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Visible-light-promoted radical alkylation/cyclization of allylic amide with *N*-hydroxyphthalimide ester: Synthesis of oxazolines

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ABSTRACT

An efficient photocatalytic alkylation/cyclization of allylic amide with *N*-hydroxyphthalimide ester has been developed. The transformation is taken advantage of alkyl radicals to attack allylic amide with the assist of inexpensive rose bengal as photocatalyst to prepare a series of alkyl substituted oxazolines in moderate to excellent yields. High regioselectivity, operational safety, mild conditions and excellent substrate generality give this protocol broad application prospects.

Nitrogen-containing heterocyclic compounds with unique biological and pharmacological activities are usually used as structural units of drugs and pesticides [1-9]. As a kind of *N*-heterocycle, oxazolines exhibit various notable bioactivities, such as antimicrobial, antimalarial, antiviral, antioxidant, antitumor (Fig. 1) [10-13]. The traditional methods for synthesis of oxazolines are realized *via* the condensation of β-aminoalcohols with carboxylic acids, aldehydes, esters or nitriles (Scheme 1a) [14]. Additionally, [2 + 3] cyclization of olefins and amides (or benzoyl azides) is an efficient strategy for the synthesis of oxazolines (Scheme 1b) [15, 16]. Furthermore, allylic amide cyclization reaction provides a reliable approach to obtain oxazolines which focused on a halocyclization reaction with cationic halogen to form five-membered heterocycles (Scheme 1c) [17-20]. Recently, the cyclization of allylic amide based on radical coupling has become a new strategy for preparation of oxazolines (Scheme 1d) [21-25]. Although these processes are essential, some drawbacks such as hard conditions, the use of large amounts of metal complexes and oxidants, substrate limitations, still limit the further application.

The visible-light mediated organic transformations which promoted chemical reactions by absorbing light as activation energy under very mild conditions have attracted widespread attention since the seminal work of MacMillan, Yoon, and Stephenson [26-45]. Meanwhile, the alkyl *N*-hydroxyphthalimide (NHP) esters which could be easily reduced by photocatalysts to generate extensive kinds of alkyl radicals with the eliminating of CO_2 and phthalimide anion are demonstrated to be effective alkyl precursors [46-55]. Consistent with our ongoing research on photocatalytic radical-mediated C–H functionalization [56-60], herein, we uncover a metal and oxidant free approach to afford a variety of oxazolines through the radical alkylation/cyclization of allylic amide with *N*-hydroxyphthalimide (NHP) ester (Scheme 1e). This method features excellent regioselectivities, mild conditions, excellent substrate generality and good yields.

To begin our study, *N*-(2-phenylallyl)benzamide **1a** and *t*–butyl NHP esters **2a** were utilized as model substrates to optimize the reaction conditions. Initially, the transformation was studied with $Ir(ppy)_3$ as a photocatalyst, irradiated with 3 W bule LEDs in DMSO under N_2 atmosphere for 36 h. Fortunately, the target 5-neopentyl-2,5-diphenyloxazoline 3aa was formed in 70% yield (Table 1, entry 1). In order to increase the yield of desired product, a variety of photocatalysts such as Rose bengal, Na_2-Eosin Y, methylene blue, $Ru(bpy)_3Cl_2$ were investigated (Table 1, entries 2–5). The experiment results revealed that only Rose bengal exhibited a better efficiency with a yield of 75%. Subsequently, a variety of commonly used solvents including DMF, MeCN, EtOAc, DCE, DCM were screened (Table 1, entries 6–10). Disappointingly, the yield was decreased when DMF, MeCN, EtOAc were employed, and no product was found with DCE or DCM as solvent. Thus, DMSO is still the most suitable solvent. To further improve the efficiency of this

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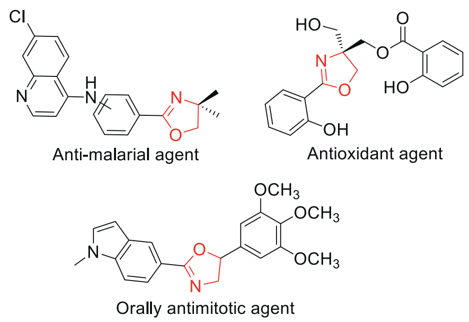
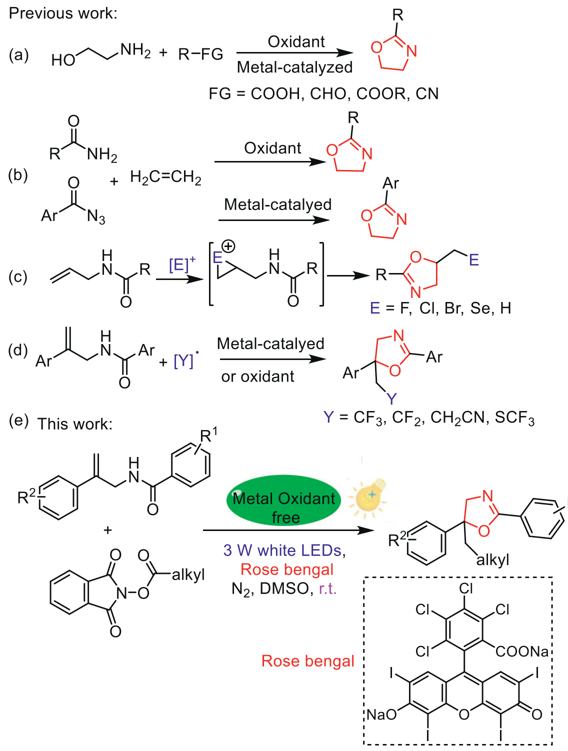


Fig. 1. Examples of oxazoline-type pharmaceutical.

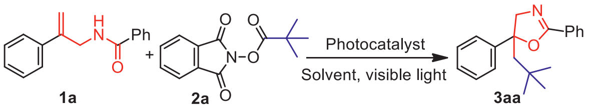


Scheme 1. Strategies for the synthesis of oxazolines.

transformation, 3 W blue LEDs were replaced by white or green LEDs (Table 1, entries 11 and 12). To our delight, the yield of **3aa** was increased from 75% to 83% as 3 W white LEDs was applied. Contrast experiments indicated that either photocatalyst or visible light is indispensable for this transformation (Table 1, entries 13 and 14). Furthermore, only an extremely low yield was obtained when this reaction was executed under air (Table 1, entry 15).

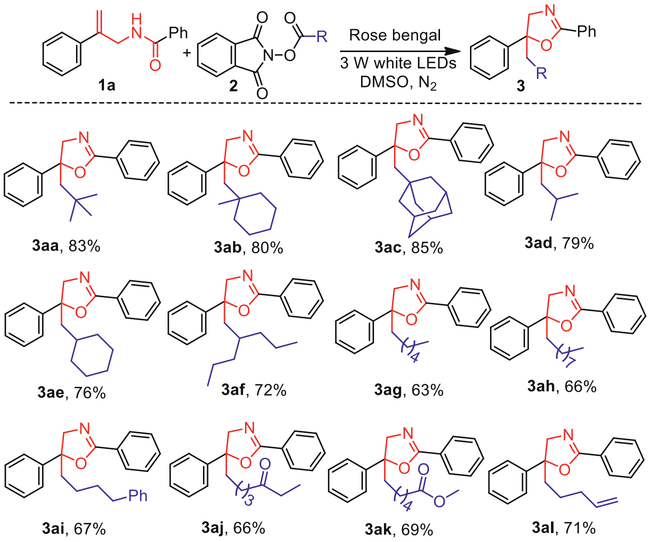
After determining the optimal reaction conditions, including Rose bengal as a photosensitizer at room temperature in DMSO by irradiation of 3 W white LEDs under N_2 atmosphere for 36 h, the scope of NHP esters was examined through the radical alkylation/cyclization of **1a**. It can be concluded from Scheme 2 that this protocol is applicable to different types of NHP esters, affording the desired products in moderate to excellent yields. Initially, the tertiary alkyl NHP esters containing *t*–butyl, methylcyclohexyl and adamantyl showed excellent tolerance for this transformation, and gave the desired products **3aa**-**3ac** in excellent yields. Subsequently, secondary alkyl NHP esters were experimented under optimal conditions, and the results exhibited that alkyl NHP esters including isopropyl, cyclohexyl, 3-heptyl were also well adapted to this protocol and the corresponding products **3ad**-**3af** were obtained in 72% to 79% yields. It is worth mentioning that primary

Table 1
Optimization of the reaction conditions.[a]



Entry	Photocatalyst	Solvent	Yield (%) [b]
1	Ir(ppy)$_3$	DMSO	70
2	Rose bengal	DMSO	75
3	Na_2-Eosin Y	DMSO	67
4	Methylene blue	DMSO	56
5	Ru(bpy)$_3$Cl$_2$	DMSO	50
6	Rose bengal	DMF	64
7	Rose bengal	MeCN	47
8	Rose bengal	EtOAc	46
9	Rose bengal	DCE	0
10	Rose bengal	DCM	0
11[c]	Rose bengal	DMSO	83
12[d]	Rose bengal	DMSO	46
13	–	DMSO	0
14[e]	Rose bengal	DMSO	0
15[f]	Rose bengal	DMSO	13

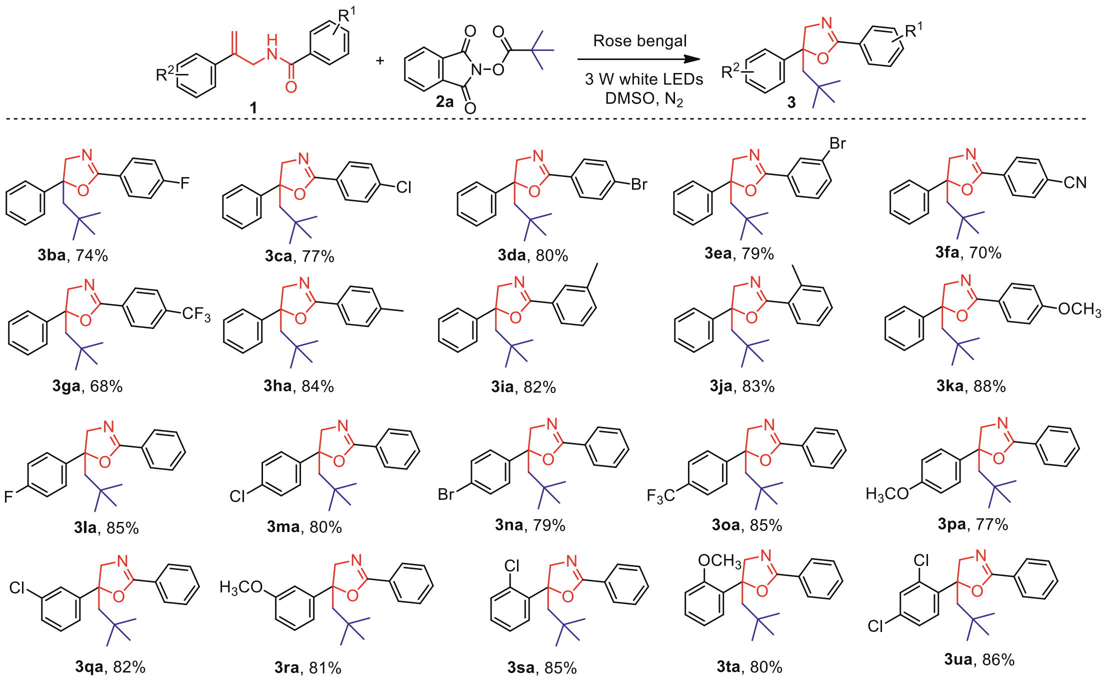
[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.9 mmol), catalyst (0.012 mmol), solvent (3.0 mL), r.t., 3 W blue LEDs, 36 h, under N_2 atmosphere.
[b] Isolated yield base on **1a**.
[c] 3 W white LEDs.
[d] 3 W green LEDs.
[e] Without light.
[f] Under air .



Scheme 2. Scope of alkyl NHP esters. Reaction conditions: **1a** (0.6 mmol), **2** (0.9 mmol), Rose bengal (0.012 mmol) in DMSO (3.0 mL) at room temperature with irradiation by 3 W white LEDs under N_2 atmosphere for 36 h.

alkyl NHP esters which could generate primary alkyl radicals were also suitable well for this protocol. For example, 63%–67% yields can be obtained by taking *n*-pentyl, *n*-octane and 3-phenylpropyl as the reactive radicals to participate in the reaction (**3ag**-**3ai**). Additionally, the primary alkyl NHP esters containing functional groups involving carbonyl, ester and alkenyl on aliphatic chain are apposite to this transformation and provided the desired product in yields of 66%–71% (**3aj**-**3al**).

After the scope of alkyl NHP esters was screened, a variety of allylic amides were then experimented in alkylation/cyclization reaction with *t*–butyl NHP ester **2a** under the standard conditions. As given in Scheme 3, this protocol was found to be applicable to various allylic amides containing different functional groups and

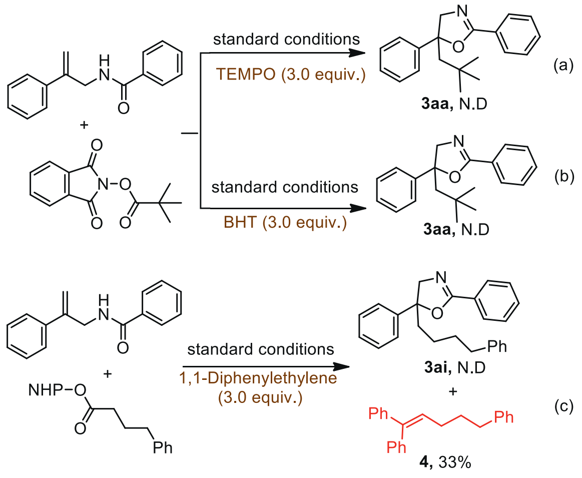


Scheme 3. Scope of allylic amides. Reaction conditions: **1** (0.6 mmol), **2a** (0.9 mmol), Rose bengal (0.012 mmol) in DMSO (3.0 mL) at room temperature with irradiation by 3 W white LEDs under N_2 atmosphere for 36 h.

gave the corresponding products in moderate to excellent yields. Initially, allylic amides with different substituents of R^1 were investigated. The experimental results indicated that the allylic amides possessing virous halogens (**1b**-**1e**), such as F, Cl and Br at different position of acylbenzene, all proceeded well and provided the desired products in yields of 74%–80%. Remarkably, even cyano and trifluoromethyl groups which are considered as strong electron withdrawing group were also well suitable for this protocol, and moderate yields have been obtained (**3fa**, **3ga**). Additionally, when the substituents R^1 were replaced by electron-donating groups including methyl and methoxy, the desired products were obtained in 82%–88% yields (**3ha**-**3ka**). Then, the electronic effect of R^2 group was screened. Substrates with electron-withdrawing or electron-donating groups at the *para* position of the benzene ring exhibited good reactivity for this reaction (**3la**-**3pa**). The transformation also survived well and provided the products in 80%–85% yields when substrates with substituents at different position of the benzene ring (**3qa**-**3ta**) were used. Satisfactorily, this protocol was also suitable for disubstituted substrate, afforded the desired product in 86% yield (**3ua**).

In order to explore the reaction mechanism, several control experiments were carried out as shown in Scheme 4. A radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (3.0 equiv.) was applied to the model reaction, and this alkylation/cyclization reaction was totally suppressed (Scheme 4a). The same result was obtained when using BHT as another radical scavenger in the same system (Scheme 4b). These results revealed that the transformation might be carried on with a radical mechanism. To confirm the existence of alkyl radical, 1,1-diphenylethylene was added into the transformation between NHP ester and allylic amide under the standard conditions, the adduct 4 was obtained as the only product in a yield of 33% (Scheme 4c). Furthermore, EPR experiment was performed and strong signal peaks of alkyl radical adduct with DMPO were detected (for details, see Supporting information).

In addition, the Stern-Volmer experiment was carried out and the results indicated that Rose bengal* was quenched by alkyl NHP esters, suggesting that the reaction might proceed through an oxidative quenching process (Fig. 2).



Scheme 4. Control experiment.

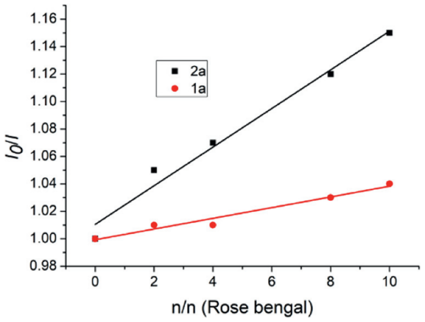
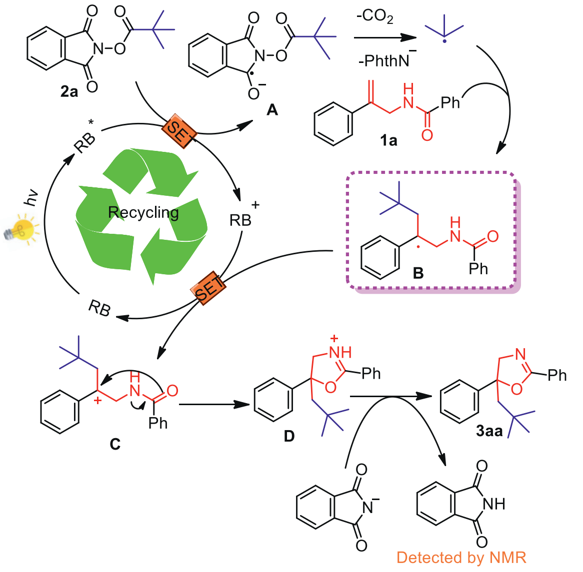


Fig. 2. Stern–Volmer plot: fluorescence quenching of Rose bengal using *N*-(2-phenylallyl) benzamide **1a** and *t*-butyl NHP ester **2a**.

According to the above-mentioned observations and previous literature reports [61], a plausible mechanism for this transformation was proposed in Scheme 5. Initially, the photosensitizer Rose bengal (RB) was irradiated by 3 W white LEDs to form its acti-



Scheme 5. Proposed reaction mechanism.

vated species, which can transfer a single electron to NHP ester **2a** to generate the radical **A**, accompanied by the oxidation of RB* to its oxidative state RB$^+$ ($E_{1/2}$RB$^+$/RB* = −1.32 V *vs.* SCE, $E_{1/2}$ (NHP esters) ≈ −1.26 V *vs.* SCE) [62,63]. Then the *t*-butyl radical was formed *via* release of carbon dioxide and phthalimide anion from radical **A**, which was subsequently captured by the double bond in allylic amide to give the radical **B**. Through a single electron transfer process between RB$^+$ and radical **B**, the carbocation intermediate **C** was generated. The desired product **3aa** was finally obtained after undergoing an intramolecular cyclization of C between carbocation and carbonyl, followed by a deprotonation process with phthalimide anion.

In summary, we successfully synthesized a series of oxazoline derivatives through the alkylation/cyclization reaction of allylic amide with NHP ester by employing a metal-free photocatalytic system under white LEDs irradiation. A wide range of alkyl NHP esters and allylic amides bearing different types of substituents were demonstrated to survive for this protocol, and provided a variety of oxazolines in moderate to excellent yields. Furthermore, this method has the characteristics of high regioselectivity, operational simplicity, mild conditions and excellent substrate generality.

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.09.067.

References

[1] L. Feng, K.W. Yang, L.S. Zhou, et al., Bioorg. Med. Chem. Lett. 22 (2012) 5185–5189.
[2] Z.J. Zhao, S.T. Harrison, J.W. Schubert, et al., Bioorg. Med. Chem. Lett. 26 (2016) 2952–2956.
[3] S.H. Sharma, J.L. Pablo, M.S. Montesinos, A. Greka, C.R. Hopkins, Bioorg. Med. Chem. Lett. 29 (2019) 155–159.
[4] T. Scattolin, I. Caligiuri, N. Mouawad, et al., Eur. J. Med. Chem. 179 (2019) 325–334.
[5] A. Al-Azmi, Curr. Org. Chem. 23 (2019) 721–743.
[6] P. Devendar, R.Y. Qu, W.M. Kang, B. He, G.F. Yang, J. Agric. Food Chem. 66 (2018) 8914–8934.
[7] H. Prinz, A.K. Ridder, K. Vogel, et al., J. Med. Chem. 60 (2017) 749–766.
[8] K.M. Lincoln, T.E. Richardson, L. Rutter, et al., ACS Chem. Neurosci. 3 (2012) 919–927.
[9] Y.T. Zhang, Y.L. Shao, J.L. Gong, et al., J. Org. Chem. 84 (2019) 2798–2807.
[10] C.J. Waschinski, J.C. Tiller, Biomacromolecules 6 (2005) 235–243.
[11] E.E. Gordey, P.N. Yadav, M.P. Merrin, et al., Bioorg. Med. Chem. Lett. 21 (2011) 4512–4515.
[12] C. Gros, J. Fahy, L. Halby, et al., Biochimie 94 (2012) 2280–2296.
[13] T. Berranger, Y. Langlois, Tetrahedron Lett 36 (1995) 5523–5526.
[14] M. Trose, F. Lazreg, M. Lesieur, C.S.J. Cazin, J. Org. Chem. 80 (2015) 9910–9914.
[15] S. Minakata, Y. Morino, T. Ide, Y. Oderaotoshi, M. Komatsu, Chem. Commun. (2007) 3279–3281.
[16] P. Bellotti, J. Brocus, F.E. Orf, et al., J. Org. Chem. 84 (2019) 6278–6285.
[17] A. Jaganathan, A. Garzan, D.C. Whitehead, R.J. Staples, B. Borhan, Angew. Chem. Int. Ed. 50 (2011) 2593–2596.
[18] V. Rauniyar, A.D. Lackner, G.L. Hamilton, F.D. Toste, Science 334 (2011) 1681–1684.
[19] E. Cahard, N. Bremeyer, M.J. Gaunt, Angew. Chem. Int. Ed. 52 (2013) 9284–9288.
[20] Q. Yin, S.L. You, Org. Lett. 16 (2014) 2426–2429.
[21] L. Liu, Y.H. He, Z. Guan, Tetrahedron 75 (2019) 130716.
[22] J.P. Yu, H.J. Yang, H. Fu, Adv. Synth. Catal. 356 (2014) 3669–3675.
[23] M. Zhu, R.X. Li, Q.Q. You, W.J. Fu, W.S. Guo, Asian. J. Org. Chem. 8 (2019) 2002–2005.
[24] Y. Nagao, K. Hiroya, Synlett 31 (2020) 813–817.
[25] W.J. Fu, X. Han, M. Zhu, et al., Chem. Commun. 52 (2016) 13413–13416.
[26] T.P. Yoon, M.A. Ischay, J. Du, Nat. Chem. 2 (2010) 527–532.
[27] J.M.R. Narayanam, C.R. Stephenson, J. Chem. Soc. Rev. 40 (2011) 102–113.
[28] C.K. Prier, D.A. Rankic, D.W.C. MacMillan, Chem. Rev. 113 (2013) 5322–5363.
[29] M.N. Hopkinson, B. Sahoo, J.L. Li, F. Glorius, Chem. Eur. J. 20 (2014) 3874–3886.
[30] J. Xu, L. Huang, L. He, et al., Green Chem 23 (2021) 2123–2129.
[31] J. Xu, H.D. Zhang, J.M. Zhao, et al., Org. Chem. Front. 7 (2020) 4031–4042.
[32] J. Xu, H.Y. Yang, L. He, Org. Lett. 23 (2021) 195–201.
[33] Y.Q. Guo, R.G. Wang, H.J. Song, Y.X. Liu, Q.M. Wang, Org. Lett. 22 (2020) 709–713.
[34] Q. Wang, Y. Qu, Y.X. Liu, H.B. Song, Q.M. Wang, Adv. Synth. Catal. 361 (2019) 4739–4747.
[35] Q. Wang, Y. Qu, Q. Xia, et al., Chem. Eur. J. 24 (2018) 11283–11287.
[36] W.B. He, L.Q. Gao, X.J. Chen, et al., Chin. Chem. Lett. 31 (2020) 1895–1898.
[37] K.J. Liu, Z. Wang, L.H. Lu, et al., Green Chem 23 (2021) 496–500.
[38] L.Y. Xie, S. Peng, L.H. Yang, et al., Green Chem 23 (2021) 374–378.
[39] X.X. Zhao, B. Li, W.J. Xia, Org. Lett. 22 (2020) 1056–1061.
[40] J.L. Wang, B.B. Huang, C. Yang, W.J. Xia, Chem. Commun. 55 (2019) 11103–11106.
[41] Y.T. Zhao, W.J. Xia, Chem. Soc. Rev. 47 (2018) 2591–2608.
[42] R. Lin, H. Sun, C. Yang, W. Shen, W. Xia, Chem. Commun. 51 (2015) 399–401.
[43] J.B. Shen, J. Xu, L. He, et al., Org. Lett. 23 (2021) 1204–1208.
[44] L. Huang, J. Xu, L. He, et al., Chin. Chem. Lett. 32 (2021) 3627-3631.
[45] Y. Lang, C.J. Li, H. Zeng, Org. Chem. Front. 8 (2021) 3594–3613.
[46] G.Z. Wang, R. Shang, Y. Fu, Org. Lett. 20 (2018) 888–891.
[47] A. Tlahuext-Aca, R.A. Garza-Sanchez, F. Glorius, Angew. Chem. Int. Ed. 56 (2017) 3708–3711.
[48] J. Yang, J. Zhang, L. Qi, C. Hua, Y. Chen, Chem. Commun. 51 (2015) 5275–5278.
[49] W.M. Cheng, R. Shang, M.C. Fu, Y. Fu, Chem. Eur. J. 23 (2017) 2537–2541.
[50] J.C. Yang, J.Y. Zhang, J.J. Zhang, X.H. Duan, L.N. Guo, J. Org. Chem. 83 (2018) 1598–1605.
[51] Y.H. Jin, H.J. Yang, H. Fu, Org. Lett. 18 (2016) 6400–6403.
[52] C. Jin, Z.Y. Yan, B. Sun, J. Yang, Org. Lett. 21 (2019) 2064–2068.
[53] Z.Y. Yan, B. Sun, X. Zhang, et al., Chem. Asian. J. 14 (2019) 3344–3349.
[54] B. Sun, T.W. Xu, L. Zhang, et al., Synlett 31 (2020) 363–368.
[55] B. Sun, D.Y. Li, X.H. Zhuang, et al., Synlett 31 (2020) 677–682.
[56] B. Sun, P.Y. Huang, Z.Y. Yan, et al., Org. Lett. 23 (2021) 1026–1031.
[57] B. Sun, R. Zhu, X.H. Zhuang, et al., Org. Lett. 23 (2021) 617–622.
[58] X.H. Zhuang, X.Y. Shi, R. Zhu, et al., Org. Chem. Front. 8 (2021) 736–742.
[59] B. Sun, X.Y. Shi, X.H. Zhuang, et al., Org. Lett. 23 (2021) 1862–1867.
[60] J. Yang, B. Sun, H. Ding, et al., Green Chem 23 (2021) 575–581.
[61] S. Das, S.K. Parida, T. Mandal, et al., Org. Chem. Front. 8 (2021) 2256–2262.
[62] M. Singsardar, S. Mondal, S. Laru, A. Hajra, Org. Lett. 21 (2019) 5606–5610.
[63] G. Pratsch, G.L. Lackner, L.E. Overman, J. Org. Chem. 80 (2015) 6025–6036.