce the epoxide and carbon dioxide and the alkyl radical. The acylperoxy radical reacts with styrene followed by epoxide formation (Scheme 2, eq 5). The acylperoxy radical can either abstract a hydrogen atom from aldehyde to produce peracid and eventually epoxide (Scheme 2, eqs 4 and 6).

It can be concluded that the TBHP/isobutyraldehyde/oxygen system is very efficient for epoxidation of alkenes and the operation conditions are mild. The optimum reaction conditions were found to be 0.3 equivalent of TBHP, 4 equivalent of IBA and a reaction temperature of 60 °C, with acetonitrile as the solvent. TBHP could accelerate the production of carbonyl radical and its peroxidation.

This epoxidation process has three advantages compared with other reported epoxidation processes. The first one is that the reaction can be carried out at lower temperature, within a short reaction time and with high selectivity. The second is that molecular oxygen can be used as efficient oxidant. And the third advantage is that this oxidative system could work very well in the absence of metal catalyst, which could reduce economy cost and metallic pollution.

Supporting Information Summary

The Supporting Information for this article contains the Experimental Section explaining all the experimental details along with the isolation and spectral data of styrene oxide and cyclooctene oxide.

Acknowledgements

The work was supported by the Natural Science Foundation of Jiangsu Province (China) (No. BK20140969), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and the open fund of Jiangsu Key Lab of Biomass Energy and Materials (JSBEM201603).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkene epoxidation · Isobutyraldehyde · Metal free · Molecular oxygen · Radical

[1] a) A. Corma, I. Domínguez, A. Doménech, V. Fornés, C. J. Gómez-García, T. Ródenas, M. J. Sabater, *J. Catal.* **2009**, *265*, 238–244; b) T. Roy, R. I.

- Kureshy, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *ChemPlusChem*, **2015**, *80*, 1038–1044.
- [2] a) H. Noh, Y. Cui, A. W. Peters, D. R. Pahls, M. A. Ortuño, N. A. Vermeulen, C. J. Cramer, L. Gagliardi, J. T. Hupp, O. K. Farha, *J. Am. Chem. Soc.*, **2016**, *138*, 14720–14726; b) W. Guo, G. Wang, Q. Wang, W. Dong, M. Yang, X. Huang, J. Yu, Z. Shi, *J. Mol. Catal. A: Chem.* **2013**, *378*, 344–349.
- [3] a) M. Jafarpour, A. Rezaeifard, M. Ghahramaninezhad, F. Feizpour, *Green Chem.*, **2015**, *17*, 442–452; b) D. S. Doke, S. B. Umbarkar, M. B. Gawande, R. Zboril, A. V. Biradar, *ACS Sustainable Chem. Eng.* **2017**, *5*, 904–910; c) X. Chen, B. Gao, Y. Su, H. Huang, *Adv. Synth. Catal.* **2017**, *359*, 2535–2541; d) A. Farokhi, H. H. Monfared, *J. Catal.* **2017**, *352*, 229–238; e) F. Yang, B. Wang, S. Zhou, S. Long, X. Liu, Y. Kong, *Microporous Mesoporous Mater.* **2017**, *246*, 215–224; f) Y. Li, S. Zhao, Q. Hu, Z. Gao, Y. Liu, J. Zhang, Y. Qin, *Catal. Sci. Technol.* **2017**, *7*, 2032–2038; g) G. D. Sala, L. Giordano, A. Lattanzi, A. Proto, A. Scettri, *Tetrahedron* **2000**, *56*, 3567–3573; h) J. M. Botubol-Ares, J. R. Hanson, R. Hernández-Galán, I. G. Collado, *ACS Omega* **2017**, *2*, 3083–3090.
- [4] a) L. Salem, *Electrons in Chemical Reactions. First Principles*, Wiley-Interscience, New York, **1982**; b) K. Chen, P. Zhang, Y. Wang, H. Li, *Green Chem.* **2014**, *16*, 2344–2374.
- [5] M. Tada, R. Coquet, J. Yoshida, M. Kinoshita, Y. Iwasawa, *Angew. Chem. Int. Ed.* **2007**, *46*, 7220–7223.
- [6] a) G. Xu, Q. H. Xia, X. H. Lu, Q. Zhang, H. J. Zhan, *J. Mol. Catal. A: Chem.* **2007**, *266*, 180–187; b) X. Song, W. Zhu, K. Li, J. Wang, H. Niu, H. Gao, W. Gao, W. Zhang, J. Yu, M. Jia, *Catal. Today* **2015**, *259*, 59–65.
- [7] a) Y. Yang, Y. Zhang, S. Hao, Q. Kan, *Chem. Eng. J.* **2011**, *171*, 1356–1366; b) A. B. Sorokin, *Chem. Rev.* **2013**, *113*, 8152–8191; c) T. Cruchter, M. G. Medvedev, X. Shen, T. Mietke, K. Harms, M. Marsch, E. Meggers, *ACS Catal.* **2017**, *7*, 5151–5162.
- [8] a) S. Wertz, A. Studer, *Green Chem.* **2013**, *15*, 3116–3134; b) A. Dos Santos, L. E. Kaiim, L. Grimaud, *Org. Biomol. Chem.* **2013**, *11*, 3282–3287; c) L. Melone, C. Punta, *Beilstein J. Org. Chem.* **2013**, *9*, 1296–1310.
- [9] P. J. Dunn, *Chem. Soc. Rev.* **2012**, *41*, 1452–1461.
- [10] F. Minisci, C. Gambarotti, M. Pierini, O. Porta, C. Punta, F. Recupero, M. Lucarini, V. Mugnaini, *Tetrahedron Lett.* **2006**, *47*, 1421–1424.
- [11] N. Tada, H. Okubo, T. Miura, A. Itoh, *Synlett* **2009**, *18*, 3024–3026.
- [12] G. Xu, Q.-H. Xia, X.-H. Lu, Q. Zhang, H.-J. Zhan, *J. Mol. Catal. A: Chem.* **2007**, *266*, 180–187.
- [13] a) N. Anbazhagan, G. Imran, A. Qurashi, A. Pandurangan, S. Manimaran, *Microporous Mesoporous Mater.* **2017**, *247*, 190–197; b) A. Bento, A. Sanches, P. D. Vaz, C. D. Nunes, *Top Catal.* **2016**, *59*, 1123–1131; c) C. I. Fernandes, N. U. Silva, P. D. Vaz, T. G. Nunes, C. D. Nunes, *Appl. Catal. A-Gen.* **2010**, *384*, 84–93.
- [14] Y. Yao, X. Zhang, J. Peng, Q. Yang, *Chem. Commun.* **2015**, *51*, 3750–3753.
- [15] K. R. Lassila, F. J. Waller, S. E. Werkheiser, A. L. Wressell, *Tetrahedron Lett.* **1994**, *35*, 8077–8080.
- [16] a) X. Zhou, H. Ji, *Chem. Eng. J.* **2010**, *156*, 411–417; b) P. Zhang, Y. Wang, H. Li, M. Antonietti, *Green Chem.* **2012**, *14*, 1904–1908; c) V. Panwar, P. Kumar, S. S. Ray, S. L. Jain, *Tetrahedron Lett.* **2015**, *56*, 3948–3953.
- [17] B. B. Wentzel, P. L. Alsters, M. C. Feiters, R. J. M. Nolte, *J. Org. Chem.* **2004**, *69*, 3453–3464.
- [18] K. Kaneda, S. Haruna, T. Imanaka, M. Hamamoto, Y. Nishiyama, Y. Ishii, *Tetrahedron Lett.* **1992**, *33*, 6827–6830.
- [19] a) K. Tong, K. Wong, T. Chan, *Org. Lett.* **2003**, *5*, 3423–3425; b) X. T. Ma, X. H. Lu, C. C. Wei, Z. S. Zhao, H. J. Zhan, D. Zhou, Q. H. Xia, *Catal. Commun.* **2015**, *67*, 98–102; c) X. He, L. Chen, X. Zhou, H. Ji, *Catal. Commun.* **2016**, *83*, 78–81.
- [20] P. Karandikar, A. J. Chandwadkar, M. Agashe, N. S. Ramgir, S. Sivasanker, *Appl. Catal. A-Gen.* **2006**, *297*, 220–230.
- [21] a) Y. Qi, Y. Luan, J. Yu, X. Peng, G. Wang, *Chem. Eur. J.* **2015**, *21*, 1589–1597; b) W. Guo, C. Wang, P. Lin, X. Lu, *Appl. Energy* **2011**, *88*, 175–179; c) L. H. Gan, S. H. Goh, K. S. Ooi, *J. Am. Oil Chem. Soc.* **1992**, *69*, 347–351.
- [22] S. N. Rao, K. N. Munshi, N. N. Rao, *J. Mol. Catal. A: Chem.* **2000**, *156*, 205–211.

Submitted: February 9, 2018

Revised: April 20, 2018

Accepted: April 22, 2018