Catal Lett
DOI 10.1007/s10562-015-1581-9

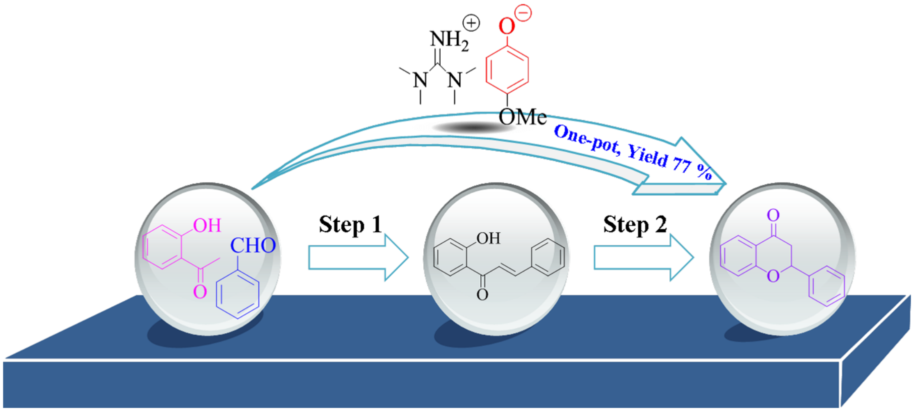
Facile One-Pot Synthesis of Flavanones Using Tetramethylguanidinum-Based Ionic Liquids as Catalysts

Yan Zhou[1] · Wei Huang[1] · Xiang-Shu Chen[1] · Zhi-Bin Song[1] · Duan-Jian Tao[1]

Received: 6 May 2015 / Accepted: 5 July 2015

Abstract Several tetramethylguanidinum-based ionic liquids (TMGILs) were prepared, characterized and used as catalysts in one-pot synthesis of flavanones. The results indicated that TMGILs composed of phenolate anion was beneficial for one-pot synthesis of flavanones, and [TMG][4-MeO–PhO] induced the good yields of flavanones owing to the electron-donating effect of methoxy substituent on phenolate anion. Furthermore, [TMG][4-MeO–PhO] was found to be used repetitively at least five times without obvious decrease in activity and quantity.

Graphical Abstract



Keywords Ionic liquid · Flavanones · One-Pot synthesis · Phenolate anion

1 Introduction

As being the secondary metabolites in plant, flavanones are the important precursors for the production of many valuable-added flavanone derivatives such as flavones, isoflavones, flavonols and dihydroflavonols [1]. Thus, over the past decade, significant efforts have been put into developing efficient synthetic strategies to prepare flavanones,

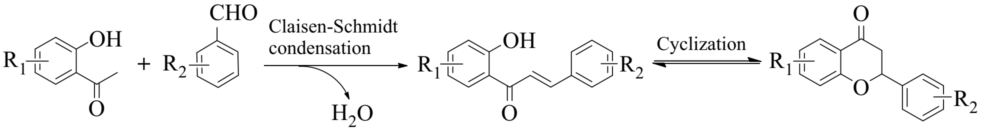
---

Electronic supplementary material The online version of this article (doi:10.1007/s10562-015-1581-9) contains supplementary material, which is available to authorized users.

✉ Xiang-Shu Chen
cxs66cn@jxnu.edu.cn

✉ Zhi-Bin Song
zbsong@jxnu.edu.cn

[1] Key Laboratory of Functional Small Organic Molecules, Ministry of Education, College of Chemistry and Chemical Engineering, Center of Analysis and Testing, Jiangxi Normal University, Nanchang 330022, People's Republic of China



Scheme 1 Two-step routes for the synthesis of flavanones

including condensation of phenylpropiolic acid with phenols [2, 3], microwave-irradiation of phloroglucinol and β-ketoesters [4], intramolecular cyclization of 2′-hydroxychalcones [5].

In terms of economic and environmental points of view, the synthesis of flavanones using 2′-hydroxychalcones as raw materials has received significant attention. As shown in Scheme 1, the two-step protocol for the preparation of flavanones involves the Claisen–Schmidt condensation of 2′-hydroxyacetophenone with aldehydes to form 2′-hydroxychalcones, and follows a cyclization to flavanones. Till now, various catalysts have been reported for this synthetic route to preparation of flavanones and their derivatives [6, 7]. For example, silicotungstic acid [8] and animal bone meal catalysts [9] were used as efficient catalyst for the synthesis of 2′-hydroxychalcones. Silica supported-double metal cyanides [10], N-methyl imidazole [11] displayed excellent catalytic performance for isomerisation of 2′-hydroxychalcones to flavanones. Despite the great yields and selectivities, there has been little mention paid to the one-pot synthesis of flavanones. A facile and efficient one-pot chemosynthesis of flavanones thus continues to be appealing.

Recently, ionic liquids (ILs) have been attracting attention in the synthesis of heterocyclic compounds due to their specific properties such as designable structure, low volatility, high thermal and chemical stability [12, 13]. As our continuous work on the synthesis and utilization of ILs in green and sustainable catalysis [14], five tetramethylguanidinum-based ionic liquids (TMGILs) were prepared, characterized, and used as catalysts for one-pot synthesis of flavanones in this work. The reaction parameters such as reaction time, solvent, temperature, catalyst dosage, and molar ratio of reactants were studied in detail to obtain the optimum conditions. In addition, the reusability of TMGILs was explored, and a plausible reaction mechanism involving the catalytic role of phenolate anion of TMGILs was then proposed.

2 Experimental

2.1 Materials

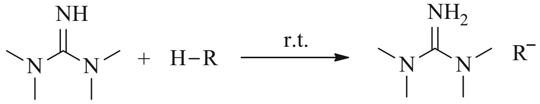
Tetrahydrofurfuryl alcohol (THFA, purity ≥99 %), 2′-hydroxyacetophenone (HAC, purity ≥99 %), 1,1,3,3,-tetramethylguanidine (TMG, purity ≥98 %), phenol (PhOH, purity ≥99.5 %), 4-fluorophenol (4-F-PhOH, purity ≥99 %), and 4-methoxyphenol (4-MeO–PhOH, purity ≥99 %) were purchased from Aladdin (Shanghai, China), and other reagents such as aromatic aldehydes, ethanol, and ethyl acetate were of analytical grade and used without any further purification.

2.2 Catalyst Preparation and Characterization

Five TMGILs were prepared by the neutralization reactions of tetramethylguanidine with acetic acid, glycine, phenol, 4-fluorophenol, and 4-methoxyphenol, respectively (Scheme 2). The preparation process was similar to the procedure described in our previous work [15]. All the yields of these TMGILs were more than 90 %, and the structures of TMGILs were then confirmed by ^{1}H, ^{13}C NMR and FT-IR spectroscopy (available as the supplementary data).

2.3 Evaluation of Catalysts

In a typical run, the one-pot reaction was carried out in a 25 mL stainless round-bottomed flask equipped with a magnetic stirrer and reflux condenser. Weighed amounts of 2′-hydroxyacetophenone, aldehyde, solvent and TMGIL catalyst were mixed and allowed to proceed for 2–9 h with the vigorous stirring and heating at the designed temperature. Qualitative analyses of products were examined by a Thermo Trace 1300 GC-ISQ. For ingredient of products analysis, the reaction samples were collected and analyzed periodically by a gas chromatography-flame ionization detector (GC-FID) (Agilent 7890B, HP-5 column, 30 m × 0.32 mm × 0.25 µm). Nitrogen was used as the carrier gas at a flow rate of 1.5 mL/min. The detailed temperature conditions were described as follows: the injector and detector temperatures were set as 250 and



R = Gly, Ac, PhO, 4-F-PhO, 4-MeO-PhO

Scheme 2 Structures of TMGILs

250 °C, respectively; the column temperature was increased stepwise to 220 °C, holding at 80 °C for 3 min, increasing to 220 °C at 30 °C min^{-1}, holding at 220 °C for 5 min. Then the conversion of 2′-hydroxyacetophenone and selectivity of flavanone were calculated according to the area of chromatograph peaks using flavone as an internal standard.

3 Results and Discussion

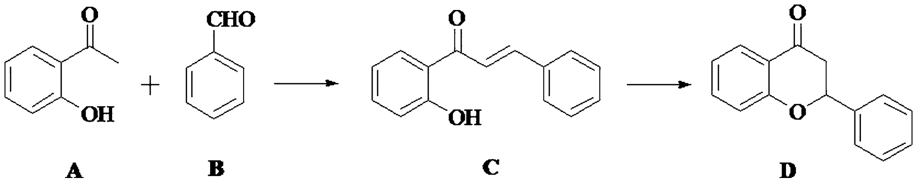
3.1 Catalyst Selection

In order to get the catalytic activity of TMGILs, the reaction of benzaldehyde and 2′-hydroxyacetophenone was selected as a model reaction, and the results are listed in Table 1. It was found that TMGILs exhibited various catalytic activities and the catalytic performances of TMGILs were closely relevance to the structures of their anions. For example, [TMG][4-MeO–PhO], [TMG][4-F–PhO], and [TMG][PhO] catalyzed this reaction to have excellent conversions of 2′-hydroxyacetophenone and considerable selectivities of flavanone, whereas [TMG][Gly] and [TMG][Ac] led to very poor conversions (Entries 1–5). This implies that TMGILs composed of phenolate anions are favorable to the one-pot synthesis of flavanone. For comparison, several conventional basic catalysts such as TMG, NaOH, K_2CO_3, and DBU were employed. It was demonstrated that these basic catalysts induced high conversions of 2′-hydroxyacetophenone but their selectivities of flavanone were relatively low (Entries 6–9). This shows that the Claisen–Schmidt condensation reaction is easily performed in the presence of strong basic catalysts [16], but the second step of the interconversion of 2′-hydroxychalcone to flavanone is hard to carry out.

Moreover, it was indicated that the substituent on phenolate anion had an obvious impact on reaction selectivity. The electron-donating methoxyl group could improve the yield of flavanone. With an electron-donating substituent on phenyl ring, the pK_b value of 4-methoxyphenol decreases (e.g. the pK_b of phenol and 4-methoxyphenol is 4.02 and 3.79), and the basicity thus is strengthened [17]. This implies that 4-methoxyphenate anion could weaken the intramolecular hydrogen bond interaction of 2′-hydroxychalcone effectively, and then 2′-hydroxychalcone was converted to flavanone with a considerable yield (see the below section of Reaction Mechanism).

In addition, we compared the catalytic performance of [TMG][4-MeO–PhO] with the results of other catalysts in the previous literatures [18–25] (Table 2). It was found that over-high temperature and too long reaction time were often taken to achieve a moderate catalytic performance. By contrast, TMGILs composed of phenolate anions showed better catalytic activities for one-pot synthesis of flavanone under mild conditions.

Table 1 Catalyst screening for one-pot synthesis of flavanone[a]



Entry	Catalyst	Conversion of A (%)	Yield (%)[b]	
			C	D
1	[TMG][Ac]	8	4	4
2	[TMG][Gly]	25	11	14
3	[TMG][PhO]	90	35	55
4	[TMG][4-F–PhO]	86	27	59
5	[TMG][4-MeO–PhO]	97	20	77
6	TMG	97	46	51
7	NaOH	94	46	48
8	K_2CO_3	96	42	54
9	DBU	91	44	47

[a] Reaction conditions: 70 °C, 8 h, 5 mmol B, molar ratio of A:B = 1:1.3, catalyst (0.3 mol/mol B), 2 mL THFA

[b] Determined by GC

Table 2 Catalytic performance of various catalysts

Catalyst	Reaction condition	Yield (%)	Reference
MgO	160 °C, 90 min, 0.1 wt%, DMSO/4-nitrobenzene	62	[18]
SBA-15-NH_2	150 °C, 8 h, 0.15 g, free-solvent	64	[19]
CHMgO	60 °C, 8 h, 4.43 mmol, free-solvent	58	[20]
Aminopropylated Silica	140 °C, 10 h, 0.15 g, free-solvent	61	[21]
L-Proline	80 °C, 18 h, 30 mol%, DMF	70	[22]
TESP-[MIm]Cl/Zn–Al	140 °C, 6 h, 35 mol%, free-solvent	68	[23]
$[LiAl_2(OH)_6](CO_3)_{0.5}\cdot nH_2O$	160 °C, 60 min, 0.1 wt%, DMSO	59	[24]
Cs-MgO	140 °C, 20 min, 5 wt%, DMF	73	[25]
[TMG][4-MeO–PhO]	70 °C, 8 h, 30 mol%, THFA	77	This work

Table 3 Effect of solvent on the synthesis of flavanone[a]

Entry	Solvent	Conversion of A (%)	Yield(%)[b]	
			C	D
1	THFA	94	27	67
2	MeOH	94	31	63
3	EtOH	87	32	55
4	THF	81	32	49
5	DMSO	80	34	46
6	DMF	82	36	46
7	Cyclohexanemethanol	85	29	56
8	Dimethylacetamide	71	27	44
9	Dichloromethane	55	19	36
10	Ethyl acetate	66	24	42
11	Ethyl lactate	33	10	23

[a] Reaction conditions: 70 °C, 6 h, 5 mmol B, molar ratio of A:B = 1:1, [TMG][4-MeO–PhO] catalyst (0.3 mol/mol B), 2 mL solvent

[b] Determined by GC

3.2 Optimization of Reaction Conditions

Firstly, the effect of solvents on the synthesis of flavanone was investigated and the results are listed in Table 3. It was indicated that alcohol solvents were better than other solvents in the conversion of 2′-hydroxyacetophenone and the selectivity of flavanone (Entries 1–3). It may be due to the better solubility of alcohols in this reaction mixture compared with other solvents. THFA was then chosen as solvent for further experiments. Reaction temperature is essential to the isomerization of 2′-hydroxychalcone to flavanone. As seen from Table 4, flavanone could be effectively synthesized at a relatively high temperature. For example, the conversion of 2′-hydroxyacetophenone and selectivity of flavanone increased obviously from 50 °C to 70 °C (Entries 1, 2). However, when the temperature increased to 100 °C and 130 °C (Entries 3, 4), the conversion of 2′-hydroxyacetophenone and selectivity of flavanone only improved with a limited extent. Therefore, an optimized reaction temperature would choose at 70 °C.

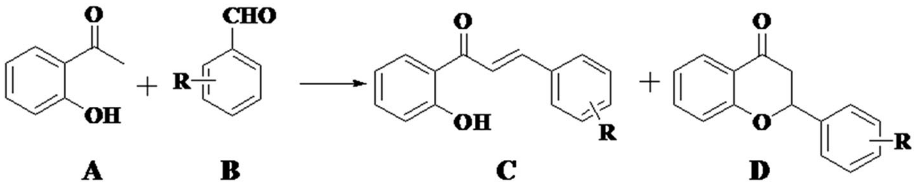
Table 4 Optimization of other parameters[a]

Entry	Temperature (°C)	Molar ratio	Catalyst loading (mol/mol B)	Time(h)	Conversion of A (%)	Yield(%)[b]	
						C	D
1	50	1:1	0.3	9	88	29	59
2	70	1:1	0.3	6	94	26	68
3	100	1:1	0.3	4	97	27	70
4	130	1:1	0.3	2	98	27	70
5	70	1:1.3	0.3	8	97	20	77
6	70	1:1.5	0.3	5	94	19	75
7	70	1:2	0.3	6	90	18	72
8	70	1:1.3	0.1	9	42	13	29
9	70	1:1.3	0.5	5	97	30	67
10	70	1:1.3	0.7	4	97	31	66

[a] Reaction conditions: [TMG][4-MeO–PhO] as catalyst, 5 mmol B, 2 mL THFA

[b] Determined by GC

Table 5 One-pot synthesis of various flavanones[a]



Entry	R	Conversion of A (%)	Time (h)	Yield (%)[c]	
				C	D
1	H	97	8	20	77
2	4-Br	99	6	22	77
3	2-Cl	99	5	21	78
4	4-Me	94	8	29	65
5[b]	4-OMe	95	1.5	31	64
6[b]	3,4-OMe	94	2.5	27	67

[a] Reaction conditions: 70 °C, 5 mmol B, molar ratio of A:B = 1:1.3, [TMG][4-MeO–PhO] catalyst (0.3 mol/mol B_1), 2 mL THFA. Reaction products were identified by GC–MS

[b] Reaction temperature 130 °C

[c] Determined by GC

In addition, the effect of molar ratio of benzaldehyde to 2′-hydroxyacetophenone on the one-pot reaction was studied (Table 4). It was showed that increasing the amount of benzaldehyde was beneficial to the yield of flavanone. Nevertheless, further increasing the amount of benzaldehyde did not substantially improve the conversion of 2′-hydroxyacetophenone (Entries 5–7). So the optimal molar ratio of 2′-hydroxyacetophenone to benzaldehyde suggests to be 1:1.3. The influence of catalyst loading was also evaluated, and the results showed that catalyst loading had an obvious effect on the conversion of 2′-hydroxyacetophenone (Entries 5, 8–10). The conversion of 2′-hydroxyacetophenone increased from 42 to 97 % with the rise of catalyst loading from 0.1 to 0.3 mol/mol. However, when the catalyst loading was further added to 0.5 and 0.7 mol/mol, the conversion of 2′-hydroxyacetophenone improved limitedly. This means that too large catalyst loading is not necessary and 0.3 mol/mol of catalyst was taken as the optimum catalyst loading.

3.3 One-Pot Reaction of Various Benzaldehydes

With the optimized reaction condition, the reactions of 2′-hydroxyacetophenone with various benzaldehydes were further examined. The results are summarized in Table 5. It was observed that most of these flavanones could be obtained with good yields, and the electronic nature of the substituents on benzaldehydes had an obvious impact on the selectivities of flavanones. The chloro- and bromo-substituents, as being electron-withdrawing groups, are favorable for this one-pot reaction (Entries 2, 3). However, the electron-donating substituents decrease the reactivities of benzaldehyde (Entries 4–6).

3.4 Reaction Mechanism

On the basis of the above-mentioned results and the previous literatures [8, 16], we proposed a plausible mechanism for the one-pot synthesis of flavanone (Fig. 1). Firstly, chalcone **1** is formed from 2′-hydroxyacetophenone and benzaldehyde through a typical Claisen–Schmidt condensation pathway. Subsequently, [4-MeO–PhO] anion could make an effective contaction with chalcone **1** to weaken its intramolecular hydrogen bond interaction. Then the activated hydroxyl group undergoes an intramolecular cyclization smoothly to give intermediate **2**. After the catalyst [TMG][4-MeO–PhO] is regenerated, intermediate **3** can be formed. Finally, flavanone is produced from intermediate **3** via a keto-enol tautomerism pathway.

3.5 Recycling of Catalyst

To test the activity and stability of TMGILs, the catalyst [TMG][4-MeO–PhO] was recycled and reused for five times. As shown in Fig. 2, it was indicated that no obvious drop in either flavanone yield or selectivity was observed during these five successive recycles, showing that the catalyst [TMG][4-MeO–PhO] is stable enough for this one-pot reaction.

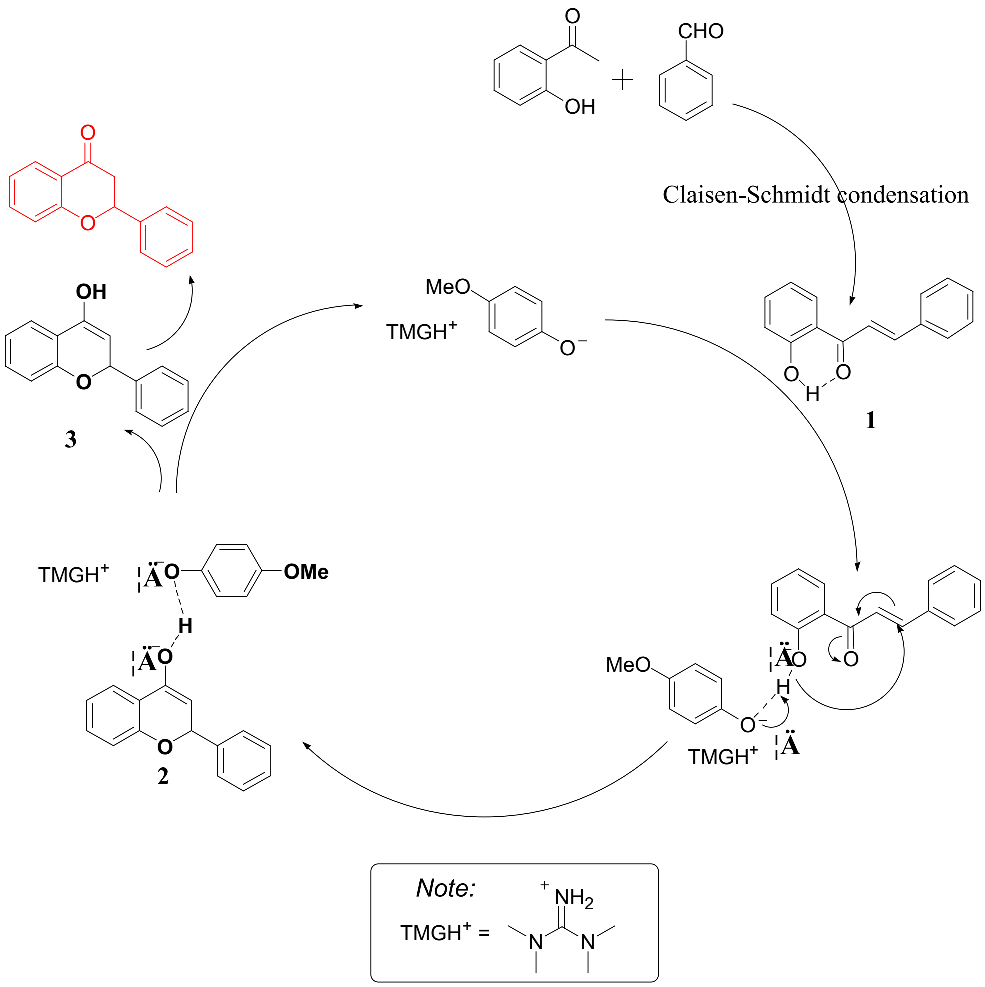


Fig. 1 Plausible reaction mechanism for [TMG][4-MeO–PhO] catalyzed one-pot synthesis of flavanone

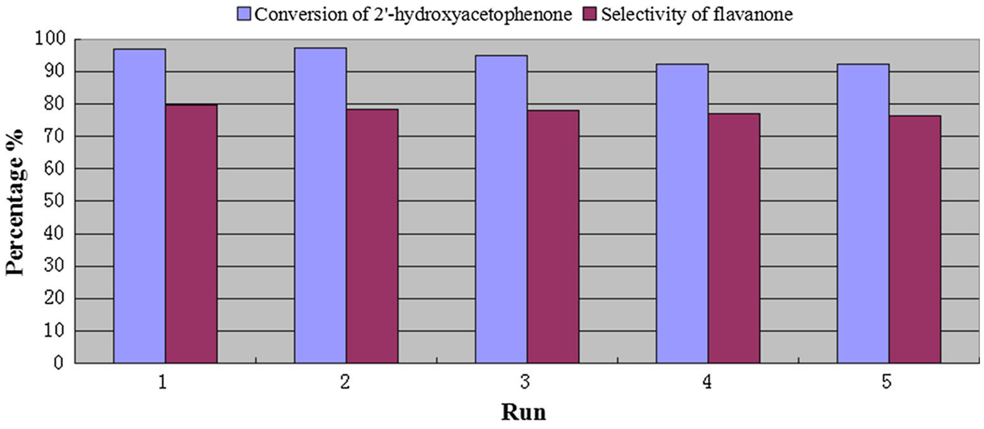


Fig. 2 The recycle and reuse of [TMG][4-MeO–PhO]

4 Conclusions

In this work, [TMG][4-MeO–PhO] was found to be an efficient and reusable catalyst for the synthesis of flavanones through one-pot reaction of various benzaldehydes with 2′-hydroxyacetophenone under mild conditions. And [TMG][4-MeO–PhO] could be readily recovered and reused up to five times without significant losses in catalytic activity.

Acknowledgments We thank the financial support by the National Natural Science Foundations of China (No. 21206063), the Department of Science and Technology of Jiangxi Province (Nos. 20151BAB213016, 20123BBE50081, 20132BDH80003), and the Sponsored Program for Cultivating Youths of Outstanding Ability in Jiangxi Normal University.

References

1. Spencer JPE (2009) The impact of flavonoids on memory: physiological and molecular considerations. Chem Soc Rev 38:1152
2. Lebedev MV, Nensjdenko VG, Balenkov ES (1998) Synthesis 89
3. Bianco A, Cavarischia C, Farina A, Guiso M, Marra C (2003) Tetrahedron Lett 44:9107
4. Seijas JA, Tato MPV, Martlnez MM, Parga JR (2002) Green Chem 4:390
5. Tanaka K, Sugino T (2001) Green Chem 3:133
6. Ahmed N, Ali H, van Lier JE (2005) Tetrahedron Letts. 46:253
7. Ahmed N, van Lier JE (2007) Tetrahedron Letts. 48:13
8. Rajput JK, Kaur G (2012) Tetrahedron Lett 53:646
9. Riadi Y, Abrouki Y, Mamouni R, Haddad MEI, Routier S, Guillaumet G, Lazar S (2012) Chem Cent J 6:60
10. Ahmed N, Konduru NK, Praveen, Kumar A, Kamaluddin (2013) J Mol Catal A 373:135
11. Wang P, Yang J-B, Cai J, Sun C-L, Li L-S (2013) J Serb Chem Soc 78:917
12. Maton C, De Vos N, Stevens CV (2013) Chem Soc Rev 42:5963
13. Hallett JP, Welton T (2011) Chem Rev 111:3508
14. Ouyang F, Zhou Y, Li ZM, Hu N, Tao DJ (2014) Korean J Chem Eng 31:1377
15. Tao DJ, Hu WJ, Chen FF, Chen XS, Zhang XL, Zhou Y (2014) J Chem Eng Data 59:4031
16. Muller BM, Mai J, Yocum RA, Adler MJ (2014) Org Biomol Chem 12:5108
17. Liptak MD, Gross KC, Seybold PG, Feldgus S, Shields GC (2002) J Am Chem Soc 124:6421
18. Drexler MT, Amiridis MD (2003) J Catal 214:136
19. Wang XG, Lin KSK, Chan JCC, Cheng S (2004) Chem Commun 23:2762
20. Abello S, Medina F, Rodriguez X, Cesteros Y, Salagre P, Sueiras JE, Tichit D, Coq B (2004) Chem Commun 9:1096
21. Wang XG, Tseng YH, Chan JCC, Cheng SF (2005) J Catal 233:266
22. Chandrasekhar S, Vijeender K, Reddy KV (2005) Tetrahedron Lett 46:6991
23. Kunde LB, Gade SM, Kalyani VS, Gupte SP (1881) Catal Commun 2009:10
24. French D, Schifano P, Cortés-Concepción J, Hargrove-Leak S (2010) Catal Commun 12:92
25. Pal P, Pahari SK, Sinhamahapatra A, Giri AK, Bajaj HC, Panda AB (2013) Rsc Adv 3:2802