Chinese Chemical Letters 34 (2023) 107913

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Efficient synthesis of cyclic imides by the tandem *N*-arylation-acylation and rearrangement reaction of cyanoesters with diaryliodonium salts

Zhiyuan Bao, Chao Chen*

MOE Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology, Department of Chemistry, Tsinghua University, Beijing 100084, China

ARTICLE INFO

Article history:
Received 22 August 2022
Revised 9 October 2022
Accepted 17 October 2022
Available online 20 October 2022

Keywords:
Cyclic imides
Cyanoesters
Diaryliodonium salts
N-Arylation-acylation
Rearrangement

ABSTRACT

Available online An efficient method for the synthesis of multi-substituted cyclic imides was developed with cyanoesters and diaryliodonium salts. This method proceeds through a cascade of *N*-arylation-acylation and rearrangement to give target heterocycles in good yields (up to 99%). This method has the major advantages of a broad substrate scope, excellent functional group compatibility. The strategy was also extended to the fused cyclic imides, such as malonimides, succinimides and glutarimides.

The cyclic imide scaffold as a core structural motif widely exists in a range of materials, pharmaceuticals, agrochemicals and polymer chemistry [1–5]. In particular, the amides are versatile synthetic building blocks in material science [1,6]. For example, perylenetetracarboxyl diimide **I**, a brilliant charge-transport materials [7], contains an imide moiety. In addition, various important marketed drugs or prodrugs such as cycloxygenase-2-itopride with anti-inflammatory activiy **II** [8], 4-oxo-lactams **III** [9] with molecular recognition, Leukocyte Exfoliation inhibitors **IV** [10], CFRP initiators precursor **V** (Fig. 1) [11], all have a cyclic imide backbone.

Traditionally, the cyclic imides including phthalimides and unsubstituted cyclic imides are synthesized from dicarboxylic acids or anhydrides by heating with amines (Scheme 1a) [12,13]. This method typically requires high temperatures and an excess amount of promoter (Lewis acid, base, dehydrating agent, or ionic liquids). Recent years, phthalimides have been formed *via* carbonylation of 1,2-diiodoarenes with amines [14–18] or benzamides with CO (Scheme 1b, **I**, **II**) [19–23]. Furthermore, oxidative coupling [24] and three-component coupling reactions [25,26] have expanded the range of substrates (Scheme 1b, **III**, **IV**). In these cases, noble metals, carbonyl catalysts or CO are essential. Many efforts have been devoted to the synthesis of phthalimides. However, few effective methods for the synthesis of unsubstituted cyclic imides have been reported thus far. Herein, we would like to report a general and mild method to synthesize cyclic imides with cyanoesters and diaryliodonium salts *via* a tandem arylation-acylation and rearrangement sequence (Scheme 1c). This method with high tolerance of functional groups only used simple and accessible substrates. This strategy could also be applied to the fused cyclic imides such as malonimides, succinimides and glutarimides.

During previous studies on the nitriles and diaryliodonium salts [27–39], our group developed an efficient and economical synthesis of heterocycles *via* the cascade reaction. Miao [40] and Novák [41] groups further applied this strategy to copper-catalyzed divergent cyclizations of 2-formylbenzomitrile and diaryliodonium salts and oxidative ring closure of *ortho*-cyanoanilides with hypervalent iodonium salts (Scheme 1c). Motivated by this, we envisioned that the diaryliodonium salts **1** could be attacked by cyanoesters **2** to give *N*-arylation intermolecular **6**. Then passed through the nucleophilic addition of ester to nitriles moiety and an intramolecular 1,3-(O-N) acyl transfer rearrangenent to give target heterocycles **3** (Scheme 1d).

Our investigation of this Cu-catalyzed tandem process commenced with cyanoesters **2a** and diaryliodonium **1a** as the model to survey reaction conditions. In the presence of 10% of $Cu(OTf)_2$ as catalyst in DCE, the *N*-aryl-substituted amide **3aa** was detected in 51% NMR yield at 130 °C (Table 1, entry 1). To our delight, **3aa** was obtained by changing the $Cu(OTf)_2$ catalyst to $Zn(OTf)_2$ or $FeBr_2$ in 63% and 62% yields, respectively (Table 1, entries 2 and 3). Eventually, the yield was increased to 80% with CuBr as catalyst in DCE (Table 1, entry 4). The screening of solvents showed that other sol-

---

* Corresponding author.
E-mail address: chenchao01@mails.tsinghua.edu.cn (C. Chen).

https://doi.org/10.1016/j.cclet.2022.107913

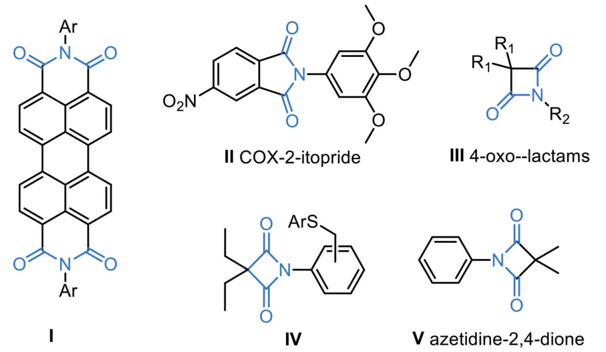
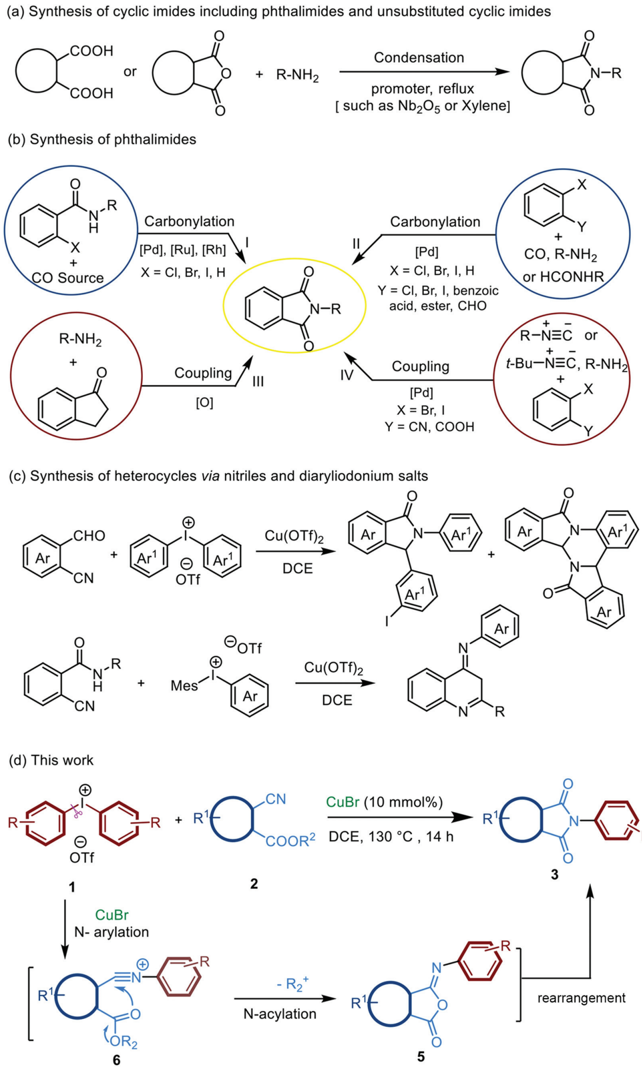


Fig. 1. The representative important molecules with *N*-aryl cyclic imide backbone.

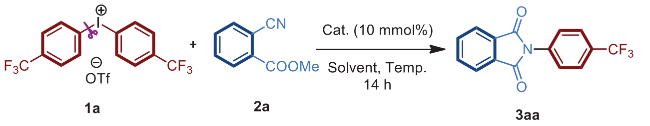


Scheme 1. The methods for the synthesis of the cyclic amides.

vents such as DCM, THF could also enabled this transformation, but not as efficient as DCE (Table 1, entries 4, 5 and 7). However, in the presence of some highly polar or protic solvents like MeCN, DMF, EtOH, no detectable **3aa** was produced (Table 1, entries 6, 8 and 9). The yield decreased at lower temperature (Table 1, entries 10-12) and no product was detected at 35 °C.

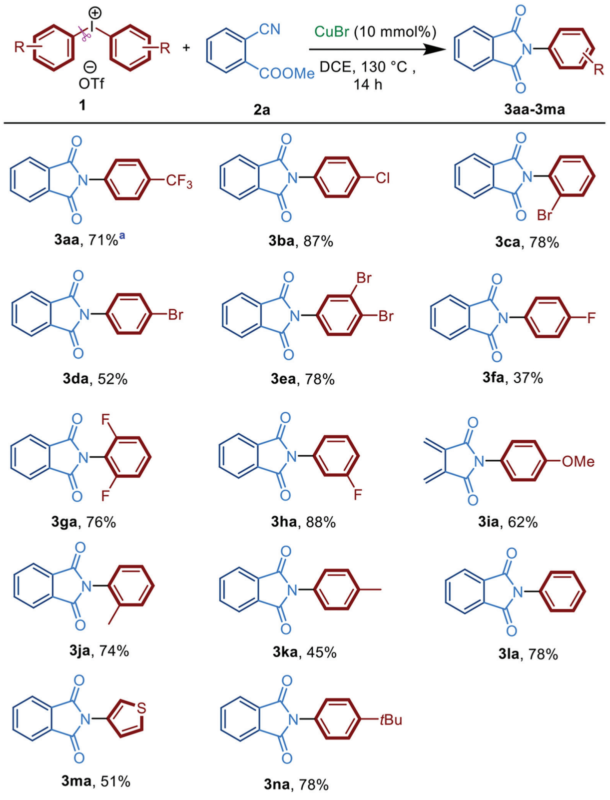
The substrate scope of the functionalized diaryliodoniums **1** was then examined (Scheme 2). Under the optimal reaction conditions, a wide range of diaryliodoniums **1** reacted with cyanoesters **2a** to form *N*-aryl-substituted amides **3** in moderate to excellent yields. Interestingly, diaryliodoniums with a range of substituents involving halogen atoms, electron-withdrawing and electron-donating groups all worked well with **2a**. Apparent substituent effect was observed. Electron-withdrawing substitutes show better effect on the reaction than electron-donating substitutes (**3aa**-**3la**). Diaryliodonium salts with electron-withdrawing groups including CF_3, Cl, Br, F gave the product **3aa**-**3ha** in 37%-88% yield. On the other hand, diaryl-iodonium salts bearing

Table 1
The optimization of synthesis of succinimide **3aa** from diaryliodoni-um **1a** and cyanoesters **2a** in presence of catalyst.[a]

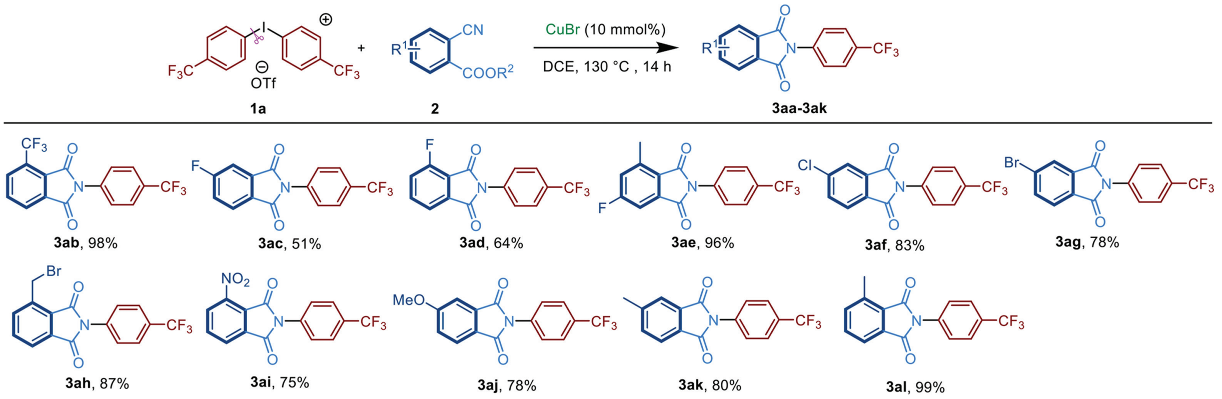


Entry	Temp. (°C)	Catalyst	Solvent	NMR yield (%)
1	130	$Cu(OTf)_2$	DCE	51
2	130	$Zn(OTf)_2$	DCE	63
3	130	$FeBr_2$	DCE	62
4	130	CuBr	DCE	80
5	130	CuBr	DCM	66
6	130	CuBr	MeCN	n.d.
7	130	CuBr	THF	51
8	130	CuBr	DMF	n.d.
9	130	CuBr	EtOH	n.d.
10	100	CuBr	DCE	63
11	80	CuBr	DCE	60
12	35	CuBr	DCE	n.d.

[a] Reaction conditions: 0.2 mmol diaryliodonium **1a**, 0.2 mmol cyanoesters **2a**, 2.86 mg CuBr, 2 mL solvent, N_2, 14 h. The yield was determined by ^1H NMR analysis using tetrachloroethane as the internal standard. n.d. = not detected.



Scheme 2. Substrate scope of diaryliodonium **1.** Reactions were performed on 0.4 mmol scale; isolated yield. [a] Cyanoesters **2a** was replaced by dodecyl 2-cyanobenzoate **(2a')**, the product **3aa** was still well obtained. For **3na**, unsymmetric hypervalent iodine of (4-*t*Bu-Ph-)I+MesOT^{f-} was used.



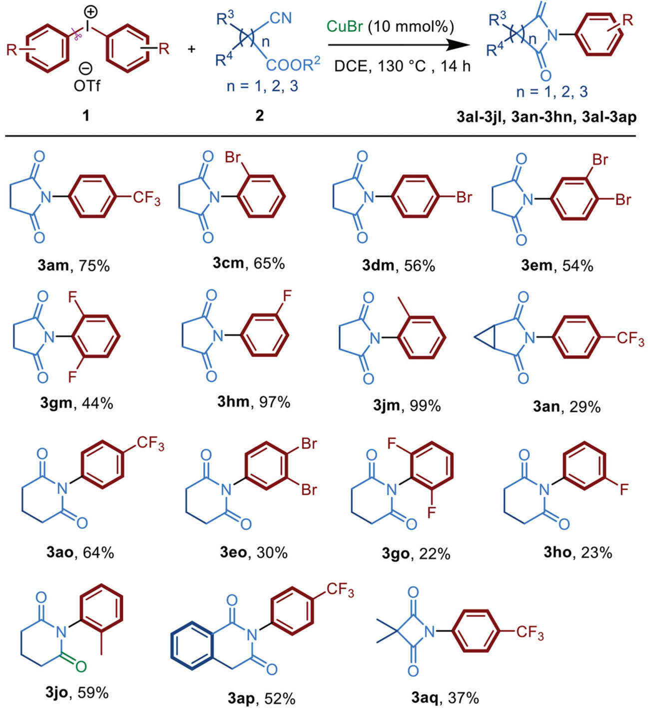
Scheme 3. Substrate scope of aryl-cyanoesters **2**. Reactions were performed on 0.4 mmol scale; isolated yield.

Me or MeO groups afford the corresponding imides **3ia**-**3ka** in yields ranging from 44% to 75%. Regardless of *m*-substituent, *o*-substituent, *p*-substituent or di-substituent, products **3** could be obtained in moderate to good yields (up to 88%). Interestingly, S-containing heterocyclic diaryliodonium salts, which often poison noble-metal centers, was also converted into product **3ma** with 51% yield. Several unsymmetric diaryliodonium salts were used to explore the preference of the transfer of aryl group in the reagents. It was found when using unsymmetric hypervalent iodine like (4-^{t}Bu-Ph-)I$^+$MesOTf$^-$ including the aryl group with large sterically hindered group, no transfer product of Mes was detected, but only the other transfer product **3na** (Scheme 2) was detected.

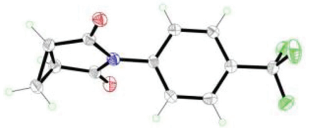
Next, the scope of the reaction with respect to aryl-cyanoesters **2** was evaluated with (4-CF$_3$Ph)$_2$I$^+$OTf$^-$ **1a** (Scheme 3). Electron-donating or electron-withdrawing substitutes show little effect on the reaction in moderate to good yield. Aryl-substituted cyanoesters **2**, including halo (CF$_3$, Cl, Br, F), NO$_2$, Me and MeO substituents were all converted into the corresponding amide **3ab**-**3al** in yields from 51% to 99%. In addition, different substituent positions, mono- or di-substituted aryl-cyanoesters **2** could react well.

Finally, a variety of alkyl-substituted cyanoesters **2** were investigated (Scheme 4). Various unsubstituted cyclic imides, such as malonimides, succinimides and glutarimides were formed with moderate to excellent yields. Fortunately, succinimides **3am**-**3jm** were proven to have good functional group tolerance. A range of substituents involving halogen atom, electron-withdraw and electron-donating groups all worked well in yields from 44% to 99%. However, cyclopropane-substituted succin-imide **3an** were synthesized in low yield. The structure of **3an** was confirmed by single crystal X-ray diffraction (Scheme 5). Apart from this, glutarimides **3ao**-**3jo** and **3ap** could be well synthesized. It should be noted that more ring-strain hindered malonimide **3aq** could also be prepared.

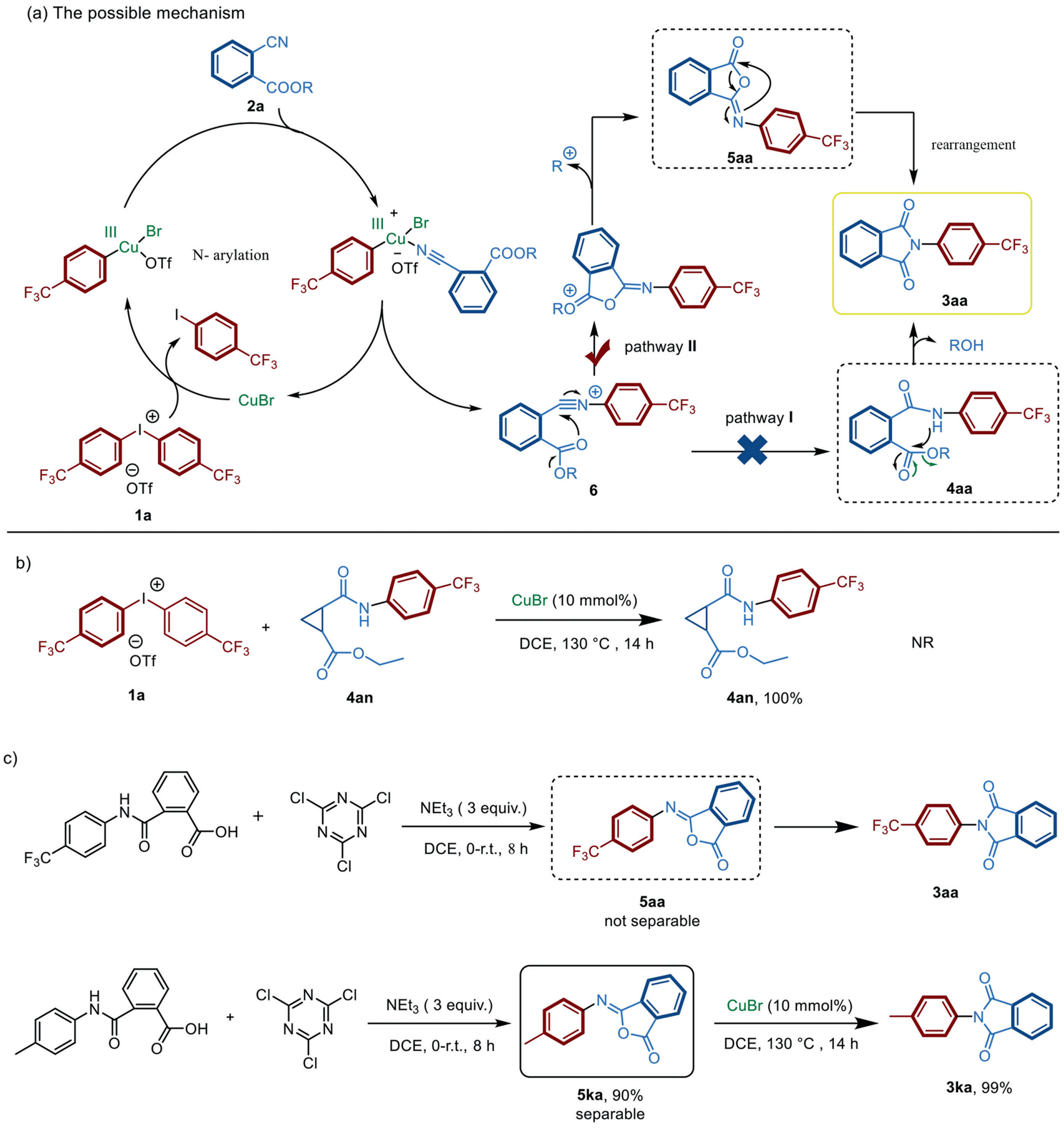
To gain insights into the mechanism of this tandem *N*-arylation-acylation and rearrangement reaction, a few experi-ments were conducted. Based on the above results and the previous studies in diaryliodonium-involved cascade reactions, we proposed two possible pathways with cyanoesters **2a** and diaryliodonium **1a** as the model. Firstly, cyanoesters reacted with diaryliodonium salts to form the arylnitrilium cation intermediate **6**. One possible pathway **I** (Scheme 6a, pathway **I**): this cation intermediate **6** was easy to transform to amide intermediate **4aa** under transition metal catalysis. In the next step, the product was afforded by an intramolecular cyclization *via* the nucleophilic attack of amide to ester moiety to. To demonstrate whether this process experi-enced an intermediate amide, the reaction of amide **4an** with diaryliodonium salt **1a** under the optimal conditions did not produce corresponding products **3an** (Scheme 6b). This result excluded the possibility of pathway **I**. The other pathway **II**: the cation intermediate **6** *via* intramolecular cyclization transformed to isophthalimide intermediate **5aa** followed by an intramolecular 1,3-(O-N) acyl transfer rearrangenent to give **3aa**. To investigate this pathway, intermediate **5aa** was tried to be separated, but it was too active to be isolated and rapidly converted into the final product **3aa**. On contrast, intermediate **5ka** could be isolated (Scheme 6c). The reaction of isophthalimide intermediate **5ka** with diaryliodonium salt **1a** was carried out and pleasantly, products **3ka** could be further afforded in 99% yield (Scheme 6c). Above results demonstrated that isophthalimide **5** might be crucial intermediate in this reaction.



Scheme 4. Substrate scope of alkyl-cyanoesters **2**. Reactions were performed on 0.4 mmol scale; isolated yield.



Scheme 5. The X-ray structure of the *N*-substituted imide **3an** (CCDC: 2191460)



Scheme 6. Mechanistic studies.

Based on the above-mentioned results, we may come to a plausible reaction mechanism for the reaction between diaryliodonium salts and cyanoesters (Scheme 6a, pathway **II**). Initially, diaryliodonium salts **1a** was affected by copper salts to generate electrophilic species, Ar-Cu^{III} [27–39], which was easily coordinated by cyanoester **2a**. Then the cation **6** with high electrophilicity was afforded *via* elimination of CuBr. Next, the isophthalimide cation intermediate was obtained through the intramolecular nucleophilic addition of the ester to the nitrile group. Immediately after the alkyl cation leaved, the isophthalimide intermediate **5aa** was formed. Ultimately, by means of intramolecular 1,3-(O-N) acyl transfer rearrangement [40–44] to afford *N*-aryl-substituted cyclic amide **3aa**.

In summary, we have developed a novel and efficient strategy for cyclic imides *via* the CuBr-catalyzed tandem *N*-arylation-acylation reaction. This method has excellent functional group compatibility with the simpler and more accessible cyanoesters and diaryliodonium salts as substrate. A wide range of cyclic imides including phthalimides and unsubstituted cyclic imides are synthesized in good yields (up to 99%). This method has also been successfully applied to the generation of fused cyclic imides including malonimides, succinimides and glutarimides.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (Nos. 21871158 and 22071129).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107913.

References

[1] Z. Cheng, X. Zhu, E.T. Kang, K.G. Neoh, Macromolecules 39 (2006) 1660–1663.
[2] J.A. Letizia, M.R. Salata, C.M. Tribout, et al., J. Am. Chem. Soc. 130 (2008) 9679–9694.
[3] U. Sharma, P. Kumar, N. Kumar, B. Singh, Mini-Rev. Med. Chem. 10 (2010) 678–704.
[4] Y.J. Wu, G. Liao, B.F. Shi, Green Synth. Catal. 3 (2022) 117–136.

[5] P. Tang, H. Wang, W. Zhang, F.E. Chen, Green Synth. Catal. 1 (2020) 26–41.
[6] D.H. Tuo, Y.F. Ao, Q.Q. Wang, D.X. Wang, CCS Chem. 4 (2022) 2806–2815.
[7] Y.J. Xu, S.W. Leng, C.M. Xue, et al., Angew. Chem. Int. Ed. 46 (2007) 3896–3899.
[8] A.A.M. Abdel-Aziz, K.E.H. El Tahir, Y.A. Asiri, Eur. J. Med. Chem. 46 (2011) 1648–1655.
[9] J. Mulchande, R.C. Guedes, W.Y. Tsang, et al., J. Med. Chem. 51 (2008) 1783–1790.
[10] J. Mulchande, R. Oliveira, M. Carrasco, et al., J. Med. Chem. 53 (2010) 241–253.
[11] S. Shau, T. Juang, W. Ting, et al., Polym. Chem. 2 (2011) 2341–2349.
[12] M.A. Ali, S.M.A.H. Siddiki, K. Kon, J. Hasegawa, K.I. Shimizu, Chem. Eur. J. 20 (2014) 14256–14260.
[13] X.R. Li, J. Zhan, Y.S. Li, Macromolecules 37 (2004) 7584–7594.
[14] M.V. Khedkar, S.R. Khan, D.N. Sawant, D.B. Bagal, B.M. Bhanage, Adv. Synth. Catal. 353 (2011) 3415–3422.
[15] P. Wójcik, A.M. Trzeciak, Appl. Catal. A 560 (2018) 73–83.
[16] C. Hong, A. Howard, Org. Lett. 12 (2010) 4126–4129.
[17] D.N. Sawant, Y.S. Wagh, K.D. Bhatte, B.M. Bhanage, Eur. J. Org. Chem. 353 (2011) 6719–6724.
[18] F.H. Ji, J.X. Li, X.W. Li, et al., J. Org. Chem. 83 (2018) 104–112.
[19] D. Ya, T.K. Hyster, T. Rovis, Chem. Commun. 47 (2011) 12074–12076.
[20] S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, J. Am. Chem. Soc. 131 (2009) 6898–6899.
[21] N. Sharmaa, G. Sekar, Adv. Synth. Catal. 358 (2016) 314–320.
[22] S.P. Chavan, B.M. Bhanage, Eur. J. Org. Chem. 80 (2015) 2405–2410.
[23] Y.Y. Wang, Y. Zhou, M. Lei, et al., Tetrahedron 75 (2019) 1180–1185.
[24] M. Wang, J.M. Lu, J.P. Ma, Z. Zhang, F. Wang, Angew. Chem. Int. Ed. 54 (2015) 14061–14065.
[25] X. Wang, W.F. Xiong, Y.B. Huang, et al., Org. Lett. 19 (2017) 5818–5821.
[26] B. Wang, D. He, B. Ren, T. Yao, Chem. Commun. 56 (2020) 900–903.
[27] Y. Wang, C. Chen, J. Peng, M. Li, Angew. Chem. Int. Ed. 52 (2013) 5323–5327.
[28] X. Su, C. Chen, Y. Wang, et al., Chem. Commun. 49 (2013) 6752–6754.
[29] Y. Wang, C. Chen, S. Zhang, et al., Org. Lett. 15 (2013) 4794–4797.
[30] X. Pang, C. Chen, X. Su, M. Li, L. Wen, Org. Lett. 16 (2014) 6228–6231.
[31] J. Peng, C. Chen, J. Chen, et al., Org. Lett. 16 (2014) 3776–3779.
[32] J. Chen, C. Chen, J. Chen, G. Wang, H. Qu, Chem. Commun. 51 (2015) 1356–1359.
[33] G. Wang, C. Chen, J. Peng, Chem. Commun. 52 (2016) 10277–10280.
[34] J. Sheng, Y. Wang, X. Su, R. He, C. Chen, Angew. Chem. Int. Ed. 56 (2017) 4824–4828.
[35] G.X. Liu, C. Wua, B.F. Chen, R. He, C. Chen, Chin. Chem. Lett. 29 (2018) 985–988.
[36] T.X. Yan, C. Chen, L.R. Wen, Chin. J. Org. Chem. 41 (2021) 3660–3667.
[37] Y.X. Wu, C. Wu, F. Wang, C. Chen, New J. Chem. 46 (2022) 945–949.
[38] Y.R. Niu, C.Y. Cao, C.X. Ge, H.M. Qu, C. Chen, Chin. Chem. Lett. 33 (2022) 1541–1544.
[39] C.Y. Cao, Y.R. Niu, Y.C. Jiang, H.M. Qu, C. Chen, Chin. J. Org. Chem. 42 (2022) 2098–2105.
[40] L. Liu, J. Qiang, S.H. Bai, et al., Adv. Synth. Catal. 359 (2017) 1283–1289.
[41] K. Aradi, Z. Novák, Adv. Synth. Catal. 357 (2015) 371–376.
[42] A. Massa, A. Roscigno, P. DeCapraris, R. Filosa, A. DiMola, Adv. Synth. Catal. 352 (2010) 3348–3354.
[43] V. More, A. DiMola, M. Perillo, et al., Synthesis 18 (2011) 3027–3031.
[44] P. Antico, V. Capaccio, A. DiMola, A. Massa, L. Palombia, Adv. Synth. Catal. 354 (2012) 1717–1724.