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Rh-Catalyzed cascade C–H activation/C–C cleavage/cyclization of carboxylic acids with cyclopropanols†

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Merging both C–H and C–C activation in a tandem process is a marked challenge. A novel Rh(III)-catalyzed C–H activation/ring opening C–C cleavage/cyclization of carboxylic acids with cyclopropanols was developed for the synthesis of 3-substituted phthalides and α,β-butenolides. This reaction displays excellent functional group tolerance with respect to both carboxylic acids and cyclopropanols and features relatively mild conditions. Remarkably, the utility of this method was highlighted by the rapid construction of bioactive compounds bearing a 3-substituted phthalide framework *via* late-stage functionalization.

Rh(III)-catalyzed functionalizations of a C–H bond have provided a straightforward tool for the expeditious assembly of complex molecules from simple and readily available feedstocks in the last decade.[1] On the other hand, metal-catalyzed ring opening reactions *via* C–C bond cleavage have also been identified as an efficient strategy to construct natural products.[2] Although these two significant strategies have broad applications, they almost evolved individually and their combination with each other is still in its infancy. Arguably merging both C–H and C–C activation in a tandem process would give us an ideal method to increase the structural diversities of molecules, but is a marked challenge.[3]

Three-membered cyclopropanols, a class of versatile synthetic building blocks, have attracted considerable attention for their reactivity in metal-catalyzed ring opening C–C bond cleavage with different electrophiles and nucleophiles, leading to various types of C–C or C–X bond formation (Fig. 1).[4] Despite these advantages, the substrates need prefunctionalization and transformations involving C–H coupling partners have been rarely reported. In 2016, Li and his co-workers realized an elegant Rh(III)-catalyzed oxidative coupling between arenes and cyclopropanols *via* a C–H activation/C–C cleavage process.[3c] Very recently, Shen and Han developed a Cu(II)-mediated ring opening/alkynylation of tertiary cyclopropanols with terminal alkynes.[5] Although these studies showed the advantages of step and atom economy through C–H activation, the development of a new reaction mode of cyclopropanols *via* a cascade C–H activation/C–C cleavage strategy is still difficult but is highly desirable. As part of our continuing efforts on exploring new C–H functionalizations,[6] we envisioned that carboxylic acids with cyclopropanols would be ideal substrates for a new cascade reaction mode design due to three reasons: (1) carboxylic acids and cyclopropanols are easily available and

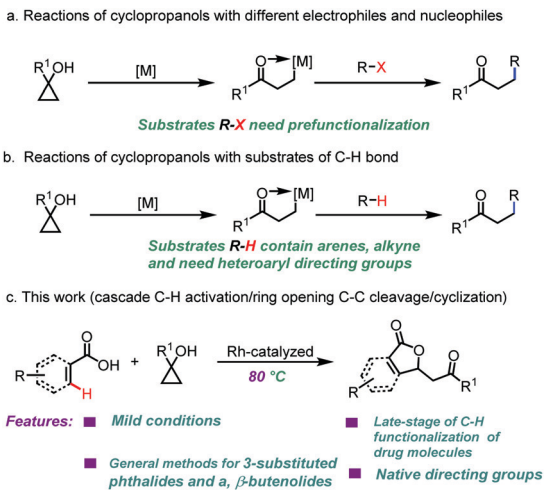

Fig. 1 Ring opening C–C cleavage reactions of cyclopronanols.

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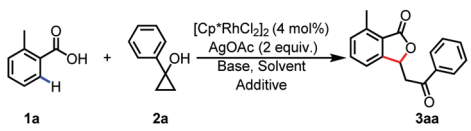
diversified; (2) cyclopropanols are prone to undergo ring opening and used as good nucleophiles; (3) if successful, this reaction would provide a powerful and general protocol for accessing 3-substituted phthalides and α,β-butenolides.[7] Notably, the phthalides and α,β-butenolides are an important class of natural heterocyclic products, which have attracted broad attention because of their various pharmacological activities.[8]

However, there is one challenging issue to be addressed in this scenario: metal-catalyzed ring opening/β-H elimination or protodemetallation or dimerization[9] of cyclopropanols might become the predominant pathway instead of cascade C–H activation/C–C cleavage. Herein, we report a Rh(III)-catalyzed cascade C–H activation/ring opening C–C bond cleavage/cyclization of carboxylic acids with cyclopropanols for the synthesis of 3-substituted phthalides and α,β-butenolides under mild conditions.

To test our hypothesis, we commenced our optimization studies by choosing *ortho*-methylbenzoic acid (**1a**) and 1-phenylcyclopropan-1-ol (**2a**) as model substrates (Table 1). When they were performed in 1,4-dioxane at 80 °C, in the presence of $[Cp^*RhCl_2]_2$/AgOAc and K_2CO_3 (0.5 equiv.) for 24 h, the desired product **3aa** was indeed obtained in 21% yield[10] (Table 1, entry 1). Notably, switching K_2CO_3 to Cs_2CO_3 and increasing the amount of Cs_2CO_3 to 1.0 equiv. provided **3aa** in 34% yield (Table 1, entry 4). Further solvent screening indicated that the yield of **3aa** could be significantly enhanced to 55% in CH_3CN (Table 1, entry 7). Considering that **2a** could undergo a ring opening/protonation to produce byproduct propiophenone; therefore, we increased the amount of **2a** to 2.5 equiv. and the yield of **3aa** was improved to 63% (Table 1, entry 8). To our delight, the Rh(III)-catalyzed C–H activation/ring opening was facilitated by adding 4 Å MS at 0.1 g $mmol^{-1}$ loading, affording **3aa** in 75% isolated yield (Table 1, entry 10). And switching Cs_2CO_3 to K_3PO_4 afforded **3aa** in 63% yield.

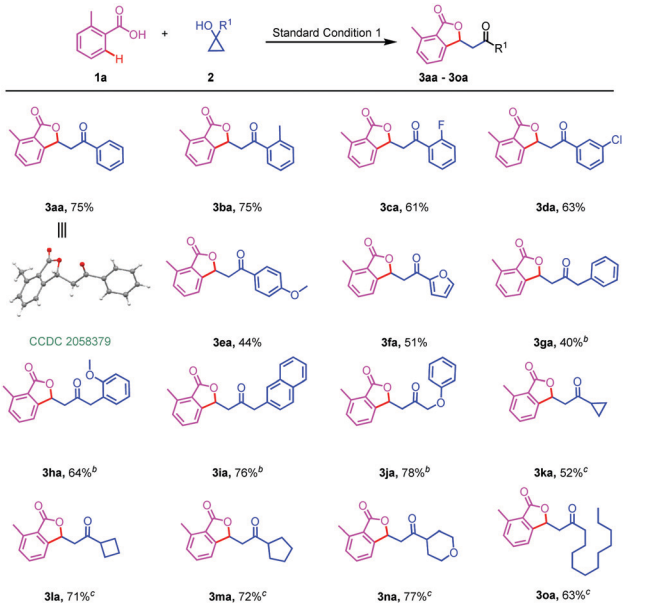
Table 1 Optimization of the reaction conditions[a]



Entry[a]	Base (equiv.)	Additive (equiv.)	Solvent	Yield[c]
1	K_2CO_3 (0.5)	—	1,4-dioxane	21%
2	Cs_2CO_3 (0.5)	—	1,4-dioxane	24%
3	Na_3PO_4 (0.5)	—	1,4-dioxane	22%
4	Cs_2CO_3 (1)	—	1,4-dioxane	34%
5	Cs_2CO_3 (1)	—	DCE	Trace
6	Cs_2CO_3 (1)	—	DCM	Trace
7	Cs_2CO_3 (1)	—	MeCN	55(59)%[d]
8[b]	Cs_2CO_3 (1)	—	MeCN	63%
9[b]	Cs_2CO_3 (1)	4 Å MS (0.05 g $mmol^{-1}$)	MeCN	61%
10[b]	Cs_2CO_3 (1)	4 Å MS (0.1 g $mmol^{-1}$)	MeCN	72(75)%[d]
11[b]	K_3PO_4	4 Å MS (0.1 g $mmol^{-1}$)	MeCN	63%[d]

[a] Reaction conditions: **1a**, **2a** (2 equiv.), $[Cp^*RhCl_2]_2$ (4 mol %), AgOAc (2 equiv.), base, solvent (0.5 mL), additive, 80 °C. [b] **2a** (2.5 equiv.). [c] The yields were determined by ^1H NMR and CH_2Br_2 was an internal standard. [d] Isolated yield.

Table 2 Scope of cyclopropanols[abcd]

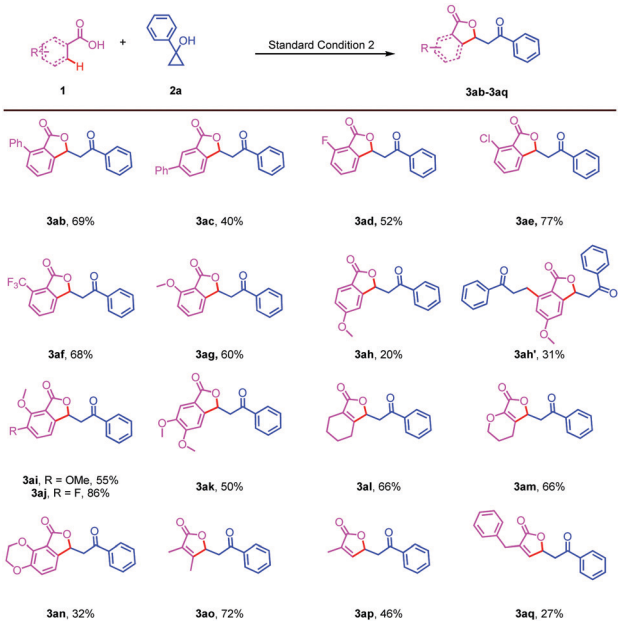


[a] Standard conditions **1**:**1a** (0.1 mmol), **2** (0.25 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), AgOAc (0.2 mmol), Cs_2CO_3 (0.1 mmol), 4 Å MS (0.1 g $mmol^{-1}$), 80 °C, MeCN (1 mL), 24 h. [b] **3ga**, **3ha**, **3ia**, **3ja** using K_3PO_4 (0.1 mmol) as base. [c] **3ka**, **3la**, **3ma**, **3na**, **3oa** for 48 h. [d] Isolated yields.

With the optimal reaction conditions in hand, we next investigated the scope of cyclopropanol coupling with **1a**. As shown in Table 2, a variety of aryl-substituted cyclopropanols bearing both electron-withdrawing and electron-donating groups were tolerated and gave the corresponding products in modest to good yield (**3aa**, **3ba**, **3ca**, **3da** and **3ea**). It is noteworthy that the cyclopropanol substituted with furan also reacted smoothly with **1a** to give the desired product **3fa** in 51% yield. Although substituted benzylcyclopropanols exhibited low effectiveness under the standard conditions, they were amenable to the fine-tuning conditions by just changing Cs_2CO_3 to K_3PO_4 (**3ga**, **3ha**, **3ia**). Gratefully, alkyl-substituted cyclopropanols were also conducted efficiently, such as phenoxymethyl-(**3ja**), cyclopropyl-(**3ka**), cyclobutane-(**3la**), cyclopentyl-(**3ma**), and cyclohexyl-(**3na**), and they could give excellent yields after extending the reaction time. Interestingly, the substrate derived from dodecanoic acid could also provide **3oa** in 63% isolated yield.

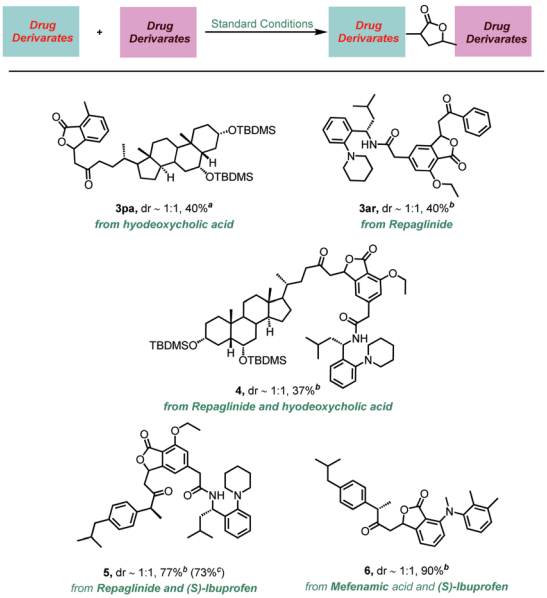
The scope of carboxylic acid substrates was next examined (Table 3). Generally, *ortho*, *meta*-substituted benzoic acids bearing electron-rich and electron-poor groups all performed well under the standard conditions (**3ab**, **3ac**, **3ad**, **3ae**, **3af**, **3ag** and **3ak**). Interestingly, a mixture of *mono*, *di*-substituted products (**3ah** and **3ah'**) was obtained in moderate yield due to the weak directing effect from an ester group. In addition, the incorporation of two substituents into benzoic acid (**3ai**, **3aj**, **3ak** and **3an**) also gave moderate to good yields. To our delight, various α,β-unsaturated carboxylic acids (**3al**, **3am**, **3ao**, **3ap** and **3aq**) were also suitable for the protocols with modest yields. As such, the present reaction could provide a general and efficient

Table 3 Scope of benzoid acids[ab]



[a] Standard Conditions 2 : **1** (0.1 mmol), **2a** (0.25 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), AgOAc (0.2 mmol), K_3PO_4 (0.1 mmol), 4 Å MS (0.1 g $mmol^{-1}$), 80 °C, MeCN (1 mL), 24 h. [b] Isolated yields.

Table 4 The potential utility of the protocol[abc]



[a] Standard conditions 1 : **1a** (0.1 mmol), **2p** (0.25 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), AgOAc (0.2 mmol), Cs_2CO_3 (0.1 mmol), 4 Å MS (0.1g $mmol^{-1}$), 80 °C, MeCN (1 mL), 48 h, the yield was given by isolated yield. [b] Standard conditions 2 : **1** (0.1 mmol), **2** (0.25 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), AgOAc (0.2 mmol), K_3PO_4 (0.1 mmol), 4 Å MS (0.1g $mmol^{-1}$), 80 °C, MeCN (1 mL), 24 h. [c] The yield of the gram-scale reaction.

protocol for the synthesis of 3-substituted phthalides and α,β-butenolides.

Fragment-based drug design has emerged as an efficient strategy to accelerate lead compound discovery,[11] and this encouraged us to use this Rh(III)-catalyzed C–H activation/ring opening for late-stage functionalization of important drug scaffolds and natural products (Table 4). Repaglinide, a drug molecule for diabetes, *S*(+)-Ibuprofen and Mefenamic acid, two non-steroidal anti-inflammatory drugs, and deoxycholic acid methyl ester were successfully assembled with a 3-substituted phthalide scaffold in synthetically useful yields (37–90%) albeit with a 1 : 1 dr value. To demonstrate the practicality of this protocol, a gram-scale synthesis experiment between repaglinide and *S*(+)-Ibuprofen was performed, which gave **5** in 73% yield.

To further study the mechanism of this reaction (Fig. 2), firstly, a kinetic isotope effect experiment has been established with substrates **1g** and its isotopically labeled **d–1g** under the standard conditions, and the KIE value was determined to be 2.6, indicating that C–H activation could be a rate-determining step. Secondly, it was found that 59% deuterium was observed at the *ortho*-position of **1g** when substrate **1g** with D_2O was treated in MeCN at 80 °C, in the presence of $[Cp^*RhCl_2]_2$/AgOAc and K_3PO_4 (1 equiv.) for 2 h. These results confirmed that the initial generation of rhodacycle was a reversible step. Thirdly, to examine whether an α,β-unsaturated ketone is a reaction intermediate, substrate **9** was subjected to the standard conditions and **3aa** was isolated in 44% yield, which suggested that an α,β-unsaturated ketone might be involved in the catalytic cycle (Fig. 2c).

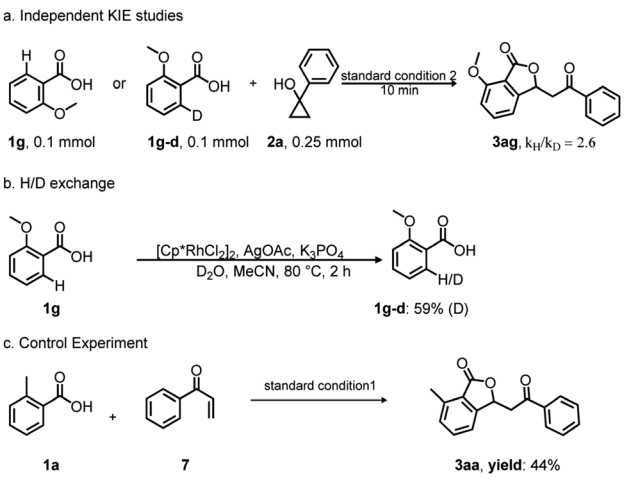


Fig. 2 Mechanistic studies.

On the basis of these experiments above and previous reports,[12] (Fig. 1) a possible mechanism was proposed in Fig. 3. The catalytically active species $[Cp^*Rh(OAc)_2]$ is first generated by a counteranion exchange from $[Cp^*RhCl_2]_2$ with AgOAc. After that, a 5-membered rhodacycle **A** could be formed *via* C–H activation, followed by ligand exchange to afford intermediate **B**. Subsequently, β-C elimination could occur to generate the intermediates **C** and a by-product **F** was formed by protonation. Next, β-H elimination might take place prior to reductive elimination to get intermediate **D**. Then migratory

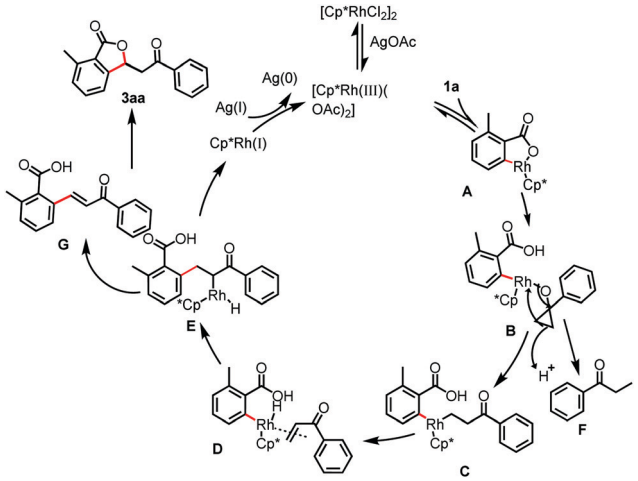


Fig. 3 Proposed mechanism.

insertion might take place to provide intermediate **E**. Finally, β-H elimination could occur instead of protonation to give the intermediate **G**, followed by Michael addition to afford desired product **3aa** with Rh (I), which was oxidized by Ag(I) and reformed the active catalyst [Cp*Rh(OAc)$_2$] for the next cycle.

In summary, we have developed a general and efficient method to synthesize 3-substituted phthalides and α,β-butenolides *via* Rh(III)-catalyzed cascade C–H activation/ring opening C–C cleavage/cyclization of carboxylic acids with cyclopropanols. The reaction is characterized by a broad substrate scope, excellent functional group tolerance, and mild conditions. Moreover, this catalytic methodology has been successfully applied to late-stage functionalization of bioactive compounds by the introduction of 3-substituted phthalides.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624–655; (*b*) T. Piou and T. Rovis, *Acc. Chem. Res.*, 2018, **51**, 170–180; (*c*) S. Rej and N. Chatani, *Angew. Chem., Int. Ed.*, 2019, **58**, 8304–8329; (*d*) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007–1020; (*e*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651–3678; (*f*) B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308–1318.

2 (*a*) P. H. Chen, B. A. Billett, T. Tsukamoto and G. Dong, *ACS Catal.*, 2017, **7**, 1340–1360; (*b*) G. Fumagalli, S. Stanton and J. F. Bower, *Chem. Rev.*, 2017, **117**, 9404–9432; (*c*) M. Murakami and N. Ishida, *J. Am. Chem. Soc.*, 2016, **138**, 13759–13769; (*d*) L. Souillart and N. Cramer, *Chem. Rev.*, 2015, **115**, 9410–9464.

3 (*a*) H.-M. Chen, G. Liao, C.-K. Xu, Q.-J. Yao, S. Zhang and B.-F. Shi, *CCS Chem.*, 2021, **3**, 455–465; (*b*) Q. Li, X. Yuan, B. Li and B. Wang, *Chem. Commun.*, 2020, **56**, 1835–1838; (*c*) X. Zhou, S. Yu, L. Kong and X. Li, *ACS Catal.*, 2016, **6**, 647–651; (*d*) Z. Nairoukh, M. Cormier and I. Marek, *Nat. Rev. Chem.*, 2017, **1**, 0035.

4 A. Nikolaev and A. Orellana, *Synthesis*, 2016, 1741–1768.

5 B. Q. Cheng, S. X. Zhang, Y. Y. Cui, X. Q. Chu, W. Rao, H. Xu, G. Z. Han and Z. L. Shen, *Org. Lett.*, 2020, **22**, 5456–5461.

6 (*a*) L. Chen, H. Quan, Z. Xu, H. Wang, Y. Xia, L. Lou and W. Yang, *Nat. Commun.*, 2020, **11**, 2151; (*b*) J. Hao, X. Guo, S. He, Z. Xu, L. Chen, Z. Li, B. Song, J. Zuo, Z. Lin and W. Yang, *Nat. Commun.*, 2021, **12**, 1304; (*c*) B. Song, P. Xie, Y. Li, J. Hao, L. Wang, X. Chen, Z. Xu, H. Quan, L. Lou, Y. Xia, K. N. Houk and W. Yang, *J. Am. Chem. Soc.*, 2020, **142**, 9982–9992; (*d*) Y. Xu, L. Chen, Y. W. Yang, Z. Zhang and W. Yang, *Org. Lett.*, 2019, **21**, 6674–6678.

7 (*a*) A. Awasthi, M. Singh, G. Rathee and R. Chandra, *RSC. Adv.*, 2020, **10**, 12626–12652; (*b*) R. Karmakar, P. Pahari and D. Mal, *Chem. Rev.*, 2014, **114**, 6213–6284; (*c*) A. Renzetti and K. Fukumoto, *Molecules*, 2019, **24**, 824.

8 (*a*) J. J. Beck and S. C. Chou, *J. Nat. Prod.*, 2007, **70**, 891–900; (*b*) N. Zheng, F. Yao, X. Liang, Q. Liu, W. Xu, Y. Liang, X. Liu, J. Li and R. Yang, *Nat. Prod. Res.*, 2018, **32**, 755–760; (*c*) J. Zou, G. D. Chen, H. Zhao, Y. Huang, X. Luo, W. Xu, R. R. He, D. Hu, X. S. Yao and H. Gao, *Org. Lett.*, 2018, **20**, 884–887.

9 (*a*) S. Cui, Y. Zhang and Q. Wu, *Chem. Sci.*, 2013, **4**, 3421–3426; (*b*) J. Kim, S. W. Park, M. H. Baik and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 13448–13451; (*c*) B. V. Pati, A. Ghosh and P. C. Ravikumar, *Org. Lett.*, 2020, **22**, 2854–2860.

10 The CCDC number of **3aa** is 2058379 and more details can be obtained from Cambridge Crystallographic Data Center†.

11 (*a*) M. Bissaro, M. Sturlese and S. Moro, *Drug Discovery Today*, 2020, **25**, 1693–1701; (*b*) B. Diethelm-Varela, *ChemMedChem*, 2021, **16**, 725–742; (*c*) A. Kashyap, P. K. Singh and O. Silakari, *Curr. Top. Med. Chem.*, 2018, **18**, 2284–2293; (*d*) V. V. Kleandrova and A. Speck-Planche, *Mini-Rev. Med. Chem.*, 2020, **20**, 1357–1374; (*e*) J. Osborne, S. Panova, M. Rapti, T. Urushima and H. Jhoti, *Biochem. Soc. Trans.*, 2020, **48**, 271–280; (*f*) L. Shi and N. Zhang, *Molecules*, 2021, **26**, 576.

12 (*a*) J. Li, Y. Zheng, M. Huang and W. Li, *Org. Lett.*, 2020, **22**, 5020–5024; (*b*) L. R. Mills, C. Zhou, E. Fung and S. A. L. Rousseaux, *Org. Lett.*, 2019, **21**, 8805–8809; (*c*) Y. H. Zhang, W. W. Zhang, Z. Y. Zhang, K. Zhao and T. P. Loh, *Org. Lett.*, 2019, **21**, 5101–5105.

