RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 12360

Bifunctional phase-transfer catalysts for synthesis of 2-oxazolidinones from isocyanates and epoxides†

Dong-Xiao Cui,‡[ab] Yue-Dan Li,‡[a] Ping Huang,[a] Zhuang Tian,[a] Yan-Yan Jia*[b] and Ping-An Wang *[a]

Received 22nd January 2020
Accepted 19th March 2020

DOI: 10.1039/d0ra00693a

rsc.li/rsc-advances

A series of bifunctional phase-transfer catalysts (PTCs) were synthesized to catalyze the [3 + 2] coupling reaction of isocyanates and epoxides to afford 2-oxazolidinones in good to high yields (up to 92% yield) using PhCl as a solvent at 100 °C within 12 h. These bifunctional PTCs were easily prepared from commercially available tertiary-primary diamines and isocyanates (or isothiocyanates, mono-squaramides, respectively) in two simple steps with good modularity and demonstrated high efficiency (2.5 mol% catalyst-loading). The synergistic interaction of the quaternary ammonium salt center and hydrogen-bond donor group in the catalyst with the substrate is crucial to this atom-economic reaction.

1 Introduction

2-Oxazolidinones and derivatives are important nitrogen and oxygen containing heterocycles present in many chemicals with different biological and pharmacologic activities,[1–3] such as **Linezolid** and **Tedizolid** as antibiotics (Fig. 1) to treat infections caused by Gram-positive bacteria that are resistant to other antibiotics.[4,5] Much attention has been paid by synthetic organic chemists to find facile methods to 2-oxazolidinones. There are many synthetic routes to 2-oxazolidinones, and these methods can be divided into two types including phosgene-involved and non-phosgene involved routes. The synthesis of 2-oxazolidinones from phosgene and vicinal amino-alcohols is not recommended, even if the yield is excellent, but its toxicity is extremely high.[6,7] Non-phosgene involved routes to 2-oxazolidinones are investigated extensively in recent years.[8–10] Among them, the ring-opening of aziridines by CO_2 and "one-pot" reaction of primary amines with epoxides and CO_2 are straightforward accesses to 2-oxazolidinones.[11–15] The [3 + 2] coupling of isocyanates with epoxides is also an atom-economic process to provide 2-oxazolidinones, and the pioneering work on this coupling was established by Speranza and Peppel in 1958 through phase-transfer catalysis with a high temperature up to 200 °C.[16] After that, several metallic catalysts have been found to catalyze this [3 + 2] coupling reaction,[17–23] but still with unsatisfactory results because of harsh conditions (*e.g.*, high catalyst-loadings, high temperature, large amount of epoxides, or with a dropwise addition of isocyanates). In 2017, Toda and colleagues[24] have discovered an elegant route to 2-oxazolidinones with high yields by using tetraarylphosphonium salts (**TAPS**) as an organocatalyst. However, organocatalyzed [3 + 2] coupling of isocyanates and epoxides to 2-oxazolidinones is still a challenge. Herein, we presented a group of bifunctional phase-transfer catalysts (**Bif-PTCs**) for synthesis of 2-oxazolidinones in good yields and high efficiency (Fig. 2).

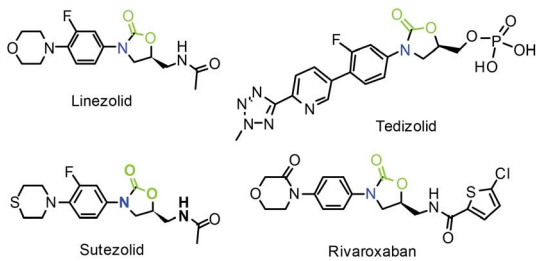


Fig. 1 Pharmaceutics containing 2-oxazolidinone motif.

2 Results and discussion

2.1. The preparation of bifunctional phase-transfer catalysts (Bif-PTCs)

The synthesis and applications of bifunctional phase-transfer catalysts are very attractive to academies and industries for their high efficiency and environmental sustainability.[25–29] These **Bif-PTCs** usually contain both one quaternary onium salt center and at least one hydrogen-bonding donor group in their

[a]*Department of Medicinal Chemistry, School of Pharmacy, The Fourth Military Medical University, Changle West Road 169, Xi'an, 710032, P. R. China. E-mail: ping_an1718@outlook.com*

[b]*Department of Pharmacy, Xijing Hospital, Fourth Military Medical University, Changle West Road 15, Xi'an 710032, P. R. China*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra00693a

‡ Co-first authors. These two authors have the same contribution to this work.

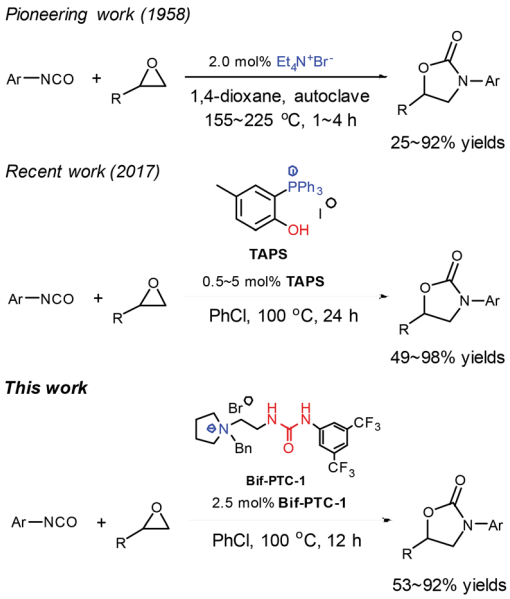


Fig. 2 Phase-transfer catalysts for synthesis of 2-oxazolidinones.

structures. The hydrogen-bonding donor groups include hydroxyl (–OH), (thio)urea and squaramide. Recently, we have reported catalytic asymmetric amination of β-nitrostyrenes by chiral **Bif-PTCs** in high yields and enantioselectivties.[30] We have also developed a group of **Bif-PTCs** for catalyzed cycloaddition of CO2 with epoxides to produce cyclic carbonates in good to excellent yields.[31] For our continuous effort on the synthesis and applications of **Bif-PTCs**, we have prepared a series of quaternary ammonium salts with one hydrogen-bonding donor for catalyzed [3 + 2] coupling of isocyanates and epoxides to 2-oxazolidinones. From commercially available tertiary-primary diamines, **Bif-PTC-1–10** were prepared in moderate to good yields through 2–4 steps. These catalysts featured by simple preparation, high modularity and good stability. There are only two simple steps including coupling reaction of tertiary-primary diamines with isocyanates and following quaternization to afford urea-containing **Bif-PTCs** (**Bif-PTC-1–7**) in good yield. In the synthetic process of thiourea-containing **Bif-PTCs** (**Bif-PTC-8** and **9**), Boc-protection and deprotection were used to avoid S-alkylation in quaternization by benzyl bromide.[32] Squaramide-containing **Bif-PTC-10** can be easily prepared from coupling of mono-ester of squaramide with 2-(pyrrolidin-1-yl)ethan-1-amine and then quaternization by benzyl bromide. The structures of these **Bif-PTCs** are listed in Fig. 3, and all **Bif-PTCs** are characterized by their NMR and HRMS.[31]

2.2. The [3 + 2] coupling of isocyanates and epoxides by Bif-PTCs

Inspired by Toda and colleagues' work, a free O–H of **TAPS** plays a role as hydrogen-bonding donor in activation of epoxides, these above prepared **Bif-PTCs** also contain free N–H in their structures, we deduced that these **Bif-PTCs** could be used as organocatalysts for synthesis of 2-oxazolidinones from the coupling of epoxides and isocyanates.

At first, we chose the coupling of phenyl glycidyl ether **1a** and *p*-chlorobenzene isocyante **2a** as a model reaction for optimization of reaction conditions, and the results are shown in Table 1. It was found that without catalyst leads to no reaction (entry 1 *vs.* 3). When **TBAB** was used as catalyst, 2-oxazolidinone **3aa** was obtained in very low yield with the recovery of the substrate epoxide **1a** (entry 2). **Bif-PTCs** with electron-donating groups at phenyl ring (such as *para*-Me or 3,5-diMe, **Bif-PTC-3**, **4**, **6** and **7**) have shown low catalytic activities to this [3 + 2] cycloaddition and produced **3aa** in low yields (entries 5, 6, 8 and 9, 38–45%). The catalysts with a urea group demonstrate better performance than catalysts with a thiourea or squaramide group in this [3 + 2] coupling reaction (entry 3 *vs.* entries 10–12). **Bif-PTC-1** is the best catalyst to provide 2-oxazolidinone **3aa** in 85% yield under standard reaction conditions. Instead of PhCl as solvent, when the coupling of **1a** and **2a** were carried out in toluene, NMP or 1,4-dioxane, the yield of **3aa** is decreased significantly (entry 3 *vs.* entries 13–15).

Increase of catalyst-loading from 2.5 mol% to 5 mol% and 10 mol%, the yield of **3aa** is promoted slightly (entry 3 *vs.* entries 16 and 17). When the reaction temperature was set at 60 °C and room temperature (r.t.), the yield of **3aa** was dropped to 45%

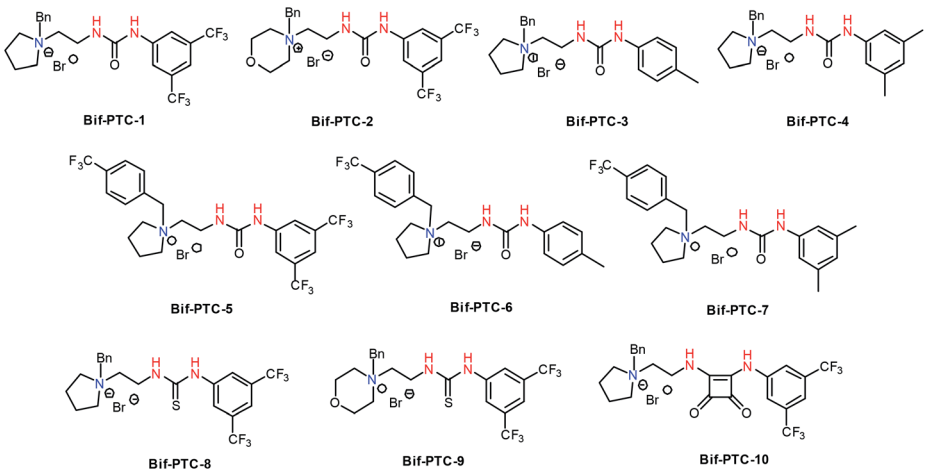
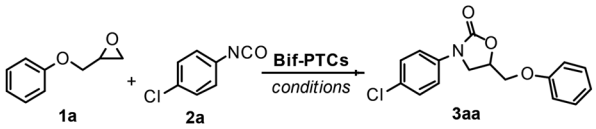


Fig. 3 The chemical structures of Bif-PTC-1–10.

Table 1 The screening of coupling reaction conditions for 2-oxazolidinone



Entry[a]	Bif-PTCs	Solvent	Temp.	Time	Yield[c] (%)
1	None	PhCl	100 °C	12 h	0
2	**TBAB**[b] (2.5 mol%)	PhCl	100 °C	12 h	12
3	**Bif-PTC-1** (2.5 mol%)	PhCl	100 °C	12 h	85
4	**Bif-PTC-2** (2.5 mol%)	PhCl	100 °C	12 h	84
5	**Bif-PTC-3** (2.5 mol%)	PhCl	100 °C	12 h	45
6	**Bif-PTC-4** (2.5 mol%)	PhCl	100 °C	12 h	40
7	**Bif-PTC-5** (2.5 mol%)	PhCl	100 °C	12 h	80
8	**Bif-PTC-6** (2.5 mol%)	PhCl	100 °C	12 h	46
9	**Bif-PTC-7** (2.5 mol%)	PhCl	100 °C	12 h	38
10	**Bif-PTC-8** (2.5 mol%)	PhCl	100 °C	12 h	24
11	**Bif-PTC-9** (2.5 mol%)	PhCl	100 °C	12 h	26
12	**Bif-PTC-10** (2.5 mol%)	PhCl	100 °C	12 h	36
13	**Bif-PTC-1** (2.5 mol%)	Toluene	100 °C	12 h	70
14	**Bif-PTC-1** (2.5 mol%)	NMP[d]	100 °C	12 h	Trace
15	**Bif-PTC-1** (2.5 mol%)	1,4-Dioxane	100 °C	12 h	32
16	**Bif-PTC-1** (5 mol%)	PhCl	100 °C	12 h	87
17	**Bif-PTC-1** (10 mol%)	PhCl	100 °C	12 h	92
18	**Bif-PTC-1** (2.5 mol%)	PhCl	r.t.	12 h	22
19	**Bif-PTC-1** (2.5 mol%)	PhCl	60 °C	12 h	45
20	**Bif-OC-1**[e] (2.5 mol%)	PhCl	100 °C	12 h	0
21	**Bif-OC-1/TBAB** (2.5 mol%)	PhCl	100 °C	12 h	75
22	**Bif-OC-1/TBAF** (2.5 mol%)	PhCl	100 °C	12 h	0
23	**Bif-OC-1/TBAI** (2.5 mol%)	PhCl	100 °C	12 h	72
24	**Bif-PTC-1** (2.5 mol%)	PhCl	100 °C	8 h	56
25	**Bif-PTC-1** (2.5 mol%)	PhCl	100 °C	4 h	33

[a] 0.2 mmol of **1a** and 0.21 mmol of **2a** in 2 mL PhCl were stirred under inert atmosphere. [b] **TBAB** = $(n\text{-Bu})_4N^+Br^-$. [c] Isolated yield based on **1a**. [d] NMP = 1-methylpyrrolidin-2-one. [e] **Bif-OC-1** is the precursor (without quaternization) of **Bif-PTC-1**.

and 22%, respectively (entry 3 *vs.* entries 18 and 19). By using **Bif-OC-1** (the precursor of **Bif-PTC-1**, without quaternization) as a catalyst, the corresponding 2-oxazolidin-one **3aa** was not obtained through the coupling process (entry 20). However, when the catalytic amount of **Bif-OC-1** and **TBAB** were used, **3aa** was obtained in 75% yield (entry 21). Switching **TBAB** to TBAF, no **3aa** is found by TLC checking (entry 22), and replacing **TBAB** with TBAI, the yield of **3aa** is 72% (entry 23). This may due to the better nucleophilicity and leaving property of Br^- than F^-. The dual role of Br^- in the catalytic cycle is a good nucleophile for ring-opening of epoxide and also a good leaving group during the cyclization. The combined use of **TBAB** and urea with electron-withdrawing group (such as CF_3) is alternative to the coupling of epoxides and isocyanates to form 2-oxazolidinones. The decrease of reaction time resulted in the decrease of yields of **3aa** (entries 24 and 25). Based on these above screening, the optimal conditions are listed as follows: 2.5 mol% of **Bif-PTC-1** as catalyst, PhCl as solvent, the reaction mixture was stirred at 100 °C for 12 h. With the optimal reaction conditions in hand, various isocyanates (**1b–f**) and epoxides (**2b–f**) were used as substrates to produce a number of 2-oxazolidinones (**3aa–fc**) in moderate to good yields. The scope of substrates was shown in Fig. 4. It was found that arylisocyanates contain one electron-donating group (*p*-Me) can afford corresponding 2-oxazolidinones in high to excellent yields (examples **3ab**, **3bb**, **3cb**, **3db** and **3eb** *vs.* the others). The glycidol-derivated epoxides provide 2-oxazolidinones in better yields than styrene oxides (**3fc** *vs.* **3ga**), it may due to the electron-withdrawing effect of aryl rings.

A plausible mechanism for **Bif-PTCs** catalyzed [3 + 2] coupling of isocyanate and epoxide is proposed in Fig. 5. At the beginning, the epoxide **1** is activated by **Bif-PTC-1** through hydrogen-bonding interaction between two N–H and O atom to form intermediate **A**, which undergoes nucleophilic attack from Br^- to give intermediate **B**, intermediate **B** attacks isocyanate **2** to yield intermediate **C**, the intramolecular ring-closing of intermediate **C** provides 2-oxazolidinone **3** with a release of **Bif-PTC-1** to take apart in the next catalytic cycle. It was found that isocyanates and epoxides are less soluble in PhCl, so the PTCs may play a role as a substrate-to-solvent transfer agent. In addition, Br^- in PTCs as a nucleophile attacks epoxide to make ring-opening process in this catalytic cycle. In order to show the application of this above [3 + 2] coupling reaction,

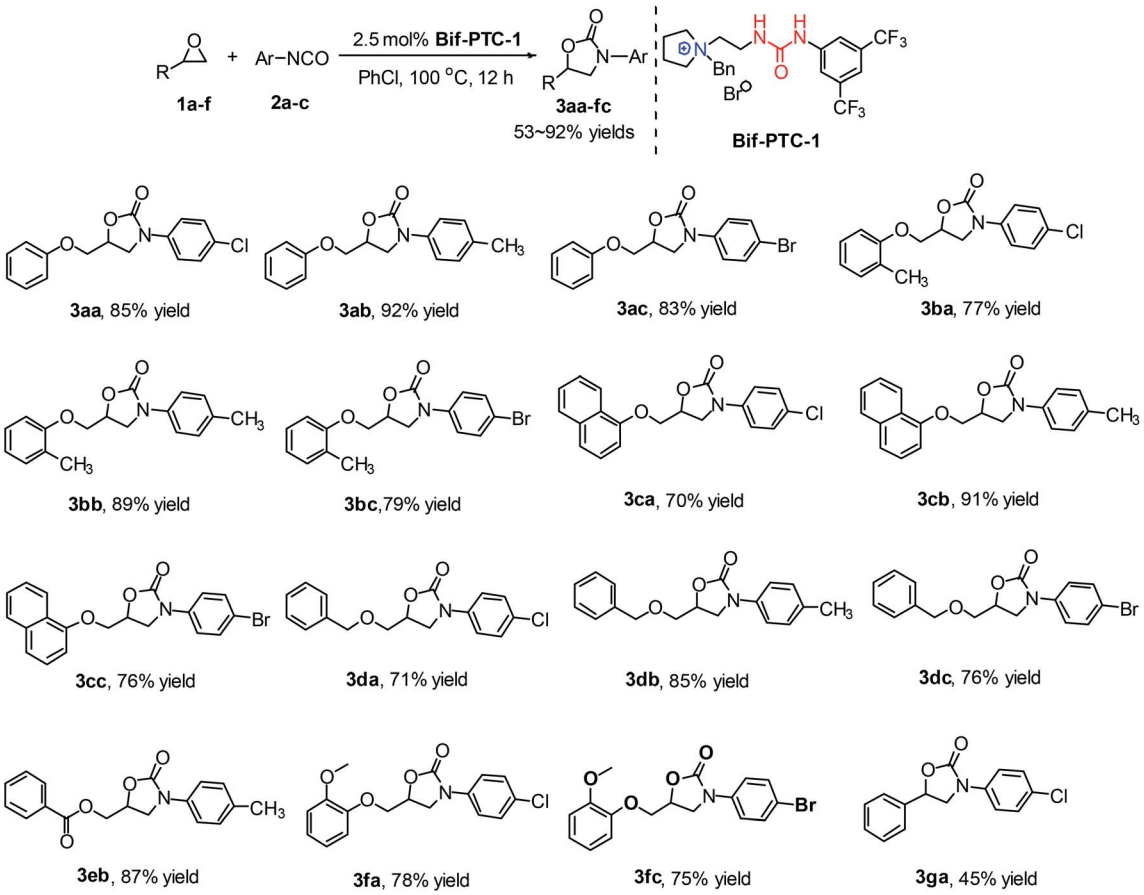


Fig. 4 The **Bif-PTC-1** catalyzed synthesis of 2-oxazolidinones.

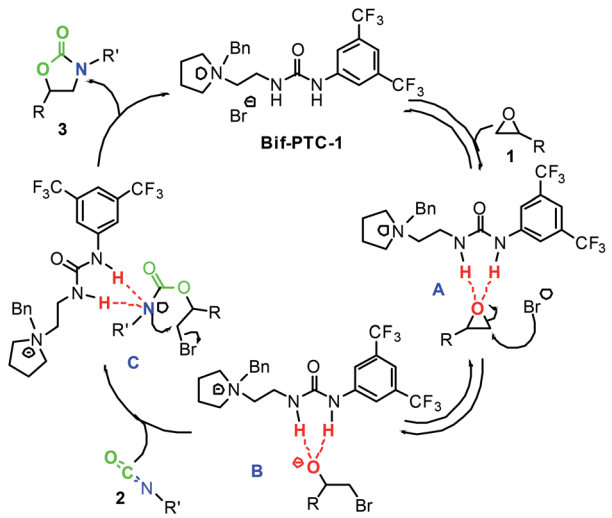
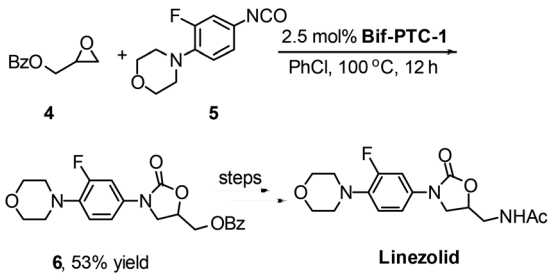


Fig. 5 The plausible catalytic cycle for **Bif-PTCs** catalyzed [3 + 2] coupling reaction.

a intermediate **6** of a potent antibiotic **Linezolid** was directly prepared in 53% yield by the coupling of epoxide **4** and isocyanate **5** under standard reaction conditions (Scheme 1).



Scheme 1 The preparation of a intermediate for **Linezolid**.

3 Experimental

3.1. General

^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, solution on a Bruker AV-400 spectrometer using TMS as an internal reference. Coupling constant (J) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High-resolution mass spectra (HRMS) were performed on a Bruker microTOF-Q II Mass Spectrometer with ES ionization (ESI). All commercially available reagents were used as received. Thin-layer chromatography on silica (with GF_{254}) was used to monitor all reactions. Products were purified by flash column

chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. The preparation and characterization data of all bifunctional phase-transfer catalysts (**Bif-PTCs**) were found in our previous report.[31]

3.2. Typical procedure for the synthesis of 2-isoxazolidinones 3

0.20 mmol of epoxide **1**, 2.7 mg of **Bif-PTC-1** (2.5 mol%), and 0.21 mmol of isocyanate **2** in 2.0 mL PhCl was stirred for 12 h at 100 °C under inert atmosphere. The solvent was evaporated under reduced pressure and the residue was purified by a flash column chromatography (petroleum ether: ethyl acetate = 2 : 1 to 1 : 3) to yield corresponding 2-oxazolidinones **3**. The characterization data of products were found in ESI.†

4 Conclusions

In conclusion, 2-oxazolidinones have been prepared through [3 + 2] coupling reactions of isocyanates and epoxides in the presence of 2.5 mol% bifunctional phase-transfer catalysts (**Bif-PTCs**) in good to excellent yields. These hydrogen-bonding donor containing **Bif-PTCs** can be easily prepared from commercially available tertiary-primary diamines and iso(thio) cyanates or mono-squaramide. Furthermore, an intermediate of **Linezolid** was also obtained in 53% yield by this simple manipulation. The synthesis of 2-oxazolidinone-containing bioactive molecules by using this strategy are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (21372259 and 81503028) for financial support.

Notes and references

1 M. Baumann, I. R. Baxendale, S. V. Ley and N. Nikzad Nikbin, *Beilstein J. Org. Chem.*, 2011, **7**, 442.
2 D. J. P. Pinto, J. M. Smallheer, D. L. Cheney, R. M. Knabb and R. R. Wexle, *J. Med. Chem.*, 2010, **53**, 6243.
3 H. Suzuki, I. Utsunomiya, K. Shudo, T. Fujimura, M. Tsuji, I. Kato, T. Aoki, A. Ino and T. Iwaki, *ACS Med. Chem. Lett.*, 2013, **4**, 1074.
4 M. F. Gordeev and Z. Y. Yuan, *J. Med. Chem.*, 2014, **57**, 4487.
5 S. J. Brickner, M. R. Barbachyn, D. K. Hutchinson and P. R. Manninen, *J. Med. Chem.*, 2008, **51**, 1981.
6 K. C. Murdock, *J. Org. Chem.*, 1968, **33**, 1367.
7 D. Crich, K. Ranganathan, S. Rumthao and M. Shirai, *J. Org. Chem.*, 2003, **68**, 2034.
8 M. Zhou, X. Zheng, Y. Wang, D. Yuan and Y. Yao, *ChemCatChem*, 2019, **11**, 5783.
9 Y. Xie, C. Lu, B. Zhao, Q. Wang and Y. Yao, *J. Org. Chem.*, 2019, **84**, 1951.
10 S. Arshadi, A. Banaei, S. Ebrahimias, A. Monfared and E. Vessally, *RSC Adv.*, 2019, **9**, 19465.
11 X. Wang, W. Gao, Z. Niu, L. Wojtas, J. A. Perman, Y. Chen, Z. Li, B. Aguila and S. Ma, *Chem. Commun.*, 2018, **54**, 1170.
12 B. Xu, P. Wang, M. Lv, D. Yuan and Y. Yao, *ChemCatChem*, 2016, **8**, 2466.
13 B. Wang, Z. Luo, E. H. M. Elageed, S. Wu, Y. Zhang, X. Wu, F. Xia, G. Zhang and G. Gao, *ChemCatChem*, 2016, **8**, 830.
14 U. R. Seo and Y. K. Chung, *Green Chem.*, 2017, **19**, 803.
15 M. Lv, P. Wang, D. Yuan and Y. Yao, *ChemCatChem*, 2017, **9**, 4451.
16 G. P. Speranza and W. J. Peppel, *J. Org. Chem.*, 1958, **23**, 1922.
17 J. E. Herweh, T. A. Foglia and D. Swern, *J. Org. Chem.*, 1968, **33**, 4029.
18 I. Shibata, A. Baba, H. Iwasaki and H. Matsuda, *J. Org. Chem.*, 1986, **51**, 2177.
19 T. Baronsky, C. Beattie, R. W. Harrington, R. Irfan, M. North, J. G. Osende and C. Young, *ACS Catal.*, 2013, **3**, 790.
20 C. Beattie and M. North, *RSC Adv.*, 2014, **4**, 31345.
21 P. Wang, J. Qin, D. Yuan, Y. Wang and Y. Yao, *ChemCatChem*, 2015, **7**, 1145.
22 J. Castro-Osma, A. Earlam, A. Lara-Sánchez, A. Otero and M. North, *ChemCatChem*, 2016, **8**, 2100.
23 X. Wu, J. Mason and M. North, *Chem.–Eur. J.*, 2017, **23**, 12937.
24 Y. Toda, S. Gomyou, S. Tanaka, Y. Komiyama, A. Kikuchi and H. Suga, *Org. Lett.*, 2017, **19**, 5786.
25 H. Wang, *Catalysts*, 2019, **9**, 244.
26 N. Lu, Y. Fang, Y. Gao, Z. Wei, J. Cao, D. Liang, Y. Lin and H. Duan, *J. Org. Chem.*, 2018, **83**, 1486.
27 Y. Liu, J. Wang, Z. Wei, J. Cao, D. Liang, Y. Lin and H. Duan, *Org. Lett.*, 2019, **21**, 5719.
28 S. Paria, Q. Kang, M. Hatanaka and K. Maruoka, *ACS Catal.*, 2019, **9**, 78.
29 R. Craig, M. Litvajov, S. A. Cronin and S. J. Connon, *Chem. Commun.*, 2018, **54**, 10108.
30 J. Z. hu, D. Cui, Y. Li, J. He, W. Chen and P. Wang, *Org. Biomol. Chem.*, 2018, **16**, 3012.
31 Y. Li, D. Cui, J. Zhu, P. Huang, Z. Tian, Y. Jia and P. Wang, *Green Chem.*, 2019, **11**, 5231.
32 J. Novacek and M. Waser, *Eur. J. Org. Chem.*, 2014, 802.

