


 Cite this: *RSC Adv.*, 2023, **13**, 18160

K₂CO₃-promoted synthesis of amides from 1-aryl-2,2,2-trifluoroethanones and amines under mild conditions†

 Pinyong Zhong,^a Yu-Chao Wang,^a Jin-Biao Liu,^b Linjun Zhang^{*b} and Nianhua Luo^{*c}

 Received 19th May 2023
 Accepted 10th June 2023

DOI: 10.1039/d3ra03329e

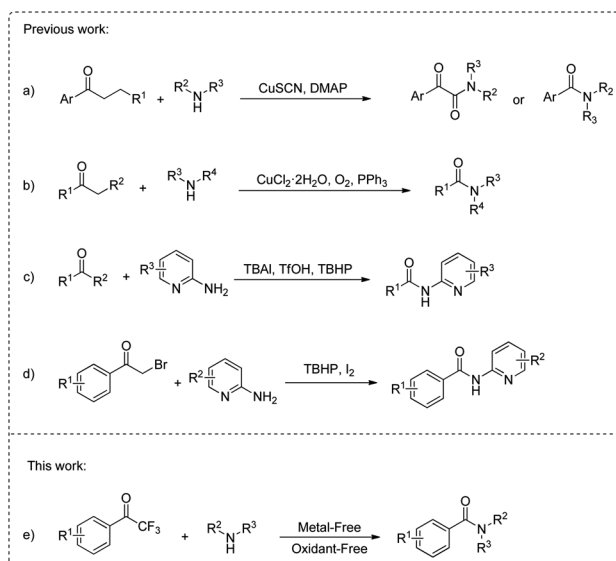
rsc.li/rsc-advances

A base-promoted amidation of 1-aryl-2,2,2-trifluoroethanones with amines *via* Haller–Bauer reaction has been developed. In this reaction, the direct transformation of 1-aryl-2,2,2-trifluoroethanones into amides *via* C(O)–C bond cleavage occurs without the use of any stoichiometric chemical oxidants or transition-metal catalysts. A series of primary and secondary amines are shown to be compatible with this transformation, and several pharmaceutical molecules were synthesized.

The introduction of amide bonds is one of the most important research topics in organic chemistry,^{1–5} as amides not only play an irreplaceable role in life, but also exist in a large number of drug molecules,⁶ materials⁷ and organic catalysts.⁸ In fact, *ca.* 25% of medicines are reported to contain amide bonds.⁹ The coupling of amines with pre-activated carboxylic acids or carboxylic acid derivatives (esters, aldehydes, acyl halides and acid anhydrides) is an effective method for constructing amide bonds.^{10–18} In recent years, alcohols,^{19–21} olefins,^{22–25} and alkynes^{26–28} have also been used as carboxylic acid substitutes to synthesize amides.

The carbon–carbon (C–C) bond is fundamental in organic compounds and has excellent stability.^{29–37} Developing new methods for constructing C–N bonds *via* C–C bond cleavage is attractive and challenging.³⁸ Recently, several examples of constructing amides *via* copper catalyzed cleavage of C(O)–C bonds of ketones have been reported.^{39–43} In 2017, Liu *et al.*⁴⁴ reported for the first time that the chemoselectivity C(α)–C(β) bond cleavage of saturated aryl ketones using copper catalyst led to α -ketoamides (Scheme 1a). Subsequently, Yang *et al.*⁴⁵ also revealed the strategy of copper-catalyzed aerobic oxidation C–C bond cleavage of simple ketones for the synthesized amides (Scheme 1b). However, the residue of transition-metal catalysts cannot be tolerated in some fields (such as pharmaceuticals). The method of constructing C–N bonds by activating C(O)–C

bonds without metal catalysis has also been reported.^{46–50} In 2018, Xu and co-workers⁵¹ reported a TBHP/TBAL-mediated method for the direct oxidative of ketones and 2-aminopyridine to synthesize *N*-(pyridine-2-yl)amides (Scheme 1c). Subsequently, a method for selective synthesis of *N*-(pyridine-2-yl)amides from α -bromoketones and 2-aminopyridine was also developed (Scheme 1d).⁵² Although these methods are effective and well examined, there are also some limitations: amines are



Scheme 1 The formation of amide bond *via* C–C bond cleavage. (a) Using simple ketones and aliphatic amines. (b) Using simple ketones and amines. (c) Using heterocyclic amines. (d) Using α -bromoketones and 2-aminopyridines. (e) Using 1-aryl-2,2,2-trifluoroethanones and amines.

^aJiangxi Provincial Key Laboratory of Functional Molecular Materials Chemistry, Jiangxi University of Science and Technology, Ganzhou 341000, China. E-mail: liujinbiao@jxust.edu.cn

^bJiangxi Province Zhonggantou Survey and Design Co., Ltd., Nanchang 330029, China. E-mail: zhanglinjun2022@163.com

^cSchool of Pharmaceutical Sciences, Gannan Medical University, Ganzhou 341000, China. E-mail: luoxiaoge102@163.com

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3ra03329e>



limited to the heterocyclic amines; using oxidants and additional additives.

Trifluoromethyl ketone, as an organofluorine compound, plays an important role in drug design and development.⁵³ In 2022, Huang *et al.*⁵⁴ conducted research on the reactivity of aryl perfluoroalkyl ketones, demonstrating that electron-deficient perfluoroalkyl groups possess the capability to function as formal leaving groups.

The base-induced cleavage of non-enolizable ketones leading to a carboxylic acid derivative and a neutral fragment in which the carbonyl group is replaced by a hydrogen is referred to as the Haller–Bauer (HB) reaction.⁵⁵ However, to the best of our knowledge, there have been no reports on the preparation of amides using 1-aryl-2,2,2-trifluoroethanones under mild conditions. Based on our group's research on amide bonds,^{56–59} we report the activation of the C(O)–C bond of 1-aryl-2,2,2-trifluoroethanones, using amine as the N source to construct amides (Scheme 1e). This method does not require the use of transition-metal catalysts and additional oxidants, providing a convenient approach to C–N bond construction.

Initially, 2,2,2-trifluoro-1-phenylethanone (**1a**) and ethylamine (**2a**) were selected as model substrates, and to our delight, when they were treated in a reaction system containing KOH in acetonitrile at 40 °C, *N*-ethylbenzamide (**3a**) was obtained in 13% yield (Table 1, entry 1). Subsequently, several solvents were screened and the results showed that DMSO was the best solvent, with a yield of 90% for **3a** (Table 1, entry 6). It is worth noting that increasing the temperature does not improve

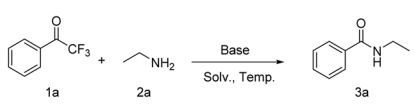
the reaction efficiency, but reducing the temperature from 40 °C to room temperature only provides 20% of the product **3a** (Table 1, entry 7–11). Subsequently, various bases including K₂CO₃, KHCO₃, NaHCO₃, KOAc, NaH₂PO₄, NaH, DMAP, and Et₃N, were screened (Table 1, entries 12–19), and it was found that K₂CO₃ was the most suitable base with a maximum yield of 93% (Table 1, entry 12). Furthermore, products **3a** could not be obtained without the addition of base (Table 1, entry 20). Based on the reaction parameters above, the optimal reaction conditions were obtained: **1a** (0.2 mmol), **2a** (0.24 mmol), K₂CO₃ (0.4 mmol) in DMSO (2 mL) at 40 °C for 2 h.

With the optimized conditions in hand, we investigated the substrate scope of this transformation using a series of trifluoroacetophenones and amines (Table 2). We first explored various aryl trifluoroacetophenones with different substituents. Excitingly, regardless of whether the aryl ring of the aryl trifluoroacetophenone contained electron-donating substituents (–Me, –OMe) or electron-withdrawing substituents (–F, –Br), it could be converted into the desired products with satisfactory yields (**3b–3f**). Additionally, disubstituted aryl trifluoroacetophenone was also tolerated in this reaction (product **3g**). Subsequently, various amines were utilized to further explore the scope of reactions. Ethylamine containing halogen substituents was compatible with this reaction (product **3h**). To our delight, ethylenediamine can produce the desired product **3i** in moderate yield. Anilines were also tolerated in this reaction. Aniline derivatives with strong electron-withdrawing substituent (such as –NO₂) or electron-donating substituent (such as –OMe) were capable of producing both the desired products (**3k** and **3l**) in moderate yields. Benzylamine derivatives with either electron-donating or electron-withdrawing substituents could also give the desired product with high yields (**3m–3q**). Secondary amines were also compatible with this scheme (product **3r**). As privileged scaffolds in drugs, the derivatization of nitrogen heterocycles has received widespread research attention. Interestingly, tetrahydropyrrole, piperidine, and morpholine were also tolerated in this scheme, obtaining the required amides with yields of 81–90% (**3s–3u**). More encouragingly, amino acid derivatives could also survive the process after the reaction temperature was raised to 70 °C and deliver the desired products with yields 51% (**3v**) and 81% (**3x**), respectively. These results indicate that this strategy of C–N bond construction has potential for late-stage functionalization of bioactive molecules. Nevertheless, both amide and trifluoromethyl alkyl ketone were not suitable for this reaction.

To demonstrate the utility of this strategy, we attempted to apply it to the synthesis of two pharmaceutical molecules (Scheme 2). Procainamide and moclobemide were obtained in yields of 72% and 89%, respectively.

To shed light on the mechanism of the reaction, we conducted several control experiments. When aniline was used as the substrate, benzoic acid was detected (Scheme 3a). However, under standard conditions, benzoic acid could not produce *N*-phenylbenzamide (Scheme 3b), indicating that it is a byproduct of amide formation. This result also suggests that this reaction may have undergone the HB reaction process. We then attempted to use benzaldehyde and acetophenone instead of

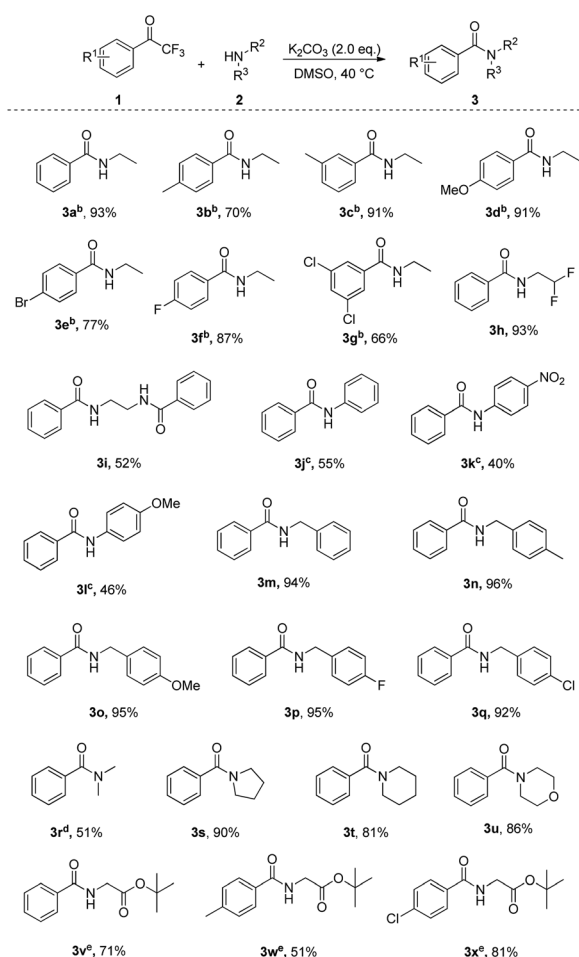
Table 1 Optimization of the reaction conditions^a



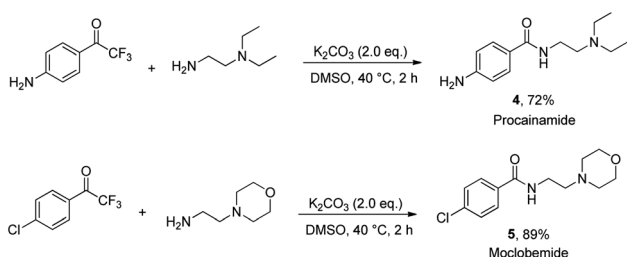
Entry	Base	Solvent	Temp./°C	Yield of 3a ^b
1	KOH	CH ₃ CN	40	13%
2	KOH	DMF	40	82%
3	KOH	THF	40	0%
4	KOH	EtOH	40	0%
5	KOH	H ₂ O	40	0%
6	KOH	DMSO	40	90%
7	KOH	DMSO	R.T	20%
8	KOH	DMSO	60	85%
9	KOH	DMSO	80	84%
10	KOH	DMSO	100	85%
11	KOH	DMSO	120	86%
12	K ₂ CO ₃	DMSO	40	93%
13	KHCO ₃	DMSO	40	41%
14	NaHCO ₃	DMSO	40	39%
15	KOAc	DMSO	40	34%
16	NaH ₂ PO ₄	DMSO	40	0%
17	NaH	DMSO	40	60%
18	DMAP	DMSO	40	0%
19	Et ₃ N	DMSO	40	0%
20	—	DMSO	40	0%

^a Reaction conditions: **1a** (0.2 mmol), **2a** (70% in water, 0.24 mmol), base (2.0 eq.), solvent (2.0 mL), air, 2 h. ^b Isolated yield based on **1a**.



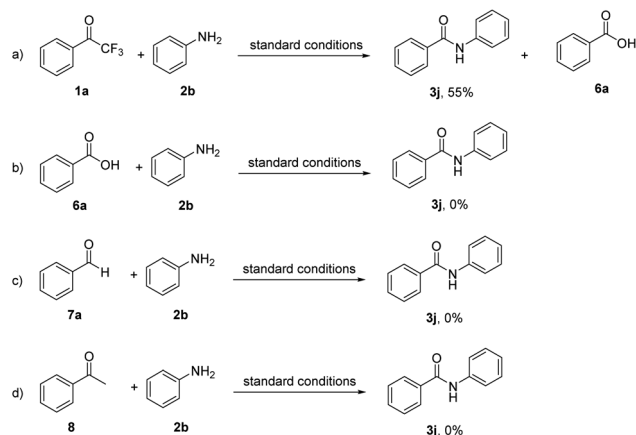
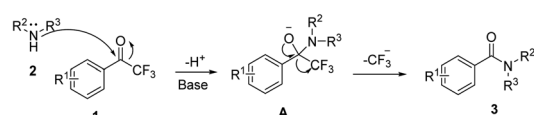
Table 2 Reaction scope^a

^a Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), K₂CO₃ (2.0 eq.) DMSO (2.0 mL), air, 40 °C, 2 h. ^b Ethylamine (70% in water). ^c Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), K₂CO₃ (2.0 eq.) DMSO (2.0 mL), air, 40 °C, 4 h. ^d Dimethylamine (40% in water). ^e Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), K₂CO₃ (3.0 eq.) DMSO (2.0 mL), air, 70 °C, 4 h.



Scheme 2 Synthetic of pharmaceutical molecules.

aniline as substrates to react under standard conditions, but did not obtain the desired product **3j** (Scheme 3c and d). These results indicate that neither benzaldehyde nor acetophenone are potential intermediates in this transformation.

Scheme 3 Control experiments.. (a) Identification of byproducts. (b) Using **6a** instead of **1a**. (c) Using **7a** instead of **1a**. (d) Using **8** instead of **1a**.

Scheme 4 A possible mechanism.

Based on the experimental results described above and previous literature,⁶⁰ a possible reaction mechanism for this transformation has been proposed in Scheme 4. Initially, the 1-aryl-2,2,2-trifluoroethanones (**1**) was attacked by the amine (**2**) under the promotion of base, leading to the formation of the intermediate **A**. Then the amide **3** was obtained *via* the electron transfer and C-C bond cleavage of intermediate **A**.

In summary, we have developed a mild and efficient methodology for the cleavage of C(O)-C bonds for the synthesis of amides. This reaction can tolerate multiple primary and secondary amines, with yields ranging from moderate to good. This strategy enriches the substrate scope for constructing amides through C-C bond cleavage. The mild reaction conditions and simple operation process do not require the use of transition-metal catalysts or additional oxidants, making this protocol highly suitable for broad synthetic applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was funded by the National Natural Science Foundation of China (21961014), the Jiangxi Provincial Key Laboratory of Functional Molecular Materials Chemistry (2021BCD42018), the Postdoctoral Merit Program of Jiangxi Province (2021KY21), and the Jinggang Scholars Program in Jiangxi Province.



Notes and references

- R. M. de Figueiredo, J. Suppo and J. Campagne, *Chem. Rev.*, 2016, **116**, 12029–12122.
- C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **4**, 345–3415.
- V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471–479.
- L. Jiang-Sheng, X. Xie, S. Jiang, Y. Pan-Pan, L. Zhi-Wei, L. Cui-Hong and L. Wei-Dong, *Org. Chem. Front.*, 2021, **8**, 697–701.
- X. C. Wang, L. Li, Z. J. Quan, H. P. Gong, H. L. Ye and X. F. Cao, *Chin. Chem. Lett.*, 2009, **20**, 651–655.
- F. Hamilton and A. MacGowan, *Nat. Microbiol.*, 2019, **4**, 1604–1605.
- S. Han and J. Wu, *Biomacromolecules*, 2022, **23**, 1892–1919.
- F. Bourgeois, J. A. Medlock, W. Bonrath and C. Sparr, *Org. Lett.*, 2020, **22**, 110–115.
- A. K. Ghose, V. N. Viswanadhan and J. J. Wendoloski, *J. Comb. Chem.*, 1999, **1**, 55–68.
- Z. Fu, X. Wang, S. Tao, Q. Bu, D. Wei and N. Liu, *J. Org. Chem.*, 2021, **86**, 2339–2358.
- G. N. Papadopoulos and C. G. Kokotos, *J. Org. Chem.*, 2016, **81**, 7023–7028.
- T. W. Bousfield, K. P. R. Pearce, S. B. Nyamini, A. Angelis-Dimakis and J. E. Camp, *Green Chem.*, 2019, **21**, 3675–3681.
- Y. Li, L. Ma, F. Jia and Z. Li, *J. Org. Chem.*, 2013, **78**, 5638–5646.
- S. Jamalifard, J. Mokhtari and Z. Mirjafary, *RSC Adv.*, 2019, **9**, 22749–22754.
- S. A. Rzhveskiy, A. A. Ageshina, G. A. Chesnokov, P. S. Gribov, M. A. Topchiy, M. S. Nechaev and A. F. Asachenko, *RSC Adv.*, 2019, **9**, 1536–1540.
- X. Xu, A. Amuti and A. Wusiman, *Adv. Synth. Catal.*, 2020, **362**, 5002–5008.
- N. Iqbal and E. J. Cho, *J. Org. Chem.*, 2016, **81**, 1905–1911.
- B. K. Zambroń, S. R. Dubbaka, D. Marković, E. Moreno-Clavijo and P. Vogel, *Org. Lett.*, 2013, **15**, 2550–2553.
- L. Bao, B. Zhang, Z. Wang and X. Chen, *Org. Chem. Front.*, 2023, **10**, 1375–1379.
- L. U. Nordstrom, H. Vogt and R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672–17673.
- Y. Zheng, X. Nie, Y. Long, L. Ji, H. Fu, X. Zheng, H. Chen and R. Li, *Chem. Commun.*, 2019, **55**, 12384–12387.
- Y. Yu, Y. Yuan and K. Ye, *Chem. Commun.*, 2023, **59**, 422–425.
- M. Maraswami, J. Goh and T. Loh, *Org. Lett.*, 2020, **22**, 9724–9728.
- S. Liu and M. Klusmann, *Chem. Commun.*, 2020, **56**, 1557–1560.
- Y. Guan, X. Min, G. He, D. Ji, S. Guo, Y. Hu and Q. Chen, *Science*, 2021, **24**, 102969.
- A. Álvarez-Pérez, M. A. Esteruelas, S. Izquierdo, J. A. Varela and C. Saá, *Org. Lett.*, 2019, **21**, 5346–5350.
- S. Mahato, S. Santra, G. V. Zyryanov and A. Majee, *J. Org. Chem.*, 2019, **84**, 3176–3183.
- X. Ji, B. Gao, X. Zhou, Z. Liu and H. Huang, *J. Org. Chem.*, 2018, **83**, 10134–10141.
- M. Subaramanian, P. M. Ramar, J. Rana, V. K. Gupta and E. Balaraman, *Chem. Commun.*, 2020, **56**, 8143–8146.
- C. Jun, *Chem. Soc. Rev.*, 2004, **33**, 610–618.
- F. Chen, T. Wang and N. Jiao, *Chem. Rev.*, 2014, **114**, 8613–8661.
- A. Masarwa and I. Marek, *Chem. - Eur. J.*, 2010, **16**, 9712–9721.
- P. Sivaguru, Z. Wang, G. Zanoni and X. Bi, *Chem. Soc. Rev.*, 2019, **48**, 2615–2656.
- M. Murakami and N. Ishida, *Chem. Rev.*, 2021, **121**, 264–299.
- L. Deng and G. Dong, *Trends Chem.*, 2020, **2**, 183–198.
- M. D. R. Lutz and B. Morandi, *Chem. Rev.*, 2021, **121**, 300–326.
- T. Zou, Y. He, R. Liu, Y. Zhang, S. Wei, J. Lu, J. Wang, L. Wang, Q. Fu and D. Yi, *Chin. Chem. Lett.*, 2023, **34**, 107822.
- B. Das, P. R. Reddy, C. Sudhakar and M. Lingaiah, *Tetrahedron Lett.*, 2011, **52**, 3521–3522.
- W. Fan, Y. Yang, J. Lei, Q. Jiang and W. Zhou, *J. Org. Chem.*, 2015, **80**, 8782–8789.
- K. Wu, Z. Huang, Y. Ma and A. Lei, *RSC Adv.*, 2016, **6**, 24349–24352.
- N. Vodnala, R. Gujjara, C. K. Hazra, D. Kaldhi, A. K. Kabi, U. Beifuss and C. C. Malakar, *Adv. Synth. Catal.*, 2019, **361**, 135–145.
- P. Subramanian, S. Indu and K. P. Kaliappan, *Org. Lett.*, 2014, **16**, 6212–6215.
- W. Ding and Q. Song, *Org. Chem. Front.*, 2015, **2**, 765–770.
- C. Liu, Z. Yang, Y. Zeng, Z. Fang and K. Guo, *Org. Chem. Front.*, 2017, **4**, 2375–2379.
- G. Yang, K. Li, W. Liu, K. Zeng and Y. Liu, *Org. Biomol. Chem.*, 2020, **18**, 6958–6964.
- R. Ballini, G. Bosica and D. Fiorini, *Tetrahedron*, 2003, **59**, 1143–1145.
- P. Biallas, A. P. Häring and S. F. Kirsch, *Org. Biomol. Chem.*, 2017, **15**, 3184–3187.
- S. N. Rao, D. C. Mohan and S. Adimurthy, *Tetrahedron*, 2016, **72**, 4889–4894.
- R. Guo, C. Zhu, Z. Sheng, Y. Li, W. Yin and C. Chu, *Tetrahedron Lett.*, 2015, **56**, 6223–6226.
- X. Sun, M. Wang, P. Li, X. Zhang and L. Wang, *Green Chem.*, 2013, **15**, 3289.
- Y. Liu, H. Sun, Z. Huang, C. Ma, A. Lin, H. Yao, J. Xu and S. Xu, *J. Org. Chem.*, 2018, **83**, 14307–14313.
- Y. Liu, L. Lu, H. Zhou, F. Xu, C. Ma, Z. Huang, J. Xu and S. Xu, *RSC Adv.*, 2019, **9**, 34671–34676.
- X. Liu, L. Liu, T. Huang, J. Zhang, Z. Tang, C. Li and T. Chen, *Org. Lett.*, 2021, **23**, 4930–4934.
- J. Huang, X. Yan and Y. Xia, *Angew. Chem., Int. Ed.*, 2022, **134**, e202211080.
- G. Mehta and R. V. Venkateswaran, *Tetrahedron*, 2000, **56**, 1399–1422.
- J. Li, Y. Wang, H. Xie, S. Ren, J. Liu, N. Luo and G. Qiu, *Mol. Catal.*, 2021, **516**, 111993.



- 57 P. Zhong, J. Wu, J. Wu, K. Liu, C. Wan and J. Liu, *Tetrahedron Lett.*, 2022, **107**, 154099.
- 58 Y. Wang, H. Xie, K. Liu, J. Li and J. Liu, *Catalysts*, 2022, **12**, 1278.
- 59 J. B. Liu, M. Ren, X. Lai and G. Qiu, *Chem. Commun.*, 2021, 57, 4259–4262.
- 60 K. Ishihara and T. Yano, *Org. Lett.*, 2004, **6**, 1983–1986.

