RSC Advances

PAPER

View Article Online
View Journal | View Issue

Open Access Article. Published on 25 August 2022. Downloaded on 11/24/2025 12:48:09 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Check for updates

Cite this: *RSC Adv.*, 2022, **12**, 24237

$BF_3 \cdot Et_2O$-Mediated annulation of α-keto acids with aliphatic ketones for the synthesis of γ-hydroxy-butenolides and γ-alkylidene-butenolides†

Zhenfeng Cheng, Qingyun Gu, Yushan Xie, Yanan Zhang and Xiaobao Zeng *

Received 22nd July 2022
Accepted 18th August 2022

DOI: 10.1039/d2ra04546j

rsc.li/rsc-advances

Annulation reaction of α-keto acids with cyclic or acyclic aliphatic ketones is reported herein to divergently access γ-hydroxy-butenolides and γ-alkylidene-butenolides depending on the amount of $BF_3 \cdot Et_2O$. This protocol features good functional tolerance and ease of operation, to open a route to access butenolides *via* an annulation and dehydration process.

Introduction

Butenolides are privileged structures widely existing in bioactive terpene natural products. Most of them are naturally-occurring structures and display various bio-activities.[1] They are also widely used in traditional Chinese medicines to relieve cough and invigorate blood circulation.[2] For example, bioactive eudesmanolides sesquiterpene atractylenolide I, II and III isolated from dried roots are used in diverse disorders like chronic asthenia, anorexia (Fig. 1).[3] Styxlactone is a new lactone isolated from Myrmekioderma Styx.[4] To this end, ever since the initial report of morpholine promoted cyclization of cyclohexanone with 2-chloro-2-methoxyethyl acetate by Baiocchi in 1979,[5] the construction of butenolides has been of interest in the synthetic community.[6] For example, Brønsted or Lewis acids promoted annulation reaction α-keto acids with linear aliphatic ketones for the preparation of butenolides have been separately developed by several groups,[7] while the preparation of highly substituted fused butenolides from α-keto acids and aliphatic ketones has not been reported yet. Thus, developing novel approaches to divergently access γ-hydroxy-butenolides and γ-alkylidene-butenolides with commercially available starting materials and ease of operation is still desirable.

On the other hand, α-keto acids have long been serving as acylating agents to deliver a carbonyl group *via* metal or oxidant-promoted decarboxylative coupling reactions.[8] However, the annulation reactions of α-keto acids are far less studied.[9] In 2015, Zhu and coworkers[10] innovatively reported a synergistic acid promoted annulation of α-keto acid with alkenes generated from tertiary alcohols to afford highly substituted butenolides (Scheme 1a). Following the preliminary report, the annulation of α-keto acid with internal[11] or terminal alkynes[12] to afford γ-hydroxybutenolides or multiply substituted butenolides was also reported by the same group (Scheme 1b). The strategy was then extended to the annulation reaction of α-keto acids with functionalized alkynes by Wang[13] and Cui group.[14] In 2018, Fan and coworkers[15] reported an elegant synthesis of furan-2(5*H*)-one fused *N*,*O*-containing bicyclic compounds *via* the

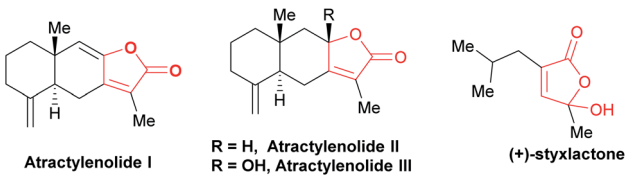
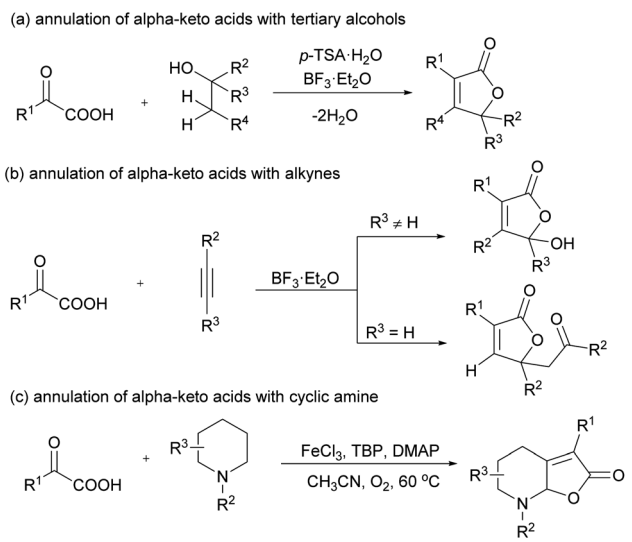


Fig. 1 Representative bioactive eremophilanolides.



Scheme 1 Previous reports in the annulation of α-keto acid.

School of Pharmacy, Nantong University, Nantong 226001, P. R. China. E-mail: zengxb@ntu.edu.cn

† Electronic supplementary information (ESI) available. CCDC 2182801. For ESI and crystallographic data in CIF or other electronic format see https://doi.org/10.1039/d2ra04546j

© 2022 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 25 August 2022. Downloaded on 11/24/2025 12:48:09 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

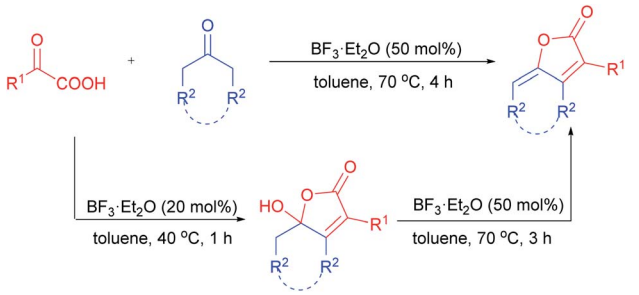
annulation reaction of *N*-aryl substituted saturated cyclic amines with α-keto acids (Scheme 1c). Despite the substantial progress achieved, the annulation with unsaturated bonds is far less than well developed.

Meanwhile, ketones are among the most readily available building blocks in organic synthesis. Great efforts have been devoted to the direct α-functionalization[16] and annulation reaction[17] of ketones by *in situ* generated enols. However, to the best of our knowledge, the simple acid-promoted annulation reaction of α-keto acid with cyclic or linear aliphatic ketones has not been explored yet. As part of our continuous effort in radical decarboxylation and annulation reaction of α-keto acid,[18] we reported herein a novel avenue to divergently access γ-hydroxy-butenolides and γ-alkylidene-butenolides *via* $BF_3 \cdot Et_2O$-catalyzed annulation of α-keto acids with aliphatic ketones (Scheme 2). Water was the only by-product generated in the transformation, thus making it a simple and efficient process for the construction of various butenolide.

Results and discussion

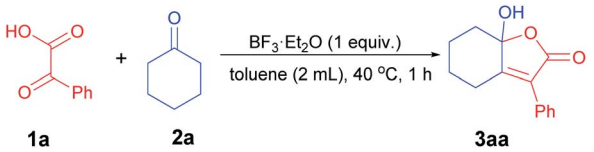
We commenced our study with **1a** (0.5 mmol) and **2a** (2.0 equiv.) as model substrates in the presence of $BF_3 \cdot Et_2O$ (1.0 equiv.) as catalyst in toluene at 40 °C, **3aa** was obtained in 70% yield (Table 1, entry 1). Inspired by the preliminary results, the effects of different catalysts were first investigated. The utilization of other Lewis acids such as $FeCl_3$ and $Bi(OTf)_3$ led to the decrease in the yield (entries 2 and 3), while product **3aa** could not be detected with *p*-TSA as catalyst (entry 4). A survey of the solvents revealed that toluene was the optimal solvent, inferior yield was obtained with MeCN, DCE, or fluorobenzene (entries 1 and 5–7). By fine-tuning the amount of $BF_3 \cdot Et_2O$, **3aa** was obtained in 86% yield (entries 8 and 9). The yield of **3aa** was decreased to 78% by lowering the ratio of **1a** : **2a** from 1 : 2 to 1 : 1.5 (entry 10). Finally, the optimal reaction conditions were deemed as entry 8 to provide product **3aa** in 86% yield after a comprehensive optimization of conditions.

Interestingly, it was found that **4aa** could be obtained in 82% yield at elevated reaction temperature by prolonging the reaction time to 4 h during the optimization process for the preparation of **3aa** (Table 2, entry 1). Then we proceeded to evaluate the effects of temperature on the reaction. The reaction was significantly affected by the temperature. A dramatic erosion in the yield of γ-alkylidene-butenolides (**4aa**) was observed when the reaction was performed at 40 °C (entry 2). Continuous increasing the temperature to 90 °C didn't improve the yield (entry 3). Then the loading of catalyst was further evaluated. A comparable yield was obtained when the loading of $BF_3 \cdot Et_2O$ was decreased to 0.5 equiv. (entry 4), however, a sharp decrease in yield was observed by lowering the loading of $BF_3 \cdot Et_2O$ to 0.2 equiv., indicating that $BF_3 \cdot Et_2O$ is crucial for the dehydration process of **3aa** to form desired product **4aa** (entry 5). Furthermore, switching to other Lewis acid provided **4aa** in decreasing yield (entries 6 and 7). The replacement of toluene with other solvents failed to improve the yield (entries 8 and 9).



Scheme 2 $BF_3 \cdot Et_2O$-catalyzed annulation of α-keto acids and aliphatic ketones.

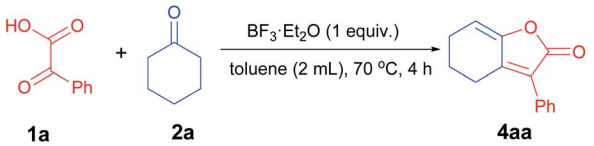
Table 1 Optimization of reaction conditions for **3aa** [a]



Entry	Variation from the standard conditions	Yield[b] (**3aa**) (%)
1	None	70
2	$FeCl_3$ instead of $BF_3 \cdot Et_2O$	45
3	$Bi(OTf)_3$ instead of $BF_3 \cdot Et_2O$	53
4	*p*-TSA instead of $BF_3 \cdot Et_2O$	n.d.
5	MeCN instead of toluene	35
6	DCE instead of toluene	46
7	Fluorobenzene instead of toluene	69
8	$BF_3 \cdot Et_2O$ (0.2 equiv.)	86
9	$BF_3 \cdot Et_2O$ (0.1 equiv.)	76
10	**1a** : **2a** = 1 : 1.5	78

[a] Standard conditions: **1a** (0.5 mmol), **2a** (2.0 equiv), $BF_3 \cdot Et_2O$ (1 equiv.), toluene (2.0 mL), 40 °C, 1 h. [b] Isolated yields.

Table 2 Optimization of reaction conditions for **4aa** [a]



Entry	Variation from the standard conditions	Yield[b] (**4aa**) (%)
1	None	82
2	40 °C instead of 70 °C	13
3	90 °C instead of 70 °C	62
4	$BF_3 \cdot Et_2O$ (0.5 equiv.)	82
5	$BF_3 \cdot Et_2O$ (0.2 equiv.)	63
6	$Sc(OTf)_3$ instead of $BF_3 \cdot Et_2O$	61
7	$AlCl_3$ instead of $BF_3 \cdot Et_2O$	55
8	Xylene instead of toluene	73
9	Chlorobenzene instead of toluene	71
10	**1a** : **2a** = 1 : 3	79

[a] Standard conditions: **1a** (0.5 mmol), **2a** (2.0 equiv.), $BF_3 \cdot Et_2O$ (1 equiv.), toluene (2.0 mL), 70 °C, 4 h. [b] Isolated yields.

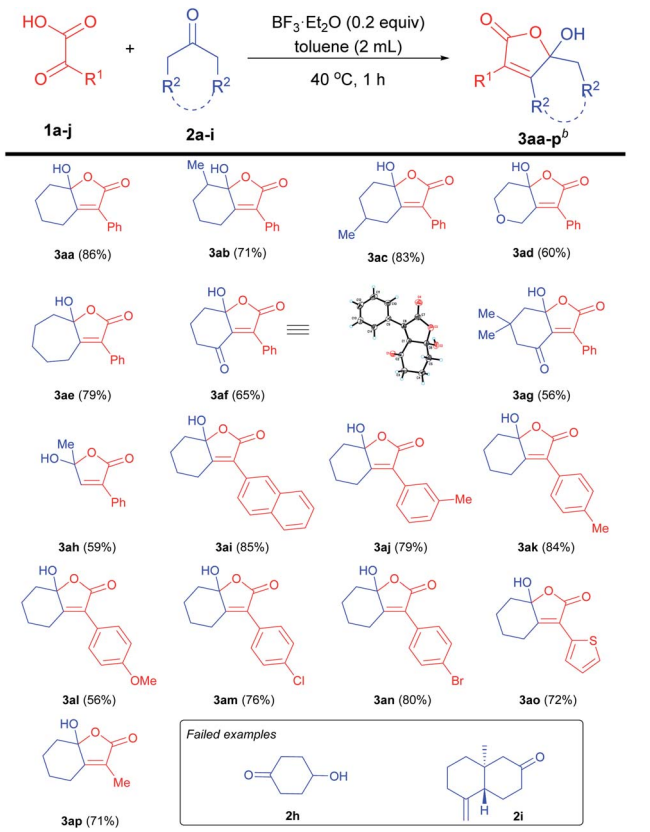
 © 2022 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 25 August 2022. Downloaded on 11/24/2025 12:48:09 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Additionally, **4aa** was afforded in a similar yield when increasing the ratio of **1a : 2a** to 1 : 3 (entry 10). Then the optimal condition for **4aa** was identified as entry 4.

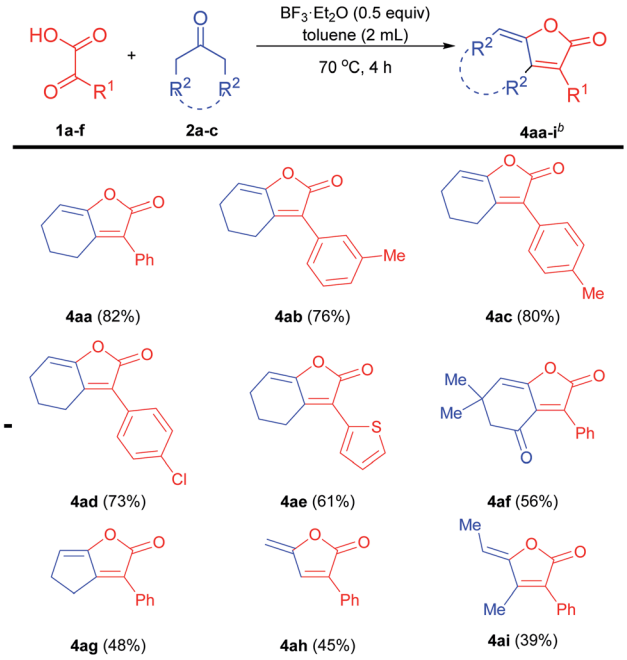
With the optimal conditions in hand, we set out to investigate the scope for the synthesis of γ-hydroxy-butenolides (**3aa–p**) (Table 3). The reaction was slightly affected by the steric hindrance of cyclohexanone, to furnish **3aa** and **3ac** with relatively higher yields than **3ab** with *ortho*-methyl substituents. Tetrahydro-4-pyrone was a suitable substrate for the reaction, to afford **3ad** with moderate yield. Additionally, seven-membered cycloheptanone proceeded well to give **3ae** in 79% yield. The reaction also tolerated 1,3-cyclohexanedione, delivering the corresponding product **3af** and **3ag** in synthetically useful yields. The structure of **3af** was unambiguously assigned by the single crystal X-ray crystallography. It was worth noting that acetone was well accommodated to afford the corresponding **3ah** in 59% yield. Encouraged by the broad generality of aliphatic ketones, we then examined the scope of α-keto acids. The reaction proceeded well when naphthenic α-keto acid was employed as the substrate to afford product **3ai** in 85% yield. Both electron-donating and withdrawing aryl substituents of α-keto acids were tolerated to give **3aj–n** in moderate to good yields. Moreover, thienyl α-keto acid reacted smoothly to deliver **3ao** in 72% yield. Notably, pyruvic acid was also compatible in this reaction, giving **3ap** in 71% yield. Disappointedly, the free hydroxyl group (**2h**) and alkenyl moiety (**2i**) could not be tolerated in the reaction.

Table 3 Substrate scope for the generation of **3aa–p** [a,b]



[a] Standard conditions: **1a** (0.5 mmol), **2a** (2.0 equiv.), $BF_3 \cdot Et_2O$ (0.2 equiv.), toluene (2.0 mL), 40 °C, 1 h. [b] Isolated yields.

Table 4 Substrate scope for the generation of **4aa–i** [a,b]

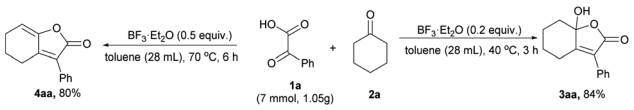


[a] Standard conditions: **1a** (0.5 mmol), **2a** (2.0 equiv.), $BF_3 \cdot Et_2O$ (0.5 equiv.), toluene (2.0 mL), 70 °C, 4 h. [b] Isolated yields.

Subsequently, the substrate scope of γ-alkylidene-butenolides **4aa–i** was examined (Table 4). The reaction worked well with aryl α-keto acids bearing methyl and chloride substituents to give **4ab–d** in good yields, indicating that the electronic properties of the phenyl ring have no obvious influence on the reaction efficiency. Significantly, α-keto acid with thienyl group was a viable substrate for the reaction to furnish **4ae** in 61% yield. In addition, both 1,3-cyclohexandione and five-membered cyclopentanone were suitable substrates to afford **4af** and **4ag** in moderate yields. It was worth mentioning that acyclic ketones such as acetone and 3-pentanone were well tolerated in the reaction to give rise to the corresponding **4ah** and **4ai** in a relatively lower yield of 45% and 39%, respectively.

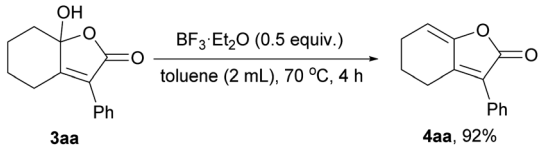
To demonstrate the practicality of this protocol, a gram-scale reaction was performed (Scheme 3). Gratifyingly, the substrates were divergently converted to **3aa** and **4aa** under standard conditions in good yields, further implying this approach's potential utility.

To delineate the mechanism, control experiment was conducted with **3aa** as substrate in the presence of excess amount

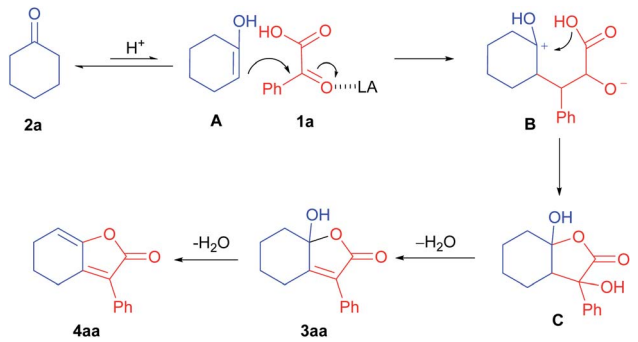


Scheme 3 Gram-scale reactions.

Open Access Article. Published on 25 August 2022. Downloaded on 11/24/2025 12:48:09 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 4 Control experiment.



Scheme 5 Plausible mechanism.

of $BF_3 \cdot Et_2O$ at 70 °C, γ-alkylidene-butenolide (**4aa**) was obtained in 92% yield, to further imply that $BF_3 \cdot Et_2O$ was crucial for the dehydration process in this transformation (Scheme 4).

Based on the results and previous reports,[10–15] we proposed a plausible pathway accounting for the formation of **3aa** and **4aa** (Scheme 5). Initially, the enolized cyclohexanone **A** from **2a** underwent nucleophilic attack with α-keto acid (**1a**) with the assistance of Lewis acid to afford intermediate **B**. The intermediate **B** was then cyclized intramolecularly to give intermediate **C**, followed by dehydration to give **3aa**. With increased amount of catalyst at elevated reaction temperature, **3aa** was able to transformed to produce **4aa** after dehydration.

Conclusions

In summary, we have developed an efficient and convenient $BF_3 \cdot Et_2O$-mediated annulation reaction of α-keto acids with aliphatic ketones to simultaneously synthesize γ-hydroxybutenolides and γ-alkylidene-butenolides. The method features good functional group tolerance and moderate to good yields, thus providing a facial and practical approach for the diversification of the library of butenolides. The application of this method for the synthesis of natural products is underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Natural Science Foundation of the Jiangsu Higher Education Institutions of China (No. 21KJB150014). The Large Instruments Open Foundation of Nantong University (No. KFJN2269). The Jiangsu College Students Innovation and Entrepreneurship Training Program (No. 202210304157Y).

Notes and references

1 (*a*) L. Wu, Z. Liao, C. Liu, H. Jia and J. Sun, *Chem. Biodiversity*, 2016, **13**, 645–671; (*b*) I. Muhammad, S. Shams ul Hassan, S. Cheung, X. Li, R. Wang, W.-D. Zhang, S.-K. Yan, Y. Zhang and H.-Z. Jin, *Fitoterapia*, 2021, **148**, 104800; (*c*) L. Li-Bin, J. Xiao, Q. Zhang, R. Han, B. Xu, S.-X. Yang, W.-B. Han, J.-J. Tang and J.-M. Gao, *J. Agric. Food Chem.*, 2021, **69**, 11878–11889; (*d*) M. Zhou, F. Duan, Y. Gao, X. Peng, X. Meng and H. Ruan, *Bioorg. Chem.*, 2021, **115**, 105247; (*e*) Z. Meng and B. Liu, *Org. Biomol. Chem.*, 2018, **16**, 957–962.

2 (*a*) W.-J. Zhang, X.-H. Li and Y.-P. Shi, *J. Nat. Prod.*, 2010, **73**, 143–146; (*b*) B. M. Fraga, *Nat. Prod. Rep.*, 2010, **27**, 1681–1708; (*c*) Q. Liu, J. H. Ahn, S. B. Kim, C. Lee, B. Y. Hwang and M. K. Lee, *Phytochemistry*, 2013, **87**, 112–118.

3 (*a*) H. Hikino, Y. Hikino and I. Yosioka, *Chem. Pharm. Bull.*, 1962, **10**, 641–642; (*b*) S. Ramesh and G. Mehta, *Tetrahedron Lett.*, 2015, **56**, 5545–5548.

4 J. Peng, S. G. Franzblau, F. Zhang and M. T. Hamann, *Tetrahedron Lett.*, 2002, **43**, 9699–9702.

5 L. Baiocchi, M. Bonanomi, M. Giannangeli and G. Picconi, *Synthesis*, 1979, 434–436.

6 (*a*) S. K. Bagal, R. M. Adlington, J. E. Baldwin, R. Marquez and A. Cowley, *Org. Lett.*, 2003, **5**, 3049–3052; (*b*) S. K. Bagal, R. M. Adlington, J. E. Baldwin and R. Marquez, *J. Org. Chem.*, 2004, **69**, 9100–9108; (*c*) P. Srinivas, D. S. Reddy, K. S. Kumar, P. K. Dubey, J. Iqbal and P. Das, *Tetrahedron Lett.*, 2008, **49**, 6084–6086; (*d*) S. Chatterjee, R. Sahoo and S. Nanda, *Org. Biomol. Chem.*, 2021, **19**, 7298–7332; (*e*) S. V. Fedoseev and M. Y. Belikov, *Chem. Heterocycl. Compd.*, 2018, **54**, 759–761.

7 (*a*) H. Wyss, L. Révész and R. Scheffold, *Helv. Chim. Acta*, 1981, **64**, 2272–2278; (*b*) Y.-H. Yang and M. Shi, *Org. Lett.*, 2006, **8**, 1709–1712; (*c*) S. D. Townsend and G. A. Sulikowski, *Org. Lett.*, 2013, **15**, 5096–5098; (*d*) A. S. Mwakaboko and B. Zwanenburg, *Eur. J. Org. Chem.*, 2016, **21**, 3495–3499; (*e*) B. Almohaywi, T. T. Yu, G. Iskander, D. S. H. Chan, K. K. K. Ho, S. Rice, D. S. Black, R. Griffith and N. Kumar, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 1054–1059.

8 (*a*) L.-N. Guo, H. Wang and X.-H. Duan, *Org. Biomol. Chem.*, 2016, **14**, 7380–7391; (*b*) F. Penteado, E. F. Lopes, D. Alves, G. Perin, R. G. Jacob and E. J. Lenardão, *Chem. Rev.*, 2019, **119**, 7113–7278.

9 (*a*) Z. He, F. Fang, J. Lv and J. Zhang, *Tetrahedron Lett.*, 2017, **58**, 1034–1036; (*b*) R. Yabe, Y. Ebe and T. Nishimura, *Chem. Commun.*, 2021, **57**, 5917–5920.

10 W. Mao and C. Zhu, *Org. Lett.*, 2015, **17**, 5710–5713.

11 W. Mao and C. Zhu, *Org. Chem. Front.*, 2017, **4**, 1029–1033.

12 W. Mao and C. Zhu, *Chem. Commun.*, 2016, **52**, 5269–5272.

13 B. Zhao, Z. Zhang, P. Li, T. Miao and L. Wang, *Org. Lett.*, 2021, **23**, 5698–5702.

 © 2022 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 25 August 2022. Downloaded on 11/24/2025 12:48:09 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

14 X. Bao, L. Zeng, J. Jin and S. Cui, *J. Org. Chem.*, 2022, **87**, 2821–2830.

15 X. Shi, Y. He, X. Zhang and X. Fan, *Adv. Synth. Catal.*, 2018, **360**, 261–266.

16 (*a*) G. A. Shevchenko, B. Oppelaar and B. List, *Angew. Chem., Int. Ed.*, 2018, **57**, 10756–10759; (*b*) I. Felker, G. Pupo, P. Kraft and B. List, *Angew. Chem., Int. Ed.*, 2015, **54**, 1960–1964; (*c*) E. A. Merritt and B. Olofsson, *Synthesis*, 2011, **2011**, 517–538; (*d*) S. Elangovan, J.-B. Sortais, M. Beller and C. Darcel, *Angew. Chem., Int. Ed.*, 2015, **54**, 14483–14486; (*e*) S. Liang, K. Xu, C.-C. Zeng, H.-Y. Tian and B.-G. Sun, *Adv. Synth. Catal.*, 2018, **360**, 4266–4292; (*f*) J. Li, Z. Yang, T. Yang, J. Yi and C. Zhou, *New J. Chem.*, 2018, **42**, 1581–1584.

17 (*a*) J.-F. Marcoux, E. G. Corley, K. Rossen, P. Pye, J. Wu, M. A. Robbins, I. W. Davies, R. D. Larsen and P. J. Reider, *Org. Lett.*, 2000, **2**, 2339–2341; (*b*) J.-F. Marcoux, F.-A. Marcotte, J. Wu, P. G. Dormer, I. W. Davies, D. Hughes and P. J. Reider, *J. Org. Chem.*, 2001, **66**, 4194–4199; (*c*) S. Agasti, T. Pal, T. K. Achar, S. Maiti, D. Pal, S. Mandal, K. Daud, G. K. Lahiri and D. Maiti, *Angew. Chem., Int. Ed.*, 2019, **58**, 11039–11043; (*d*) F. Benfatti, F. de Nanteuil and J. Waser, *Chem.–Eur. J.*, 2012, **18**, 4844–4849; (*e*) M. N. Palange, R. G. Gonnade and R. Kontham, *Org. Biomol. Chem.*, 2019, **17**, 5749–5759; (*f*) Y. Tanabe, K. Mitarai, T. Higashi, T. Misaki and Y. Nishii, *Chem. Commun.*, 2002, 2542–2543; (*g*) X. Li, Y. Wang, K. Fu, Z. Hu, Z. Li, W. Ma, M.-M. Xun and C. Yuan, *J. Heterocycl. Chem.*, 2020, **57**, 2056–2062.

18 (*a*) X. Zeng, C. Liu, W. Yang, Y. Weng, X. Wang and Y. Hu, *J. Org. Chem.*, 2019, **84**, 3656–3661; (*b*) X. Zeng, C. Liu, W. Yang, X. Wang, X. Wang and Y. Hu, *Chem. Commun.*, 2018, **54**, 9517–9520; (*c*) X. Zeng, C. Liu, X. Wang, J. Zhang, X. Wang and Y. Hu, *Org. Biomol. Chem.*, 2017, **15**, 8929–8935.