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Palladium-catalyzed cyclization of 1-alkynyl-8-iodonaphthalene and double isocyanides for the synthesis of acenaphtho[1,2-*b*]pyrroles

Shangfeng Ren[a,b,1], Keke Huang[a,1], Jin-Biao Liu[a,*], Lianpeng Zhang[c,*], Min Hou[b], Guanyinsheng Qiu[b,*]

[a] *School of Metallurgical and Chemical Engineering, Jiangxi University of Science and Technology, Ganzhou 341000, China*
[b] *College of Biological, Chemical Sciences and Engineering, Jiaxing University, Jiaxing 314001, China*
[c] *International Joint Research Center for Biomass Materials, Southwest Forestry University, Kunming 650224, China*

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ABSTRACT

A palladium-catalyzed formal [2 + 2 + 1] cyclization of 1-alkynyl-8-iodonaphthalene with double isocyanides is developed herein. The transformation worked well to produce a series of 7*H*-acenaphtho[1,2-*b*]pyrrole with a broad reaction scope. Isocyanides play a dual role in the reaction. One is a C1 building block, and another is used as C1N1 component. In the process, the [2 + 2 + 1] cyclization involves imidoylation, regioselective addition of imidoylpalladium species into alkyne, double imidoylation, and another addition of the resulting imidoylpalladium species into imine bonds.

Isocyanides-based imidoylation has attracted ever-increasing attention of synthetic chemists [1–3]. As we know, palladium catalysis was often used in isocyanides-based transformation, partially because of its ready coordination and ligand dissociation of palladium-isocyanides complexes [4–5]. In the past decades, the established achievements on palladium-catalyzed imidoylation have proved isocyanides to be a powerful C1 synthons towards cyclic products from acyclic substrates [6–7]. It is generally accepted that imidoylation under palladium catalysis represented a 1,1-insertion model of isocyanides, a reaction similar to carbonylation [8–11]. Therefore, isocyanides often served as a replacement of carbon monoxide in organic synthesis. In recent years, isocyanides-based radical cyclization has been well documented as well [12–14]. Many isocyano-containing dual-functionalized synthons, including 2-vinylphenylisocyanides [15–17], 2-alkynylphenylisocyanides [18–20], 2-arylphenylisocyanides [21–23], and 2-isocyanophenylisocyanides [24–28] *etc.*, have been recognized as efficient reaction partners. In these radical reactions, isocyanides could be installed into the cyclic products as C1N1 components.

Surprisingly, the use of simple isocyanides as C1N1 synthons remains rare in transitional metal-catalyzed annulation [29–31]. In 2009, Tsukada and co-workers found that dinucleopalladium catalyst, derived from dinuclear ligand *N,N*'-bis[2-(diphenylphsphino)phenyl]formamidinate, enabled the use of isocyanides as C1N1 synthons in the reactions with terminal alkyne to release 2-amino-4-cyanopyrroles in high yields [29]. In 2016, Zhu's findings and Jiang's findings showed that propargyl carbonate and propargyl bromide were efficient candidates to capture isocyanides for constructing fully substituted pyrroles, where isocyanides served as C1N1 synthons [30–31]. Very recently, our group developed a palladium-catalyzed [2 + 2 + 1] cyclization of internal alkynes with double isocyanides for synthesizing various pyrrolo[3,2-*c*]quinolin-2-amines [32].

On the other hand, 1-alkynyl-8-iodonaphthalene is a versatile building block for the synthesis of various fluorescent compounds [33–36]. Therefore, we would like to explore the reaction of 1-alkynyl-8-iodonaphthalene and isocyanides under palladium catalysis. Considering high ubiquity of pyrroles in medicine [37–40] together with our continuous interest in synthetic methodology development towards pyrroles [41–49], we envisioned that the palladium-catalyzed reaction of 1-alkynyl-8-iodonaphthalene and isocyanides could produce polycycles-fused pyrroles (Scheme 1), a core skeleton being always observed in many useful architectures.

Theoretically, oxidative addition of Pd(0) species into carbon-iodo bond triggered the reaction. Subsequently, it is assumed that

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* Corresponding authors.
E-mail addresses: liujinbiao@jxust.edu.cn (J.-B. Liu), lpz@zju.edu.cn (L. Zhang), qiuguanyinsheng@mail.zjxu.edu.cn (G. Qiu).

[1] These two authors contributed equally to this work.

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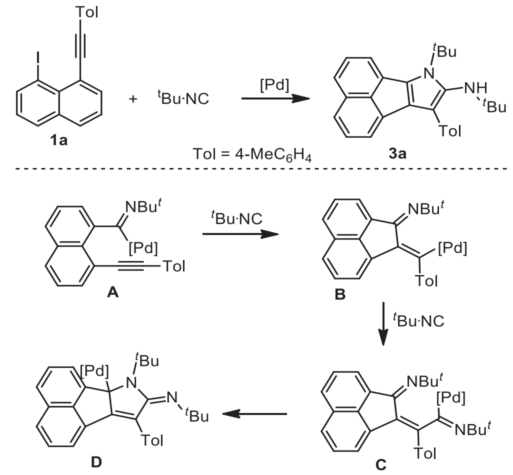
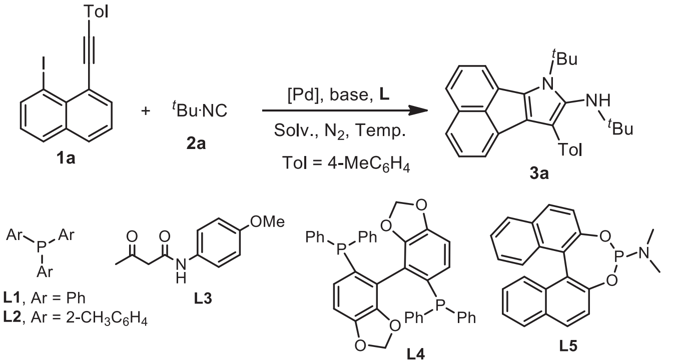


Scheme 1. Proposed route for palladium-catalyzed cyclization of 1-alkynyl-8-iodonaphthalene and double isocyanides.

Table 1
Initial studies for the reaction of [2 + 2 + 1] cyclization of 1-ethynyl-8-iodonaphthalene **1a** and isocyanides under palladium catalysis.[a]



Entry	Cat.	Base	[**L**]	Solvent	Yield of **3a** (%)
1	Pd(PPh$_3$)$_4$	Cs$_2$CO$_3$	/	Toluene	73
2	Pd(PPh$_3$)$_4$	Cs$_2$CO$_3$	/	MeCN	63
3	Pd(PPh$_3$)$_4$	Cs$_2$CO$_3$	/	DCE	75
4	Pd(PPh$_3$)$_4$	Cs$_2$CO$_3$	/	1,4-dioxane	47
5	Pd(PPh$_3$)$_4$	Cs$_2$CO$_3$	/	DMF	complex
6	Pd(OAc)$_2$	Cs$_2$CO$_3$	/	DCE	56
7	Pd(OTf)$_2$	Cs$_2$CO$_3$	/	DCE	79
8	PdCl$_2$(PPh$_3$)$_2$	Cs$_2$CO$_3$	/	DCE	48
9	Pd$_2$dba$_3$	Cs$_2$CO$_3$	/	DCE	55
10	Pd(OTf)$_2$	Cs$_2$CO$_3$	**L1**	DCE	62
11	Pd(OTf)$_2$	Cs$_2$CO$_3$	**L2**	DCE	57
12	Pd(OTf)$_2$	Cs$_2$CO$_3$	**L3**	DCE	84
13	Pd(OTf)$_2$	Cs$_2$CO$_3$	**L4**	DCE	39
14	Pd(OTf)$_2$	Cs$_2$CO$_3$	**L5**	DCE	42
15	Pd(OTf)$_2$	K$_2$CO$_3$	**L3**	DCE	39
16	Pd(OTf)$_2$	^{t}BuOK	**L3**	DCE	51
17	Pd(OTf)$_2$	K$_3$PO$_4$	**L3**	DCE	44
18	Pd(OTf)$_2$	DABCO	**L3**	DCE	27
19	Pd(OTf)$_2$	Et$_3$N	**L3**	DCE	40
20[c]	Pd(OTf)$_2$	Cs$_2$CO$_3$	**L3**	DCE	66

DCE = 1, 2-dichloroethane; MeCN = acetonitrile.

[a] Standard conditions: **1a** (0.2 mmol), [Pd] catalyst (5 mmol%), ligand (10 mmol%) *tert*–butylisocyanide **2a** (4.0 equiv.), Cs$_2$CO$_3$ (3.0 equiv.), N$_2$, 90 °C, in 2 mL solvent were stirred for overnight.

[b] Isolated yield based on **1a**.

[c] 3.0 equiv. of isocyanide is used.

imidoylation is prior to the direct addition into alkyne, thus offering imidoylpalladium species **A**. A 5-*exo-dig* cyclization happed to the resulting imidoylpalladium species **A**, with the formation of acenaphthylene-containing intermediate **B**. The intermediate **B** converted into intermediate **C** through another imidoylation. It is supposed that the addition of the resulting intermediate **C** into imino bond is of high importance to form pyrrole ring. According to the results from Tsukada in 2009 [29] and our findings in 2020 [32], it seems reliable that organopalladium species added into intramolecular imino bonds. Supposing the intermediate **D** was formed, isomerization and protonation finally provided the products **3**.

Initially, the reaction of 1-alkynyl-8-iodonaphthalene **1a** and *tert*–butyl isocyanides **2a** was employed as a model reaction. A preliminary result showed that the use of 5 mol% Pd(PPh$_3$)$_4$ in toluene enabled the aforementioned formal [2 + 2 + 1] cyclization to deliver 7*H*-acenaphtho[1,2-*b*]pyrrole **3a** in 73% isolated yield, and delightfully, the by-products, which was probably derived from intermediate **B** and **C**, were not observed. Encouraged by these positive results, other result-affecting factors including solvent, palladium source, base, ligand, and loading of substrate *etc.* were explored accordingly. The results were presented in Table 1.

Initial trials were focused on screening various solvents. As presented in Table 1, DCE was the best choice due to higher safety score [50], although leading to the desired 7*H*-acenaphtho[1,2-*b*]pyrrole **3a** in a similar yield (entry 3) to that of the reaction in toluene (entry 1). The use of other solvents did not give rise to better outcomes (entries 4 and 5).

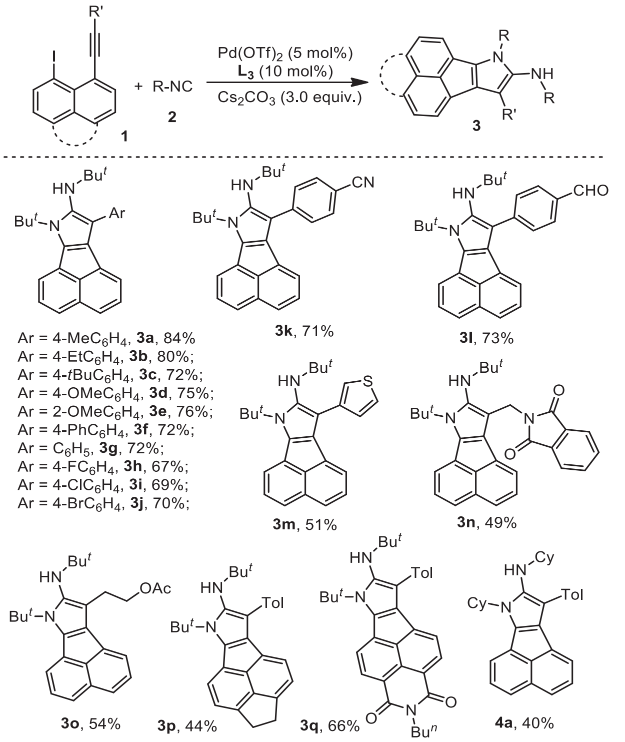
Then, the effect of palladium catalyst was also explored accordingly. From the results, the use of Pd(OTf)$_2$ improved the reaction efficiency, leading to the desired product **3a** in 79% yield (entry 7). To further improve reaction efficiency, the ligand effect was also examined. Pleasingly, the use of dicarbonyl *O,O*-ligand **L**$_3$ enabled the reaction yield to be increased to 84% (entry 12). Other monophosphine ligands and biphosphine ligands did not enhance the reaction yields. Various bases were also screened. From the results, the reactions using other bases including K$_2$CO$_3$, *t*BuOK, K$_3$PO$_4$, DABCO and Et$_3$N provided inferior results (entries 15–19). The decrease of isocyanides to 3.0 equiv. suppressed the reaction, leading to the final product **3a** in 66% yield (entry 20). Increase of isocyanide loading or palladium catalyst loading did not make significant impact on the reaction efficiency.

With the optimized conditions (entry 12, Table 1) in hand, we then explored the generality of our method. The results were illustrated in Scheme 2. From the results, an array of 7*H*-acenaphtho[1,2-*b*]pyrrole **3** was achieved in moderate to good yields accordingly. For example, the reaction of 1-(4-methoxylphenylalkynyl)-8-iodonaphthalene **1d** under standard conditions provided the corresponding product **3d** in 75% yield, while the reaction of steric substrate **1e** 1-(2-methoxylphenylalkynl)-8-iodonaphthalene gave rise to corresponding product **3e** in a similar yield. Particularly, the sensitive groups such as chloro, bromo, and aldehyde were survived in the reaction, and the corresponding products **3i**, **3j**, and **3l** were obtained in 69%, 70%, and 73% yields, respectively.

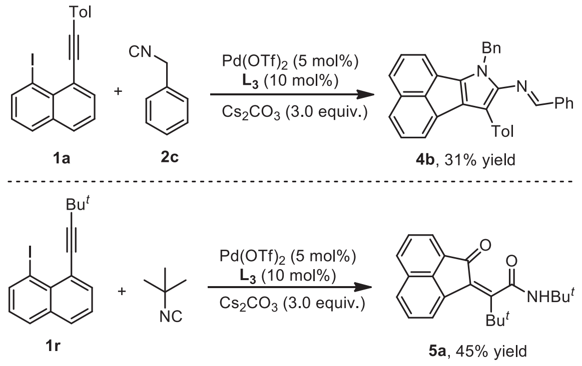
From the results noted in Scheme 2, the heteocyclic alkyne-connected substrates were compatible for the reactions. For instance, the reaction of 1-(2-thiophenylalkynl)-8-iodonaphthalene **1m** under standard conditions provided the corresponding product **3m** in 51% yield as expected. Moreover, the substrates with alkyl-linked alkynes were also efficient reaction partners. The reactions of **1n** and **1o** offered the expected products **3n** and **1o** in moderate yields.

Interestingly, substituted 1-ethynyl-8-iodonaphthalenes **1p** and **1q** were good reaction partners. The reactions of **1p** and **1q** gave rise to the corresponding multi-cyclic products **3p** and **3q** in 44% and 66% yields, respectively.

Subsequently, various isocyanides were also screened accordingly. As presented in Scheme 2, the reactions of 1-ethynyl-8-iodonaphthalene **1a** and cyclohexyl isocyanide **2b** proceeded



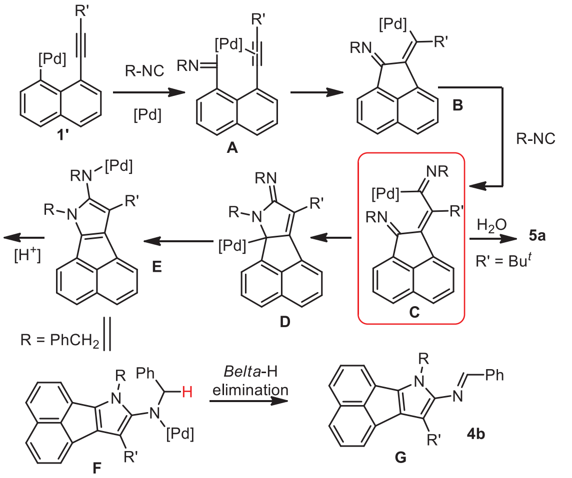
Scheme 2. Generation of **3** through the reaction of [2 + 2 + 1] cyclization of 1-ethynyl-8-iodonaphthalene and isocyanides. Reaction conditions: 1-ethynyl-8-iodonaphthalene **1** (0.2 mmol), $Pd(OTf)_2$ (5 mol%), isocyanides (4.0 equiv.), Cs_2CO_3 (3.0 equiv.), DCE (2 mL), 90 °C, overnight. Isolated yields based on 1-ethynyl-8-iodonaphthalene **1**.



Scheme 3. Generation of **4b** and **5a** through the reaction of [2 + 2 + 1] cyclization of 1-ethynyl-8-iodonaphthalene and isocyanides. Reaction conditions: 1-ethynyl-8-iodonaphthalene **1** (0.2 mmol), $Pd(OTf)_2$ (5 mol%), isocyanides (4.0 equiv.), DCE (2 mL), 90 °C, overnight. Isolated yields based on 1-ethynyl-8-iodonaphthalene **1**.

smoothly, resulting in a desired product **4a** in 40% yield. To our surprise, the reaction of benzyl isocyanide **2c** produced an unexpected product **4b** (Scheme 3). Compared to the structure of product **4a**, the product **4b** was generated through a de-hydrogenation process. This information probably provided a hint on the reaction mechanism.

In particular, the reaction of 1-(*tert*–butylalkynyl)-8-iodonaphthalene **1r** under standard conditions did not offer the desired product, but form acenaphthylenone **5a** in 45% yield (Scheme 3). It is reasoned that carbonyl group in product **5a** was ascribed to hydrolysis of *tert*–butylimido group, and the product **5a** was probably attributed to reductive elimination of the acenaphthylene-containing imidoylpalladium intermediate **C** (noted in Scheme 1) with H_2O.



Scheme 4. Plausible mechanism.

To improve the practicality of this [2 + 2 + 1] cyclization, a millimole scale reaction of **1a** (1 mmol) and *tert*–butylisocyanide (4 mmol) was carried out, and 247.6 mg of the desired product **3a** was obtained in 78% yield.

Considering the fluorescent properties of this skeleton, the photophysical properties of products **3a**, **3p** and **3q** were investigated. The UV–vis absorption spectra and fluorescence emission spectra of these compounds were measured in EtOH (0.1 mmol/L) (Fig. S1 in Supporting information). Although **3a** showed relatively weak fluorescence emission at about 590 nm, **3p** and **3q** showed strong fluorescence emission at about 590 nm and 530 nm, respectively.

In light of the aforementioned results and our previous findings, a plausible mechanism was proposed in Scheme 4. As illustrated in Scheme 4, a formal [2 + 2 + 1] cyclization of 1-ethynyl-8-iodonaphthalene and isocyanides was triggered by oxidative addition of Pd species into C-I bonds. Followed by the first imidoylation, the 1-alkynylnanaphthalene-containing palladium species **1′** converted into an imidoylpalladium species **A**. It is noteworthy that the formation of the intermediate **A** was ascribed to the priority of imidoylation of **1′** to direct addition into alkyne. A sequential *cis*-addition of the intermediate A into intramolecular triple bond released an acenaphthylene-containing vinylpalladium intermediate **B**. The second imidoylation happened to the intermediate **B** with the formation of acenaphthylene-containing imidoylpalladium intermediate **C**. It is believed that the intermediate **C** was a key intermediate in the reaction which enabled the divergent synthesis as noted in Schemes 2 and 3. When *tert*–butyl–linked substrate **1r** was used, the intermediate underwent a reductive elimination with H_2O, probably due to steric hinderance, to produce a distinctive product **5a**.

Otherwise, the intermediate **C** went through an addition into intramolecular imino group to form an intermediate **D**. Followed by isomerization, the intermediate **D** converted into intermediate **E**. Protonation of the intermediate **E** finally provided the desired products **3**. Supposing R group in intermediate **E** was a benzyl group, a β-hydride elimination tool place to release **4b**.

In conclusion, we have developed a palladium-catalyzed formal [2 + 2 + 1] cyclization of 1-ethynyl-8-iodonaphthalenes with double isocyanides. The transformation worked well to produce a series of 7*H*-acenaphtho[1,2-*b*]pyrroles with high efficiency and a broad reaction scope. It is noteworthy that isocyanides play a dual role in the reaction. One serves as C1 sources, and another is used as C1N1 building blocks. The use of isocyanides as C1N1 building blocks or π-component is ongoing in our lab, and the results will be reported in due course.

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.

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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.2022.02.028.

References

[1] J. Collet, T. Roose, E. Ruijter, et al., Angew. Chem. Int. Ed. 59 (2020) 540–558.
[2] Z. Gu, S. Ji, Acta Chim. Sin. 76 (2018) 347–356.
[3] L. Ackermann, Acc. Chem. Res. 53 (2020) 84–104.
[4] N. Liu, L. Zhou, Z. Wu, Acc. Chem. Res. 54 (2021) 3953–3967.
[5] C. Caboon, C. Bielawski, Coord. Chem. Rev. 374 (2018) 261–278.
[6] J. Wang, D. Li, Q. Zhu, Org. Biomol. Chem. 19 (2021) 6730–6745.
[7] J. Collet, T. Roose, B. Weijers, et al., Molecules 25 (2020) 4906–4958.
[8] S. Shaifali, P. Das, Chem. Rec. (2021), doi:10.1002/tcr.202100157.
[9] Y. Shi, C. Xia, Y. Huang, Chem. Asian J. 16 (2021) 2830–2841.
[10] P. Das, B. Bhanage, Adv. Synth. Catal. 362 (2020) 3022–3058.
[11] Z. Yin, J. Xu, X.F. Wu, ACS. Catal. 10 (2020) 6510–6531.
[12] B. Song, B. Xu, Chem. Soc. Rev. 46 (2017) 1103–1123.
[13] J. Lei, J. Huang, Q. Zhu, Org. Biomol. Chem. 14 (2016) 2593–2602.
[14] B. Zhang, A. Studer, Chem. Soc. Rev. 44 (2015) 3505–3521.
[15] Y. Liu, S.J. Li, X.L. Chen, et al., Adv. Synth. Catal. 362 (2020) 688–694.
[16] G. Gomes, Y. Loginova, S. Vatsadze, et al., J. Am. Chem. Soc. 140 (2018) 14272–14288.
[17] T. Mitamura, K. Iwata, A. Ogawa, J. Org. Chem. 76 (2011) 3880–3887.
[18] S. Chen, M. Oliva, L. Van Meervelt, et al., Adv. Synth. Catal. 363 (2020) 3220–3226.
[19] La-ongthong Kannika, P. Naweephattana, O. Khaikate, et al., J. Org. Chem. 85 (2020) 6338–6351.
[20] O. Khaikate, D. Soorukram, P. Leowanawat, et al., Eur. J. Org. Chem. 2019 (2019) 7050–7057.
[21] Y. Zhang, Y. Jin, Y. Wang, et al., Green Chem. 23 (2021) 6926–6930.
[22] Y. Liu, J.L. Li, X.G. Liu, et al., Org. Lett. 23 (2021) 1891–1897.
[23] Y. Liu, X.L. Chen, X.Y. Li, et al., J. Am. Chem. Soc. 143 (2021) 964–972.
[24] Y. Yuan, S.Y. Zhang, W.H. Dong, et al., Adv. Synth. Catal. 363 (2021) 4216–4221.
[25] C. Tran, S.I. Kawaguchi, F. Sato, et al., J. Org. Chem. 85 (2020) 7258–7266.
[26] Y. Liu, X.L. Chen, F.L. Zeng, et al., J. Org. Chem. 83 (2018) 11727–11735.
[27] X. Sun, W. Wang, Y. Li, et al., Org. Lett. 18 (2016) 4638–4641.
[28] X. Sun, W. Wang, M. Jia, et al., Acta Chim. Sin. 75 (2017) 115–118.
[29] N. Tsukada, M. Wada, N. Takahashi, et al., J. Organometallic Chem. 694 (2009) 1333–1338.
[30] G. Qiu, Q. Wang, J. Zhu, Org. Lett. 19 (2017) 270–273.
[31] J. Peng, Y. Gao, W. Hu, et al., Org. Lett. 18 (2016) 5924–5927.
[32] K. Huang, J.B. Liu, Z. Chen, et al., Org. Lett. 22 (2020) 5931–5935.
[33] Y. Zhang, W. Lai, L. Zhang, et al., Org. Biomol. Chem. 19 (2021) 1827–1834.
[34] K. Majeed, B. Liu, F. Zhou, et al., Synthesis (Mass) 53 (2021) 2103–2113.
[35] Y.C. Hsieh, T.C. Wu, J.Y. Li, et al., Org. Lett. 18 (2016) 1868–1871.
[36] J. Wallbaum, R. Neufeld, D. Stalke, et al., Angew Chem. Int. Ed. 52 (2013) 13243–13246.
[37] G.Y. Zhu, T.Y. Zhai, X. Li, et al., Org. Lett. 23 (2021) 8067–8071.
[38] P. Smith, Y. Jiang, Z. Tang, et al., Org. Lett. 23 (2021) 6547–6552.
[39] D. Campeau, A. Pommainville, F. Gagosz, J. Am. Chem. Soc. 143 (2021) 9601–9611.
[40] Y. Zhou, L. Zhou, L. Jesikiewicz, et al., J. Am. Chem. Soc. 142 (2020) 9908–9914.
[41] Y. Shan, L. Su, D. Chen, et al., Chin. Chem. Lett. 32 (2021) 437–440.
[42] K. Zhou, J. Huang, J. Wu, et al., Chin. Chem. Lett. 32 (2021) 37–39.
[43] D. Chen, M. Yang, J. Li, P. Cui, et al., J. Org. Chem. 85 (2020) 6441–6449.
[44] X. Chen, G. Qiu, R. Liu, et al., Org. Chem. Front. 7 (2020) 890–895.
[45] D. Chen, Y. Shan, J. Li, et al., Org. Lett. 21 (2019) 4044–4048.
[46] Y. Wu, J.Y. Chen, J. Ning, et al., Green Chem. 23 (2021) 3950–3954.
[47] Q.W. Gui, F. Teng, Z.C. Lia, et al., Chin. Chem. Lett. 32 (2021) 1907–1910.
[48] J. Jiang, Z. Wang, W.M. He, Chin. Chem. Lett. 32 (2021) 1591–1592.
[49] W.B. He, L.Q. Gao, X.J. Chen, et al., Chin. Chem. Lett. 31 (2020) 1895–1898.
[50] D. Prat, A. Wells, J. Hayler, et al., Green. Chem. 18 (2016) 288–296.