Tetrahedron Letters 66 (2021) 152835

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Direct synthesis of quinazolinones *via* the carbon-supported acid-catalyzed cascade reaction of isatoic anhydrides with amides and aldehydes

Xiangyu Zhang, Chujun Luo, Xiaoyong Chen, Weilin Ma, Bin Li *, Zirui Lin, Xiuwen Chen, Yibiao Li, Feng Xie *

School of Chemical & Environmental Engineering, Wuyi University, Jiangmen 529020, Guangdong Province, PR China

ARTICLE INFO

Article history:
Received 8 December 2020
Revised 3 January 2021
Accepted 7 January 2021
Available online 1 February 2021

Keywords:
Reusable acid
Cascade coupling
Quinazolinones
Hydrosilylation
Dihydroquinazolines

ABSTRACT

A novel catalytic system is reported for the construction of quinazolinones *via* the carbon-supported acid-catalyzed cascade coupling of isatoic anhydrides with amides and aldehydes. Subsequent selective hydrosilylation of the quinazolinones using a hydrogen-transfer strategy was also explored to provide dihydroquinazolines with structural diversity. The developed methodology proceeds with a broad substrate scope, excellent functional group tolerance, and utilizes a reusable catalyst and air as a green oxidant.

Introduction

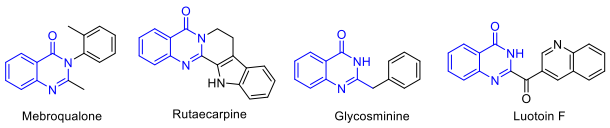
Quinazolinones are an important class of nitrogen-containing heterocycles, which are widely found in numerous natural products and synthetic drugs (Scheme 1) [1]. This class of compounds exhibits wide-ranging biological and pharmaceutical activities, such as antihypertensive, antibacterial, antitumor, and antidiabetic properties [2]. Due to their applications in medicinal chemistry, the design and synthesis of quinazolinone derivatives has received significant attention [3]. As shown in Scheme 2, conventional approaches to access this important motif are as follows: (a) condensation of *o*-aminobenzamides with aldehydes [4a], alcohols [4b], and phenylacetic acid [4c]; (b) dehydrogenative annulation of anthranilonitriles with aldehydes or their equivalents [5]; (c) Cu-catalyzed intramolecular S_NAr reaction of 2-halobenzamides with nitriles [6]; (d) palladium-catalyzed carbonylative cyclization of anthranilamides with aryl bromides using CO as a carbon source [7]; (e) aerobic annulation of amines with formaldehyde employing an imine-protection strategy [8]; and (f) palladium-catalyzed oxidative coupling of anthranilamides with isocyanides and arylboronic acids [9]. Despite impressive achievements, these approaches often suffer from limitations, including the use of harsh acids and less ecofriendly oxidants, the need for multiple prefunctionalization steps, and difficult to recycle catalysts. Therefore, from a sustainable and green chemistry perspective, the direct synthesis of quinazolinones from readily available feedstocks using recyclable catalysts, remains a challenging goal.

Typical features of supported catalysts include high stability as well as easy separation and recycling, affording them an important position in green catalysis [10]. In general, inert inorganic materials, such as active carbon, SiO_2, Al_2O_3, and molecular sieves, have been utilized as supports for heterogeneous catalysts [11]. Common features of these carriers are high specific surface areas, active functional groups, and tunable pores, which favor the diffusion and transmission of substrates [12]. In recent years, the use of formamides as an ammonia synthon or amines to construct quinazolinones has received considerable interest [13]. Moreover, compared with amines, formamides have the merits of being inexpensive and easy to handle [14].

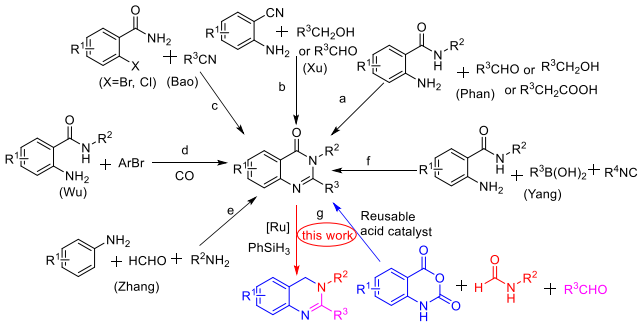
As part of our continued research interest in the construction of *N*-heterocycles using highly efficient nanocatalysts [15], we have recently reported the oxidative functionalization of cyclic amines to give quinazolinones using nanocobalt [16]. Furthermore, the Cai group has disclosed the ring-opening of isatoic anhydride and tandem oxidative isocyanide insertion to obtain quinazolinones [17]. Inspired by our previous work and this *in-situ* amidation formation strategy, herein we report the straightforward preparation of quinazolinones *via* the reusable carbon-supported acid-catalyzed direct amidation and cascade annulation of isatoic

* Corresponding authors.
E-mail addresses: andonlee@163.com (B. Li), xiefeng0401@126.com (F. Xie).

https://doi.org/10.1016/j.tetlet.2021.152835
0040-4039/



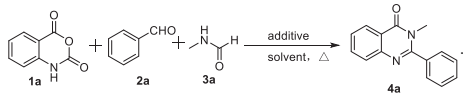
Scheme 1. Selected quinazolinone containing alkaloids and drugs.



Scheme 2. Representative methods for the synthesis of quinazolinones.

anhydride with amides and aldehydes. Additionally, we explored the selective Ru-catalyzed hydrosilylation of quinazolinones without C=N bond reduction using an inexpensive silane as the hydrogen donor. Despite significant achievements in the Ru-catalyzed hydrosilylation of primary amides [18], the selective hydrosilylation of quinazolinones to prepare dihydroquinazolines using cost-effective silanes remains to be explored.

Table 1
Optimization of the reaction conditions.[a]



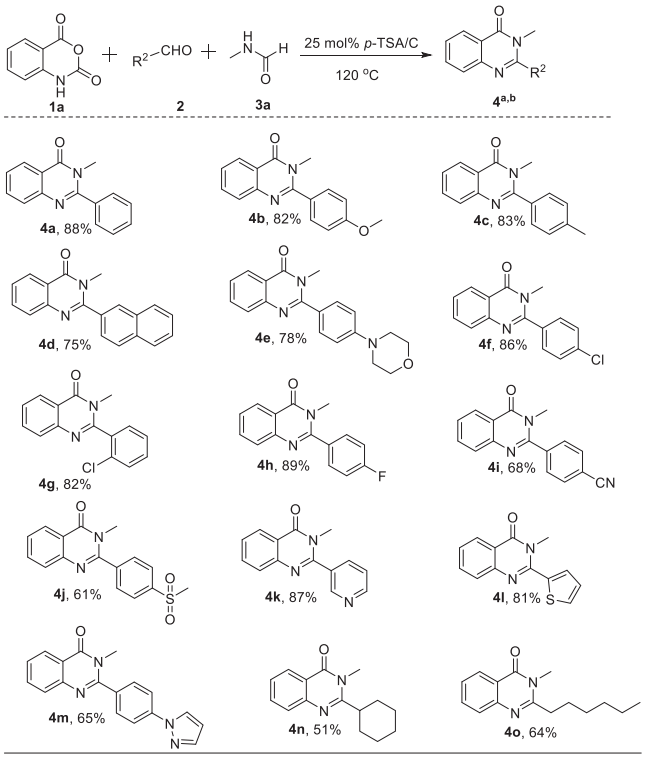
Entry	Additive	Yield **4a** (%)[b]
1	–	18
2	CF_3COOH	56
3	$Yb(OTf)_3$	43
4	$Ce(OTf)_3$	48
5	$Er(OTf)_3$	52
6	Benzoic acid	50
7	*p*-TSA	60
8	*p*-TSA/Al_2O_3 (12 wt%)	68
9	*p*-TSA/diatomite (12 wt%)	70
10	*p*-TSA/polyaniline (12 wt%)	69
11	*p*-TSA/C (12 wt%)	71
12	*p*-TSA/C	[62, 38, 26, 41, 81][c]
13	*p*-TSA/C	[76, 85][d]
14	*p*-TSA/C	[74, 86][e]
15	*p*-TSA/C	90[f]
16	*p*-TSA/C	89[g]

[a] Unless otherwise stated, all reactions were performed with 1a (0.25 mmol), 2a (0.3 mmol), 3a (2.5 mmol), additive (20 mol%), *p*-xylene (1 mL), 120 °C, 12 h.
[b] GC yield.
[c] Reactions were conducted in toluene, 1,4-dioxane, *t*-AmOH, DMF, and *N*-methylformamide, respectively.
[d] Reactions were conducted using 0.25 mmol and 0.375 mmol of 2a, respectively, *N*-methylformamide (1 mL).
[e] Reactions were conducted at 110 and 130 °C, respectively, using 2a (0.375 mmol).
[f] *N*-Methylformamide (1 mL), 2a (0.375 mmol), *p*-TSA/C (25 mol%, 12 wt%, 89 mg).
[g] *N*-Methylformamide (1 mL), 2a (0.375 mmol), *p*-TSA/C (30 mol%, 12 wt%, 107 mg).

Results and discussion

Initially, we selected the model reaction of isatoic anhydride (**1a**) with benzaldehyde (**2a**) and *N*-methylformamide (**3a**) to screen different reaction parameters. Gratifyingly, the reaction proceeded without any additive, affording **4a** in 18% yield (Table 1, Entry1). Notably, adding CF_3CO_2H (TFA) significantly improved the yield to 56% (Entry 2). *p*-TSA was the most effective additive among the various homogeneous protonic or Lewis acids examined (Entries 3–7). Because *p*-TSA was readily soluble in the reaction mixture and difficult to separate and reuse, a series of reusable porous materials were used as supports. Active-carbon-supported *p*-TSA was the best choice among the heterogeneous acid catalysts examined (Entries 8–11). Furthermore, using *N*-methylformamide as both the substrate and solvent was found to increase the yield (Entry 12). Increasing the amount of **2a** also resulted in an increased yield (Entry 13). Temperature screening (Entry 14) showed that 120 °C was sufficient for the reaction. Finally, increasing the amount of *p*-TSA/C slightly improved the yield (Entries 15 and 16). Therefore, the optimal conditions were determined as those described in Entry 15.

With the optimum conditions in hand, we next examined the substrate scope and functional group tolerance of the protocol. First, the reactions of **1a** with various aldehydes were examined (for structures, see Scheme S1 in the ESI). As shown in Scheme 3, the desired products were obtained in moderate to excellent yields (**4a–o**). Various functional groups (e.g. —OMe, —Me, naphthyl, —CN, halogens, —SO_2Me) on the aryl ring of aldehyde **2** were well tolerated, with the electronic properties of these substituents only slightly affecting the yields. In particular, electron-deficient groups (**4f–h**) afforded higher yields compared with electron-donating groups (**4b–e**). This can be attributed to the electron-withdrawing substituents enhancing the electrophilicity of the carbonyl group, which favors the coupling process. An *ortho*-substituted aromatic

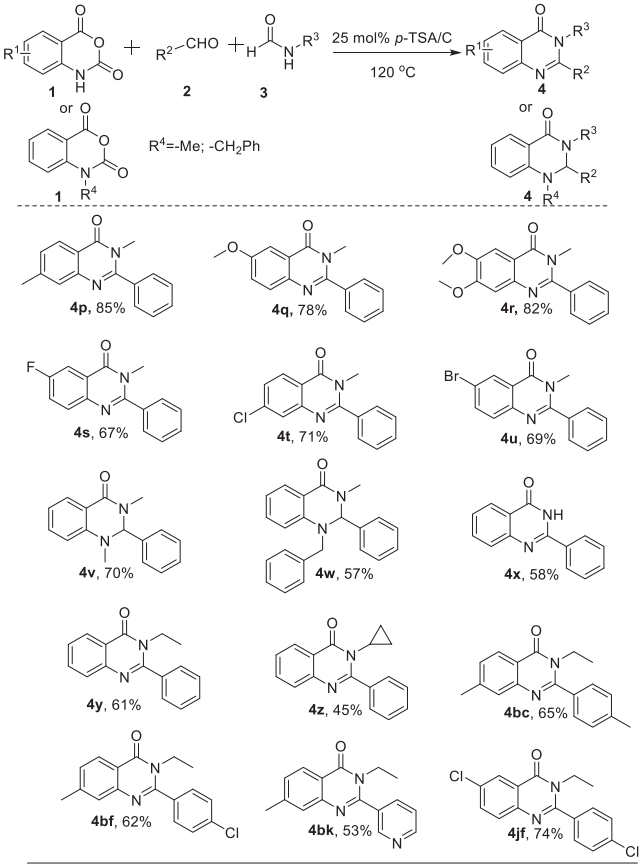


Scheme 3. Variation of the aldehydes. [a] Reagents and conditions: **1a** (0.25 mmol), **2** (0.375 mmol), **3a** (1 mL), *p*-TSA/C (25 mol%, 89 mg), 120 °C, 12 h. [b] Isolated yield.

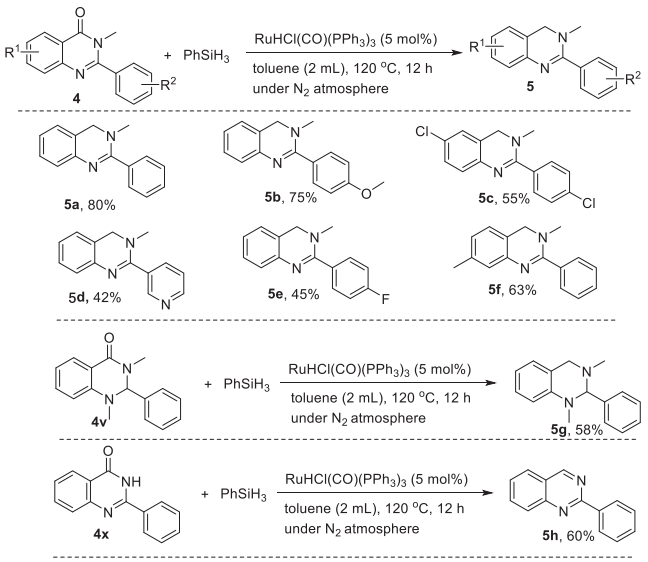
aldehyde gave the desired product (**4g**) in a lower yield than the *para*-substituted derivative (**4f**), which could be attributed to steric hindrance. Gratifyingly, a series of heteroaryl aldehydes were effectively coupled with **1a** to afford the corresponding products (**4k–m**). Notably, challenging aliphatic aldehydes were also amenable to this transformation, affording 2,3-alkyl-substituted quinazolinones in moderate yields (**4n–o**).

To further explore the substrate scope, various isatoic anhydrides were then reacted with different types of amides and aldehydes (for structures, see Scheme S1 in the ESI). Gratifyingly, all substrates afforded the desired products in moderate to excellent yields (**4p–z**, **4bc–jf**, Scheme 4). Isatoic anhydrides containing electron-donating substituents (**4p–r**) gave higher yields than those with electron-poor substituents (**4s–u**). This was attributed to the electron-rich groups enhancing the nucleophilicity of intermediate aminobenzamide **1–1**, which arises from the amidation of isatoic anhydrides by amides, favoring addition to the aldehydes. Furthermore, *N*-substituted isatoic anhydrides were also tolerated in this transformation, affording dearomatized 2,3-dihydroquinazolinones in moderate yields (**4v-w**). Interestingly, several challenging amides (**3b–d**) were effective coupling partners, affording the corresponding products in moderate yields (**4x–z**).

Next, we were interested in exploring the synthetic utility of quinazolinones to construct 3,4-dihydroquinazoline derivatives, which exhibit diverse bioactivities and act as potential pharmacophores for *T*-type calcium channel blockers and inhibitors of trypanothione reductase [19]. All substrates underwent selective hydrosilylation to afford the desired products in good yields without reduction of the C=N bond using commercially available RuHCl



Scheme 4. Variation of the coupling partners. Reagents and conditions: [a] **1** (0.25 mmol), **2** (0.375 mmol), **3** (1 mL), *p*-TSA/C (25 mol%, 89 mg), 120 °C,12 h. [b] Isolated yield.



Scheme 5. Synthetic utility of the quinazolinones.

(CO)$(PPh_3)_3$ as the catalyst and phenylsilane as the hydrogen donor (Scheme 5, 5a–f). Furthermore, dihydroquinazolinone **4v** was also tolerated in this reaction, affording 1,2,3,4-tetrahydroquinazoline (**5g**) in moderate yield. Notably, 2-phenylquinazolinone (**4x**) underwent aromatization to give 2-phenyl pyrimidine (**5h**).

To assess the stability and reusability of *p*-TSA/C, the model reaction of isatoic anhydride (**1a**) with benzaldehyde (**2a**) and *N*-methylformamide (**3a**) was performed in five successive runs. As shown in Fig. 1, the reaction maintained high catalytic activity, albeit with a slight decline in yield as the number of cycles increased, demonstrating the high durability of this catalyst. The loss of catalytic activity was attributed to the following reasons: (i) coke formation from the supported acid resulting in pore blockage; and (ii) reduction in active *p*-TSA due to mechanical abrasion-induced leaking during the reaction process.

To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 6). First, the model reaction was interrupted after 2 h to analyze the intermediates. In addition to the desired product **4a** (54% yield), incomplete dehydrogenation product dihydroquinazolinone **4a-1** and intermediate aminobenzamide **1a-1** were observed in 22% and 13% yield, respectively (Eq. 1). The model reaction using *p*-xylene was conducted to elim-

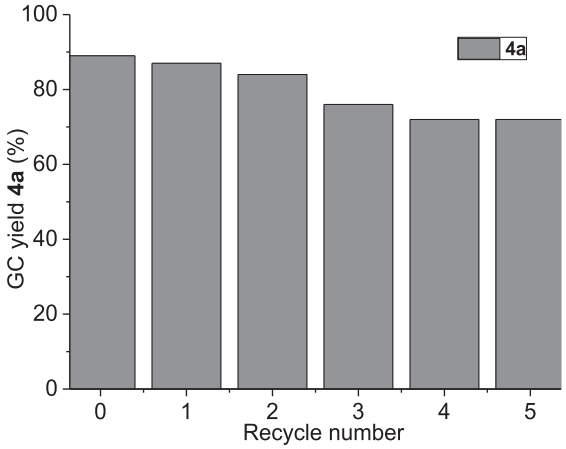
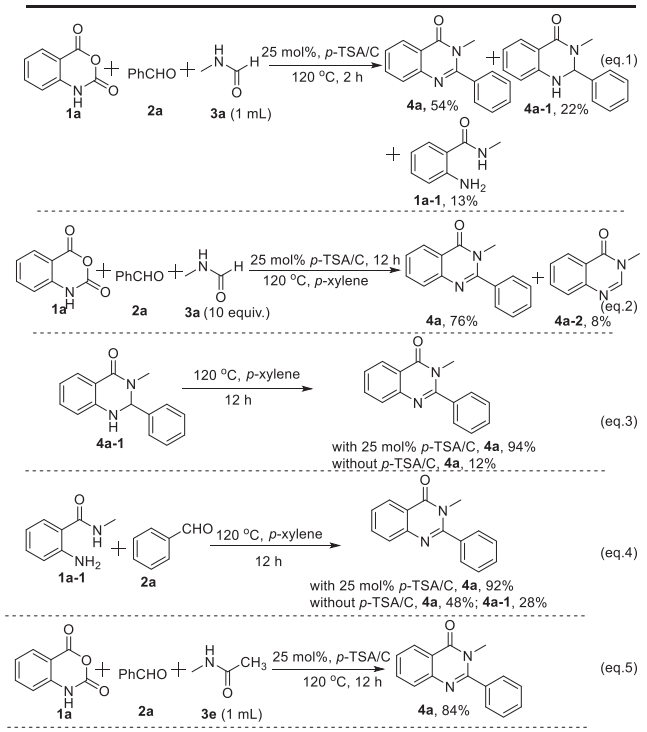


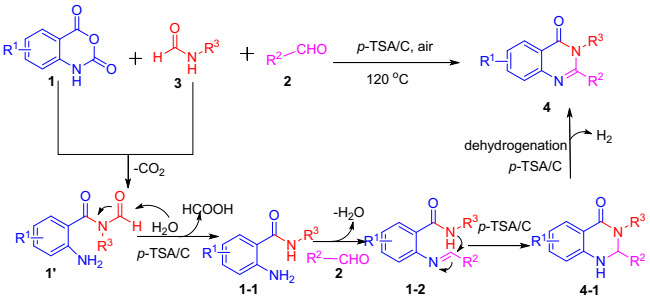
Fig. 1. Reusability of the *p*-TSA/C catalyst.



Scheme 6. Control experiments.

inate the interference effect of the solvent. This reaction proceeded smoothly, affording **4a** and condensed by-product **4a-2** in 76% and 8% yield, respectively (Eq. 2). As expected, the direct aromatization of **4a-1** gave **4a** in almost quantitative yield, while the dehydrogenation reaction of **4a-1** without catalyst gave **4a** in only 12% yield (Eq. 3). Furthermore, the cyclization of **1a-1** with aldehyde **2a** assisted by the supported acid afforded **4a** in 92% yield, while the condensation of **1a-1** and **2a** in the absence of *p*-TSA/C gave **4a** and **4a-1** in 48% and 28% yield, respectively (Eq. 4). These results indicate that **4a-1** and **1a-1** serve as the main reaction intermediates. Additionally, *p*-TSA/C contributes to the cyclization of **1a-1** and the dehydroaromatization of **4a-1**. Notably, acetamide **3e** could also be coupled with **1a** and **2a** to afford **4a** in high yield (Eq. 5), indicating amides can be used as an amine synthon.

With the results above and previous reports [20], a plausible reaction pathway was proposed (Scheme 7). Initially, amide **3** undergoes nucleophilic addition to isatoic anhydride **1** to form intermediate **1′**. Cleavage of the amide C—N bond assisted by H_2O in the presence of the acid catalyst affords **1**–**1** and HCOOH [21]. Next, intermediate **1**–**1** undergoes condensation to afford intermediate **1**–**2**, which subsequently undergoes cyclization to



Scheme 7. Plausible mechanism for the formation of **4**.

produce dihydroquinazolinone **4**–**1**. Finally, the dehydrogenation of **4**–**1** provides the desired product **4** using air as an oxidant.

Conclusion

In summary, we have developed a novel and straightforward method for the synthesis of various quinazolinones *via* the reusable carbon-supported acid-catalyzed cascade coupling of isatoic anhydrides with amides and aldehydes. Furthermore, we have explored the selective Ru-catalyzed hydrosilylation of quinazolinones without C=N bond reduction using a cost-effective silane as the hydrogen donor. The cascade coupling transformation is characterized by a broad substrate scope, excellent functional tolerance, and a reusable catalyst using air as the oxidant. This work might aid the rapid and efficient construction of quinazolinone and dihydroquinazoline derivatives with potential biological and pharmaceutical properties.

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.

Acknowledgments

We thank the National Natural Science Foundation of China (21702148), Department of Education of Guangdong province (2019KZDXM052, 2018KQNCX272, 2020KQNCX093), the Science Foundation for Young Teachers of Wuyi University (2019td06), the Innovation Industry Project of Wuyi University (2019CX24, 202011349025) and "Climbing Program" Special Funds of Guangdong Province (pdjh2021b0516) for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152835.

References

[1] a) S. Gatadi, T.V. Lakshmi, S. Nanduri, Eur. J. Med. Chem. 170 (2019) 157–172; b) T. Abe, Y. Takahashi, Y. Matsubara, K. Yamada, Org. Chem. Front. 4 (2017) 2124–2127.
[2] a) G. Yang, C. Cheng, G.-B. Xu, L. Tang, K.-L. Chua, Y.-Y. Yang, Bioorg. Med. Chem. 28 (2020) 115606; b) M.M. Aly, Y.A. Mohamed, K.A.M. El-Bayouki, W.M. Basyouni, S.Y. Abbas, Eur. J. Med. Chem. 45 (2010) 3365–3373; c) V. Alagarsamy, V. Raja Solomon, K. Dhanabal, Bioorg. Med. Chem. 15 (2007) 235–241.
[3] a) P. Ghosh, B. Ganguly, S. Das, Org. Biomol. Chem. 2020, 18, 4497-4518; b) L.-C. Wang, S. Du, Z. Chen, X.-F. Wu, Org. Lett. 2020, 22, 5567-5571; d) S. Y. Abbas, K. A. M. El-Bayouki and W. M. Basyouni, Synth. Commun., 2016, 46, 993-1035; e) P. G. Mahajan, N. C. Dige, B. D. Vanjare, H. Raza, M. Hassan, S.-Y. Seo, C.-H. Kim and K. H. Lee, J. Mol. Struct., 2019, 1198, 126915;f) T. Zahra, M.-K. Mohammad, B. Mahmood, L. Bagher and M. Mohammad, Curr. Org. Chem., 2019, 23, 1090-1130.
[4] a) F. Li, L. Lu, J. Ma, Org. Chem. Front. 2 (2015) 1589–1597; b) Y. Wang, X. Meng, G. Chen, P. Zhao, Catal. Commun. 104 (2018) 106–111; c) T.A. To, Y.H. Vo, H.T.T. Nguyen, P.T.M. Ha, S.H. Doan, T.L.H. Doan, S. Li, H.V. Le, T.N. Tu, N.T.S. Phan, J. Catal. 370 (2019) 11–20.
[5] a) Q. Wang, M. Lv, J. Liu, Y. Li, Q. Xu, X. Zhang, H. Cao, ChemSusChem 12 (2019) 3043–3048; b) W. Zhao, P. Liu, F. Li, ChemCatChem 8 (2016) 1523–1530.
[6] X. Yu, L. Gao, L. Jia, Y. Yamamoto, M. Bao, J. Org. Chem. 83 (2018) 10352–10358.
[7] X.-F. Wu, L. He, H. Neumann, M. Beller, Chem. Eur. J. 19 (2013) 12635–12638.
[8] Y. Liang, Z. Tan, H. Jiang, Z. Zhu, M. Zhang, Org. Lett. 21 (2019) 4725–4728.
[9] C. Qian, K. Liu, S.-W. Tao, F.-L. Zhang, Y.-M. Zhu, S.-L. Yang, J. Org. Chem. 83 (2018) 9201–9209.
[10] a) L. He, F. Weniger, H. Neumann, M. Beller, Angew. Chem., Int. Ed. 55 (2016) 12582–12594; b) K. Shen, X. Chen, J. Chen, Y. Li, ACS Catal. 6 (2016) 5887–5903.
[11] A. Mahajan, P. Gupta, New J. Chem. 44 (2020) 12897–12908.

[12] a) L. Liu, A. Corma, Chem. Rev. 118 (2018) 4981–5079;
b) A. Wang, J. Li, T. Zhang, Nat. Rev. Chem. 2 (2018) 65–81.
[13] a) K. Rad-Moghadam, M. Mamghani, L. Samavi, Synth. Commun. 36 (2006) 2245–2252;
b) Z. Wang, X. Wu, L. Wang, J. Zhang, J. Liu, Z. Song, Z. Tang, Bioorg. Med. Chem. Lett. 26 (2016) 2589–2593;
c) M. Heidary, M. Khoobi, S. Ghasemi, Z. Habibi, M.A. Faramarzi, Adv. Synth. Catal. 356 (2014) 1789–1794;
d) S. Rostamizadeh, A.M. Amani, G.H. Mahdavinia, H. Sepehrian, S. Ebrahimi, Synthesis 2010 (2010) 1356–1360;
e) G.R. Reddy, T.R. Reddy, R.G. Chary, S.C. Joseph, S. Mukherjee, M. Pal, Tetrahedron Lett. 54 (2013) 6744–6746.
[14] a) S. Srinivasan, P. Manisankar, Synth. Commun. 40 (2010) 3538–3543;
b) A. Schnyder, M. Beller, G. Mehltretter, T. Nsenda, M. Studer, A.F. Indolese, J. Org. Chem. 66 (2001) 4311–4315.
[15] a) F. Xie, Y. Li, X. Chen, L. Chen, Z. Zhu, B. Li, Y. Huang, K. Zhang, M. Zhang, Chem. Commun. 56 (2020) 5997–6000;
b) R. Xie, F. Xie, C.-J. Zhou, H.-F. Jiang, M. Zhang, J. Catal. 377 (2019) 449–454;
c) F. Xie, G.-P. Lu, R. Xie, Q.-H. Chen, H.-F. Jiang, M. Zhang, ACS Catal. 9 (2019) 2718–2724;
d) B. Li, S. Liu, Q. Lin, Y. Shao, S. Peng, Y. Li, Chem. Commun. 54 (2018) 9214–9217;
e) F. Xie, R. Xie, J.-X. Zhang, H.-F. Jiang, L. Du, M. Zhang, ACS Catal. 7 (2017) 4780–4785.
[16] F. Xie, Q.-H. Chen, R. Xie, H.-F. Jiang, M. Zhang, ACS Catal. 8 (2018) 5869–5874.
[17] F. Ji, M.-F. Lv, W.-B. Yi, C. Cai, Org. Biomol. Chem. 12 (2014) 5766–5772.
[18] a) B. Li, S. Liu, Q. Lin, Y. Shao, S. Peng, Y. Li, Chem. Commun. 54 (2018) 9214–9217;
b) B. Li, S. Liu, M. Wu, Q. Lin, W. Deng, S. Jiang, L. Chen, Tetrahedron Lett. 59 (2018) 3467–3472;
c) B. Li, J.-B. Sortais, C. Darcel, Chem. Commun. 49 (2013) 3691–3693;
d) B. Li, J.-B. Sortais, C. Darcel, P.H. Dixneuf, ChemSusChem 5 (2012) 396–399.
[19] a) K. McAulay, E.A. Hoyt, M. Thomas, M. Schimpl, M.S. Bodnarchuk, H.J. Lewis, D. Barratt, D. Bhavsar, D.M. Robinson, M.J. Deery, D.J. Ogg, G.J.L. Bernardes, R.A. Ward, M.J. Waring, J.G. Kettle, J. Am. Chem. Soc. 142 (2020) 10358–10372;
b) A. Chakraborty, T. Chowdhury, M.I. Menéndez, T. Chattopadhyay, ACS Appl. Mater. Inter. 12 (2020) 38530–38545;
c) Y. Nam, K.D. Ryu, C. Jang, Y.H. Moon, M. Kim, D. Ko, K.-S. Chung, M.A. Gandini, K.-T. Lee, G.W. Zamponi, J.Y. Lee, Bioorg. Med. Chem. 28 (2020) 115491.
[20] M. Heidary, M. Khoobi, S. Ghasemi, Z. Habibi, M.A. Faramarzi, Adv. Synth. Catal. 356 (2014) 1789–1794.
[21] a) G. Li, M. Szostak, Synthesis 52 (2020) 2579–2599;
b) K.R. Rao, R. Mekala, A. Raghunadh, S.B. Meruva, S.P. Kumar, D. Kalita, E. Laxminarayana, B. Prasad, M. Pal, RSC Adv. 5 (2015) 61575–61579;
c) K.R. Rao, A. Raghunadh, R. Mekala, S.B. Meruva, T.V. Pratap, T. Krishna, D. Kalita, E. Laxminarayana, B. Prasad, M. Pal, Tetrahedron Lett. 55 (2014) 6004–6006.