Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Nmp-based ionic liquids: Recyclable catalysts for both hetero-Michael addition and Knoevenagel condensation in water

Pengkun Yang, Yawei Liu, Ling Chai, Zhenzhen Lai, Xiaomin Fang, Baoying Liu, Wenkai Zhang, Minghua Lu, Yuanqing Xu & Hao Xu

To cite this article: Pengkun Yang, Yawei Liu, Ling Chai, Zhenzhen Lai, Xiaomin Fang, Baoying Liu, Wenkai Zhang, Minghua Lu, Yuanqing Xu & Hao Xu (2018) Nmp-based ionic liquids: Recyclable catalysts for both hetero-Michael addition and Knoevenagel condensation in water, Synthetic Communications, 48:9, 1060-1067, DOI: 10.1080/00397911.2018.1434544

To link to this article: https://doi.org/10.1080/00397911.2018.1434544

SYNTHETIC COMMUNICATIONS®
2018, VOL. 48, NO. 9, 1060–1067
https://doi.org/10.1080/00397911.2018.1434544

Taylor & Francis
Taylor & Francis Group

Nmp-based ionic liquids: Recyclable catalysts for both hetero-Michael addition and Knoevenagel condensation in water

Pengkun Yang, Yawei Liu, Ling Chai, Zhenzhen Lai, Xiaomin Fang, Baoying Liu, Wenkai Zhang, Minghua Lu, Yuanqing Xu, and Hao Xu

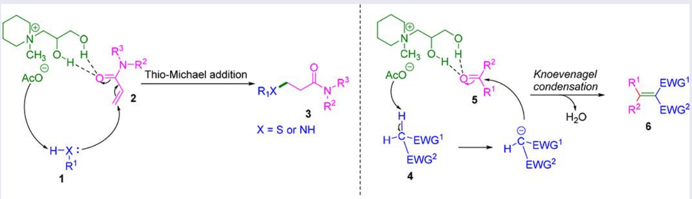
College of Chemistry and Chemical Engineering, Henan University, Kaifeng, P. R. China

ABSTRACT
A series of novel *N*-methyl piperidine (Nmp)-based ionic liquids with 1,2-propanediol group are synthesized and used as catalysts for both hetero-Michael addition of α,β-unsaturated amides and Knoevenagel condensation at room temperature in water; and all the examined substrates could be transformed into corresponding products in good to excellent yields. Meanwhile IL-catalyzed hetero-Michael addition of α,β-unsaturated amides in water has not been reported in the previous literatures. Additionally, the catalyst is recyclable for the two reactions. This finding provides a green catalyst for both hetero-Michael addition of α,β-unsaturated amides and Knoevenagel condensation in water.

ARTICLE HISTORY
Received 8 September 2017

KEYWORDS
α,β-Unsaturated amide; hetero-Michael addition; in water; ionic liquid catalyzed; Knoevenagel condensation

GRAPHICAL ABSTRACT



All the substrates work well for the transformation in water. And the IL-catalyst is recyclable and applicable for the two reactions.

Introduction

It is well known that ionic liquids (ILs) are a green alternative to volatile organic solvents, due to their unique features such as good dissolving capacity, negligible vapor pressure, and ease of recyclability. In the past few years, ILs have also displayed promising applications in the field of catalysis[1] because cations and anions of ILs can be engineered easily through rational design and screen of various component ions, and the cations and anions in well-designed ILs have positive synergetic effect in catalyzing organic reactions.[2] Hence,

CONTACT Hao Xu xuhao@henu.edu.cn College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, P. R. China.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article can be accessed on the publisher's website.

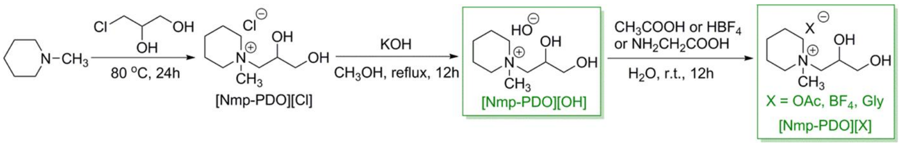
it is highly desirable to develop readily available and well-designed ILs as catalysts for diverse reactions.

Water is a green solvent because it is safe, cheap, and nontoxic. One of the challenges for organic reactions is to conduct the reaction in water. Hetero-Michael addition is an important reaction for the formation of carbon–heteroatom bond and plays a key role in the synthesis of many bioactive molecules.[3] But hetero-Michael addition performed in water is rare, especially when using relatively inactive α,β-unsaturated amides as Michael acceptors; despite the Michael adducts of various α,β-unsaturated amides have wide bioactivities.[4] Furthermore, for the thio-Michael addition of α,β-unsaturated amides, only the unsubstituted acrylamide could be transformed into the relevant thio-Michael adduct in water by previous methods[5] because of less steric hindrance and better solubility than substituted acrylamides; meanwhile IL-catalyzed hetero-Michael addition of α,β-unsaturated amides in water has not been reported in the previous literatures. In our previous work, several morpholine-based ionic liquids with 1,2-propanediol group were synthesized and applied in the Knoevenagel condensation successfully.[6] In continuation of our endeavors to develop simple and efficient methods for organic synthesis,[7] herein four basic ionic liquids based on *N*-methyl piperidine (Nmp) and 3-chloro-1,2-propanediol were successfully synthesized and developed as catalysts in hetero-Michael addition, including thio-Michael addition and aza-Michael addition. Meanwhile the novel Nmp-based ILs were also applied in the Knoevenagel condensation, and all the examined substrates provided good yields in water.

Results and discussion

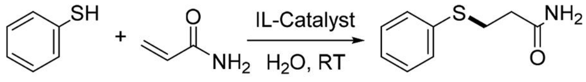
Four novel Nmp-based ionic liquids were synthesized (Scheme 1); the preparation of [Nmp-PDO][OH], [Nmp-PDO][OAc], [Nmp-PDO][BF_4], and [Nmp-PDO][Gly] were described detailly in electronic supplementary material.

Initially, Michael addition of thiophenol (**1c**) with acrylamide (**2a**) leading to 3-(phenylthio)propanamide (**3c**) was chosen as the model to optimize conditions including catalysts and solvents. As indicated in Table 1, five Nmp-based IL catalysts were screened using water as the solvent at room temperature (entries 1–5), and [Nmp-PDO][OAc] provided the highest yields (entry 3). Notably, the Michael addition could not proceed in the absence of IL catalysts (entry 6). When the reaction was performed under solvent-free conditions, a good yield of product **3c** could be obtained as well (entry 7). The effect of catalyst dosage on the model reaction was also investigated; product **3c** was still generated in moderate to good yields when the amount of catalyst was decreased (entries 8–10). However, more reaction time was needed. Therefore, the optimized IL-catalyzed conditions were as follows: [Nmp-PDO][OAc] (10 mol%) as the catalyst and water as the solvent at room temperature (Table 1).



Scheme 1. Synthesis of ionic liquids of [Nmp-PDO][X].

Table 1. Michael addition of benzenethiol (**1c**) with acrylamide (**2a**) catalyzed by Nmp-based ionic liquids: Optimization of conditions.[a]



1c **2a** **3c**

Entry	Catalysts	Solvent	Time (h)	Yield[b] (%)
1	[Nmp-PDO][Cl]	H_2O	6	57
2	[Nmp-PDO][OH]	H_2O	6	88
3	[Nmp-PDO][OAc]	H_2O	6	90
4	[Nmp-PDO][BF_4]	H_2O	6	64
5	[Nmp-PDO][Gly]	H_2O	6	86
6	Catalyst free	H_2O	24	Trace
7	[Nmp-PDO][OAc]	Neat	6	89
8[c]	[Nmp-PDO][OAc]	H_2O	24	85
9[d]	[Nmp-PDO][OAc]	H_2O	48	76
10[e]	[Nmp-PDO][OAc]	H_2O	60	52

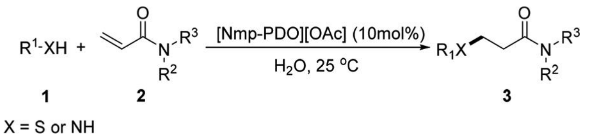
[a] Reaction conditions: benzenethiol (0.5 mmol, 47 mg), acrylamide (0.5 mmol, 36 mg), catalyst (10 mol%), solvent (1 mL), room temperature.
[b] Isolated yield.
[c] Catalyst 5 mol%.
[d] Catalyst 1 mol%.
[e] Catalyst 0.5 mol%.

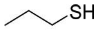
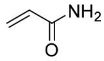
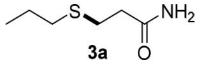
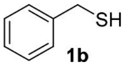
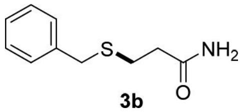
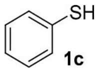
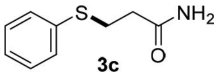
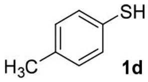
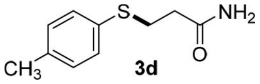
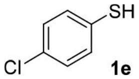
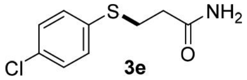
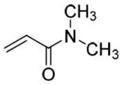
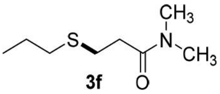
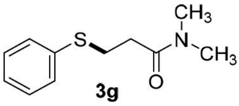
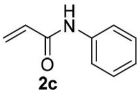
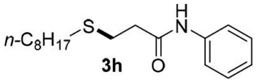
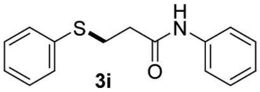
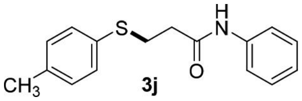
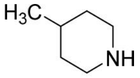
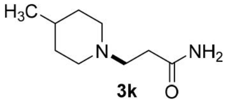
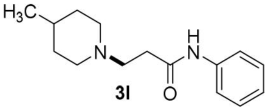
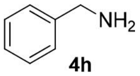
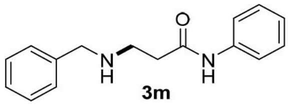
As shown in Table 2, the scope of IL-catalyzed hetero-Michael addition of α,β-unsaturated amides was investigated under the optimized conditions above. All the examined substrates showed good reactivity in water. For the thio-Michael addition, their reactivity was affected by the steric hindrance; the substrates with bigger group provided lower yields (entries 1, 2, 6, and 8). Meanwhile thiophenols could also react with α,β-unsaturated amides easily although the steric hindrance of phenyl groups was relatively larger (Table 2, entries 3–5, 7, 9, and 10); it might be because the proton (H^+) of thiophenols could be removed more easily than thiols under the catalysis of basic Nmp-based ILs. Furthermore, the aza-Michael addition of α,β-unsaturated amides could proceed smoothly as well under the optimized condition (Table 2, entries 11–13).

Encouraged by the above results, the Nmp-based IL catalysts were also attempted to catalyze the Knoevenagel condensation in water. First, Knoevenagel condensation of malononitrile (**4a**) with 2-methylbenzaldehyde (**5b**) was chosen as the model reaction to optimize conditions including catalysts and solvents (Table S1 in the supporting information). Under the optimized conditions ([Nmp-PDO][OAC] (10 mol%) as the catalyst, water as the solvent at room temperature), aryl/heteroaryl/α,β-unsaturated aldehydes as well as aliphatic ketone were completely tolerated in the reaction (Table 3). Compared with aldehydes, aliphatic ketone needed more time to react with activated methylene compounds for its higher steric hindrance (Table 3, entry 12). Moreover, for the different activated methylene compounds, Knoevenagel condensation of cyanoacetates needs more time than malononitrile, because the electron-withdrawing ability of the cyano group is stronger than ester group (Table 3, entries 13–17).

The model reactions in Tables 1 and S1 (please see Table S1 in the supporting info.) were also chosen to examine the catalyst's recyclability. The Nmp-based IL catalyst showed good recyclability for both hetero-Michael addition and Knoevenagel condensation (please see Tables S2 and S3 in the supporting info.).

Table 2. The hetero-Michael addition of α,β-unsaturated amides catalyzed by [Nmp-PDO][OAc].[a]

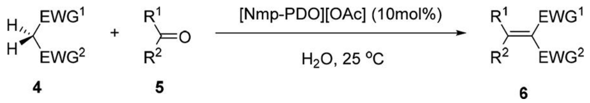


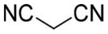
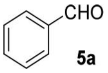
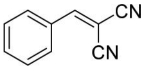
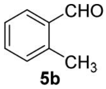
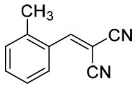
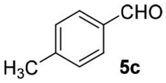
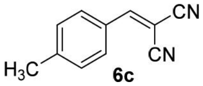
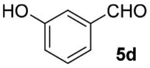
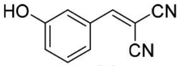
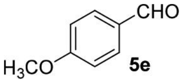
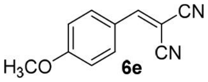
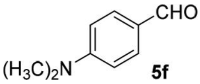
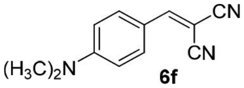
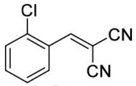
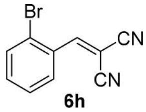
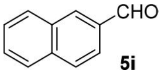
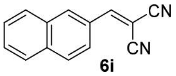
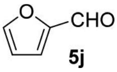
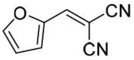
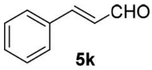
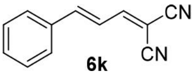
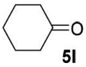
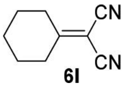
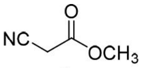
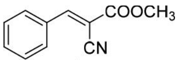
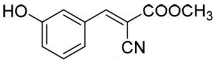
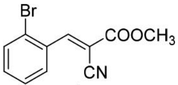
Entry	1	2	3	t/h	Yield[b]/%
1	 1a	 2a	 3a	6	94
2	 1b	2a	 3b	6	83
3	 1c	2a	 3c	6	90
4	 1d	2a	 3d	6	80
5	 1e	2a	 3e	6	82
6	1a	 2b	 3f	6	85
7	1c	2b	 3g	6	90
8	n-C_8H_{17}–SH 1f	 2c	 3h	10	73
9	1c	2c	 3i	10	81
10	1d	2c	 3j	10	87
11	 1g	2a	 3k	8	98
12	1g	2c	 3l	10	92
13	 4h	2c	 3m	8	82

[a] Reaction conditions: nucleophile **1** (0.5 mmol), α,β-unsaturated amides **2** (0.5 mmol), catalyst [Nmp-PDO][OAc] (10 mol%), water (1 mL), room temperature.

[b] Isolated yield.

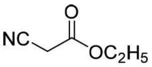
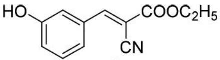
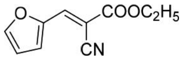
Table 3. Knoevenagel condensations catalyzed by [Nmp-PDO][OAc].[a]



Entry	4	5	6	*t*/min	Yield[b]/%
1	 **4a**	 **5a**	 **6a**	10	95
2	4a	 **5b**	 **6b**	10	94
3	4a	 **5c**	 **6c**	10	93
4	4a	 **5d**	 **6d**	10	91
5	4a	 **5e**	 **6e**	10	98
6	4a	 **5f**	 **6f**	10	91
7	4a	 **5g**	 **6g**	10	89
8	4a	 **5h**	 **6h**	10	88
9	4a	 **5i**	 **6i**	15	95
10	4a	 **5j**	 **6j**	10	93
11	4a	 **5k**	 **6k**	15	92
12	4a	 **5l**	 **6l**	1200	90
13	 **4b**	5a	 **6m**	1200	96
14	4b	5d	 **6n**	1200	90
15	4b	5h	 **6o**	1200	88

(*Continued*)

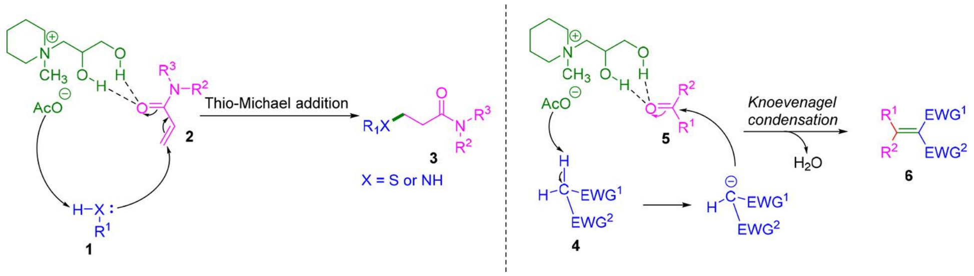
Table 3. Continued.

Entry	4	5	6	*t*/min	Yield[b]/%
16	 **4c**	**5d**	 **6p**	1200	92
17	**4c**	**5j**	 **6q**	1200	91

[a] Reaction conditions: activated methylene compound **4** (0.5 mmol), carbonyl compound **5** (0.5 mmol), catalyst [Nmp-PDO][OAc] (10 mol%), water (1 mL), room temperature.

[b] Isolated yield.

IL-catalyzed mechanisms for both hetero-Michael addition and Knoevenagel condensation are proposed in Scheme 2. First, the hydrogen bonding interactions between the hydroxyl groups of [Nmp-PDO][OAc] and the carbonyl group of **2** or **5** can be formed, which making **2** or **5** more vulnerable. Then nucleophilic attack of **1** on **2** leads to the hetero-Michael adduct **3**, or nucleophilic attack of **4** on **5** leads to the Knoevenagel condensation product **6** (Scheme 2).



Scheme 2. Possible mechanisms for both hetero-Michael addition and Knoevenagel condensations catalyzed by [Nmp-PDO][OAc].

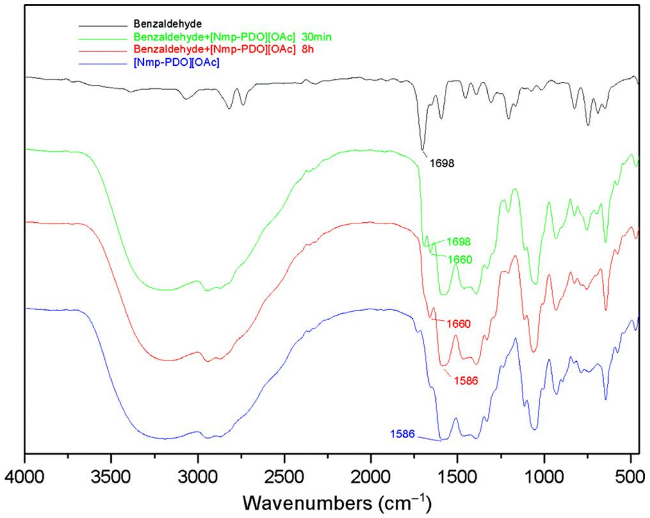


Figure 1. FTIR comparison of benzaldehyde, [Nmp-PDO][OAc], and benzaldehyde-[Nmp-PDO][OAc] mixture.

Controlled FTIR experiments were performed to verify the proposed mechanism, the FTIR spectrums of benzaldehyde, [Nmp-PDO][OAc], and benzaldehyde-[Nmp-PDO][OAc] mixture were compared, and the results are shown in Figure 1. The absorption peak of carbonyl group in benzaldehyde was at 1698 cm^{-1}, while it was redshifted to 1660 cm^{-1} in the mixture (Fig. 1). Furthermore, the ^{13}C NMR spectrums of benzaldehyde and benzaldehyde-[Nmp-PDO][OAc] mixture were also compared (Figures S3, S4 in Supplementary data); the chemical shift of carbonyl group in benzaldehyde was 193.23, while it was 193.44 in mixture. These results above hinted the existence of hydrogen bonding interactions between the carbonyl group of aldehyde and hydroxyl groups in [Nmp-PDO][OAc].

Additionally, thermal gravimetric analysis (TGA) of [Nmp-PDO][OAc] and [Nmp-PDO][Gly] was also studied at the range of 25–650 °C, with a temperature ramp rate of 10 °C/min under nitrogen atmosphere (Figures S1,S2. see supporting info.). As TG diagram indicates, [Nmp-PDO][OAc] showed a stable structure up to 210 °C (initial thermal decomposition temperature) and [Nmp-PDO][Gly] up to 200 °C.

Conclusion

Readily available and eco-friendly Nmp-based ILs are developed as the efficient and recyclable catalysts for both hetero-Michael addition of α,β-unsaturated amides and Knoevenagel condensation in water; and all the examined substrates can be transformed into corresponding products in good to excellent yields. Meanwhile the hetero-Michael addition performed in water is rare, especially when using relatively inactive α,β-unsaturated amides as Michael acceptors; and IL-catalyzed hetero-Michael addition of α,β-unsaturated amides in water has not been reported in the previous literatures. Moreover, several *N*-substituted acrylamides are successfully used as the Michael acceptors in the IL-catalyzed thio-Michael addition; only the unsubstituted acrylamide could be transformed into the relevant thio-Michael adduct in water by previous methods. Additionally, the catalyst is recyclable for the two reactions. All the results thus represent a green catalyst for both hetero-Michael addition of α,β-unsaturated amides and Knoevenagel condensation in water.

Experimental section

General procedure for Michael condensation

Sulfur or nitrogen nucleophile **1** (0.5 mmol), α,β-unsaturated amides **2** (0.5 mmol), [Nmp-PDO][OAc] (10 mol %), and water (1 mL) were added into a 25-mL Schlenk tube and stirred at room temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate (3 × 5 mL), the organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated, and purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford target product **3**.

3-(Phenylthio)propanamide (3c)

Eluent: petroleum ether/ethyl acetate (6:1). Yield 81 mg (90%). White solid, mp 116–118 °C. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.37 (d, $J = 7.3$ Hz, 2H), 7.33–7.27 (m,2H), 7.21 (t, $J = 7.3$ Hz, 1H), 5.57 (s, 2H), 3.21 (t, $J = 7.3$ Hz, 2H), 2.52 (t, $J = 7.3$ Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 173.2, 135.3, 129.8, 129.1, 126.5, 35.3, 29.2. ESI-MS $[M + H]^+$ m/z 182.18; $[M + Na]^+$ 204.15.

General procedure for Knoevenagel condensation

A mixture of activated methylene compound **4** (0.5 mmol), carbonyl compound **5** (0.5 mmol), IL catalyst (10 mol%), and water (1 mL) was stirred at room temperature in a 25-mL round-bottomed flask. Upon completion of the reaction (monitored by TLC), the reaction mixture always solidified in the round-bottomed flask, then the solidified mixture was filtered and washed with cold water (5 mL) to remove IL catalyst, and evaporated under reduced pressure to obtain the target products **6**. The product of **6l** was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (8:1) as the eluent and got pure product after the solvent was removed under reduced pressure.

2-Benzylidenemalononitrile (6a)

Yield 73 mg (95%). White solid, mp 84–85 °C. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.94–7.88 (d, 2H), 7.79 (s, 1H), 7.67–7.61 (t, 1H), 7.59–7.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 160.0, 134.7, 131.0, 130.8, 129.7, 113.7, 112.6, 82.9. APCI-MS $[M - H]^-$ m/z 154.03.

Funding

This work was supported by National Natural Science Foundation of China (Grant Nos. 21502042, 51403051, 21477033), Scientific Research Key Project Fund of Henan Provincial Education Department (Grant Nos. 15A150041, 16A150003), Scientific Research Fund of Henan University (No. 2013YBZR008).

ORCID

Hao Xu http://orcid.org/0000-0002-6069-3246

References

[1] (a) Mahato, S.; Santra, S.; Chatterjee, R.; Zyryanov, G. V.; Hajra, A.; Majee, A. *Green Chem.* **2017**, *19*, 3282–3295; (b) Mou, F.; Sun, Y.-D.; Jin, W.-W.; Zhang, Y.-H.; Wang, B.; Liu, Z.-Q.; Guo, L.; Huang, J.-B.; Liu, C.-J. *RSC Adv.* **2017**, *7*, 23041–23045; (c) Gao, X.; Yu, B.; Yang, Z.-Z.; Zhao, Y.-F.; Zhang, H.-Y.; Hao, L.-D.; Han, B.-X.; Liu, Z.-M. *ACS Catal.* **2015**, *5*, 6648–6652.

[2] (a) Wang, M.-Y.; Song, Q.-W.; Ma, R.; Xie, J.-N.; He, L.-N. *Green Chem.* **2016**, *18*, 282–287; (b) Saptal, V. B.; Bhanage, B. M. *Chem. Cat. Chem.* **2016**, *8*, 244–250.

[3] (a) Yin, Z.-W.; Zhang, J.-Z.; Wu, J.; Liu, C.; Sioson, K.; Devany, M.; Hu, C.-H.; Zheng, S.-P. *Org. Lett.* **2013**, *15*, 3534–3537; (b) Thomas, J.; Jana, S.; Sonawane, M.; Fiey, B.; Balzarini, J.; Liekens, S.; Dehaen, W. *Org. Biomol. Chem.* **2017**, *15*, 3892–3900.

[4] (a) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605–3607; (b) Huang, H.; Kang, J.-Y. *Org. Lett.* **2016**, *18*, 4372–4375.

[5] (a) Payra, S.; Saha, A.; Banerjee, S. *RSC Adv.* **2016**, *6*, 95951–95956; (b) Chaudhuri, M. K.; Hussain, S. *J. Mol. Catal. A: Chem.* **2007**, *269*, 214–217; (c) Hussain, S.; Bharadwaj, S. K.; Chaudhuri, M. K.; Kalita, H. *Eur. J. Org. Chem.* **2007**, *2007*, 374–378; (d) Krishnaveni, N. S.; Surendra, K.; Rao, K. R. *Chem. Commun.* **2005**, *5*, 669–671.

[6] Xu, H.; Pan, L.-Y.; Fang, X.-M.; Liu, B.-Y.; Zhang, W.-K.; Lu, M.-H.; Xu, Y.-Q.; Ding, T.; Chang, H.-B. *Tetrahedron Lett.* **2017**, *58*, 2360.

[7] (a) Xu, H.; Ma, S.; Xu, Y.-Q.; Bian, L.-X.; Ding, T.; Fang, X.-X.; Zhang, W.-K.; Ren, Y.-R. *J. Org. Chem.* **2015**, *80*, 1789–1794; (b) Li, H.-Y.; Jie, J.-Y.; Wu, S.-X.; Yang, X.-B.; Xu, H. *Org. Chem. Front.* **2017**, *4*, 250; (c) Su, H.-M.; Wang, L.-Y.; Rao, H.-H.; Xu, H. *Org. Lett.* **2017**, *19*, 2226–2229.