ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d0cc06834a

Received 14th October 2020,
Accepted 2nd November 2020

DOI: 10.1039/d0cc06834a

rsc.li/chemcomm

An efficient method for the synthesis of 2-pyridones *via* C–H bond functionalization†

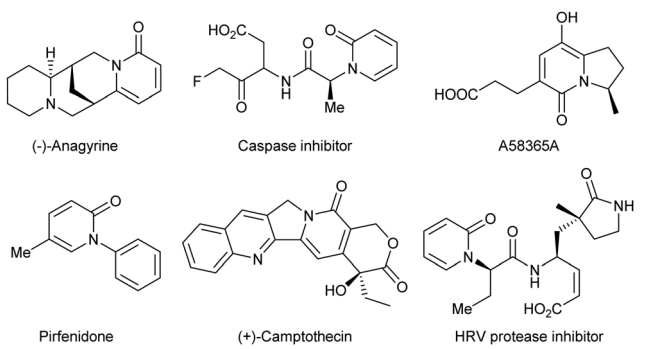
Shuguang Zhou,[ab] Duan-Yang Liu,[c] Suo Wang,[ab] Jie-Sheng Tian*[abc] and Teck-Peng Loh *[abcd]

A simple and practical method to access *N*-substituted 2-pyridones *via* a formal [3+3] annulation of enaminones with acrylates based on Rh^{III}-catalyzed C–H functionalization was developed. Control and deuterated experiments led to a plausible mechanism involving C–H bond cross-coupling and aminolysis cyclization. This strategy provides a short synthesis of structural motifs of *N*-substituted 2-pyridones.

Many functional molecules containing 2-pyridone frameworks exhibit specific and interesting bioactivities.[1] Presented in Scheme 1 are selected examples of natural products and pharmaceutical molecules with *N*-substituted 2-pyridone cores.[2] Therefore, there has been much interest focused on the development of new and efficient methods for the synthesis of 2-pyridone core structures.[3] Representative approaches include C(N)–H functionalization of 2-pyridones,[4] intramolecular cyclization reaction,[5] intermolecular cycloaddition,[6] and multicomponent domino reaction.[7] Though great progress has been achieved in the synthesis of 2-pyridone analogs, the development of effective and practical methods for the construction of novel 2-pyridones, especially functionalized *N*-substituted 2-pyridones,[8] is of great significance in synthetic and medicinal chemistry. Recently, cross-coupling reaction of enamides or cyclic enaminones with acrylates for the synthesis of linear conjugated dienes (*Z*, *E*) has been reported[9] (Scheme 2a). However, the synthesis of nitrogen-containing heterocyclic compounds or *E*, *Z*-diene structural motifs has not yet been fully explored by utilizing alkenylation of enaminones with acrylates as the key step. We envisage that it may be feasible to realize the synthesis of *E*, *Z*-diene structural fragments after undergoing C–C coupling *via* C–H functionalization and cyclization by introducing a reactive functional group on one coupling molecule. In view of this, *N*-substituted enaminones with a reactive site,[10] which can be readily prepared from commercially available ketone- or amide-containing materials, may be suitable for the control of the configuration of the coupling product through the formation of a 2-pyridone core (Scheme 2b), which was synthesized in a previous report[11] as a class of potential drug molecules in at least six steps. Here, we describe a novel strategy for the synthesis of *N*-substituted 2-pyridones through formal [3+3] annulation *via* Rh^{III}-catalyzed C–H functionalization. This approach has the advantages of using readily prepared enaminones and commercially available acrylates, one-step operation, and high efficiency. In addition, a plausible mechanism was also proposed based on control and deuterated experiments.

To verify this idea, reaction optimization was carefully studied (see the ESI,† for more details). The results showed that $[Cp^*RhCl_2]_2$ (2.0 mol%), AgOAc (8.0 mol%), $Cu(OAc)_2$ (2.0 equiv.), and KOAc (2.0 equiv.) in methanol at 90 °C under a N_2 atmosphere for 12 h were identified as the optimal reaction conditions (Table S1, ESI,† entry 11).

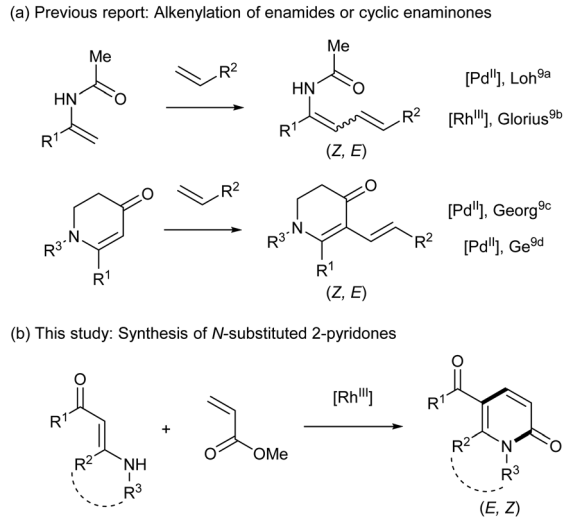
Next, we evaluated the scope of *N*-substituted enaminones in their reactions with methyl acrylate **2**. In general, a wide



Scheme 1 Examples of natural products and pharmaceutical molecules with *N*-substituted 2-pyridone cores.

[a] *Institute of Advanced Synthesis (IAS), Northwestern Polytechnical University (NPU), Xi'an 710072, China*
[b] *Yangtze River Delta Research Institute of NPU, Taicang, Jiangsu, 215400, China. E-mail: ias_jstian@njtech.edu.cn, teckpeng@ntu.edu.sg*
[c] *Institute of Advanced Synthesis (IAS), Nanjing Tech University (NanjingTech), Nanjing 211816, P. R. China*
[d] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 637371, Singapore*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0cc06834a

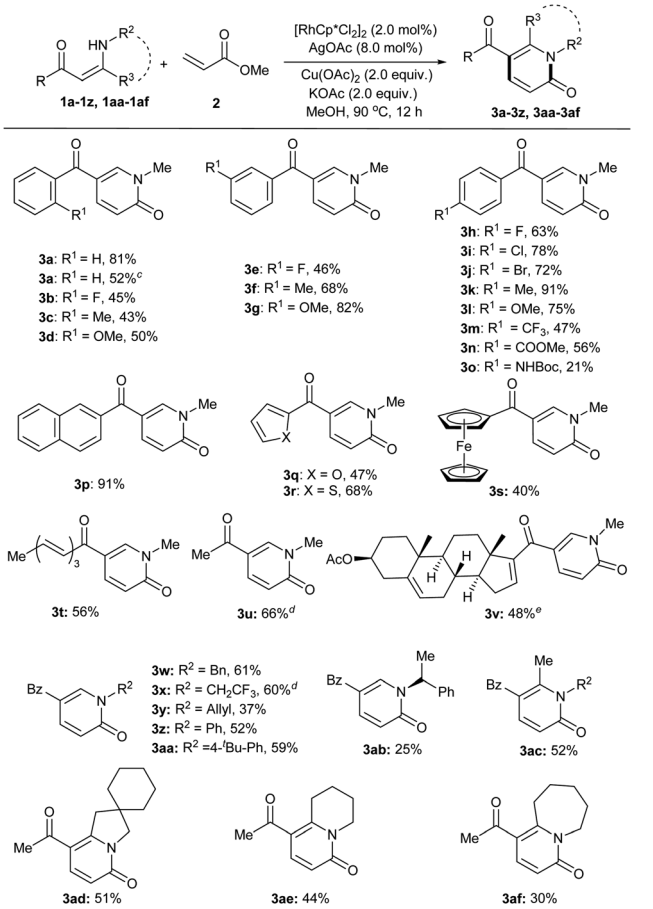


Scheme 2 Strategy for the synthesis of *N*-substituted 2-pyridones through Rh^{III}-catalyzed C–H activation.

range of structurally diverse 2-pyridone derivatives can be obtained in moderate to excellent yields, as illustrated in Table 1. *N*-Methyl enaminones tethered with a variety of aryl substituents were found to be suitable substrates for this transformation, providing the corresponding benzoyl-substituted 2-pyridone products **3a–3o** (Table 1). Upon comparison of the same group at the *ortho*-, *meta*-, and *para*-positions of the aryl ring, most of the *para*-substituted substrates showed the best reactivity, which is perhaps due to the influence of steric hindrance. Also, electronic effects played an important role in this process (**3d**, **3g** *vs.* **3l**). Additionally, the reaction displayed good compatibility to other poly- and heteroaromatic substituents, such as naphthyl **3p**, furyl **3q**, thienyl **3r**, and ferrocenyl **3s,** under the standard reaction conditions. It is noteworthy that *N*-methyl enaminones bearing conjugated polyenyl and alkyl structures worked well, generating the desired products **3t** and **3u** in 56% and 66% yields, respectively. To our delight, this protocol can be applied to the structural modification of the natural product 16-dehydropregnenolone. The broad scope of R group prompted us to further examine the other substituents of *N*-substituted enaminones to obtain the more useful 2-pyridone derivatives **3t–3af**. When the N-functional group (R^2) was changed to Bn, trifluoroethyl, allyl, Ph, and *tert*-butylphenyl, the corresponding *N*-substituted 2-pyridones **3w–3aa** were successfully obtained in 37–61% yields. What's more, enaminone **1ab** equipped with a chiral amino group displayed reactivity to give the target product **3ab**. Then, alteration of the R^3 substituent to a methyl group proceeded smoothly. Intrigued by the scope of R^2 and R^3 groups investigated, bicyclic *N*-substituted 2-pyridone frameworks were further pursued. Luckily, azabicyclic compounds **3ad–3af** with a 2-pyridone core and a 5, 6, or 7-membered ring can also be efficiently constructed. Additionally, the potential utility of this method was demonstrated on the basis of modification of natural products and low catalytic loading (0.2 mol%) on a 2.0 mmol scale.

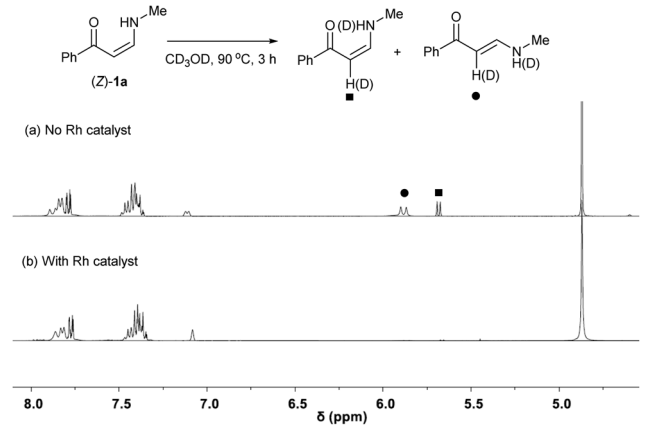
To better understand the mechanism of the synthesis of 2-pyridone derivatives through the Rh^{III}-catalyzed formal [3+3] annulation of *N*-substituted enaminones with methyl acrylate, several deuterium-labeling and control experiments (see the

Table 1 Scope of *N*-substituted enaminones[ab]

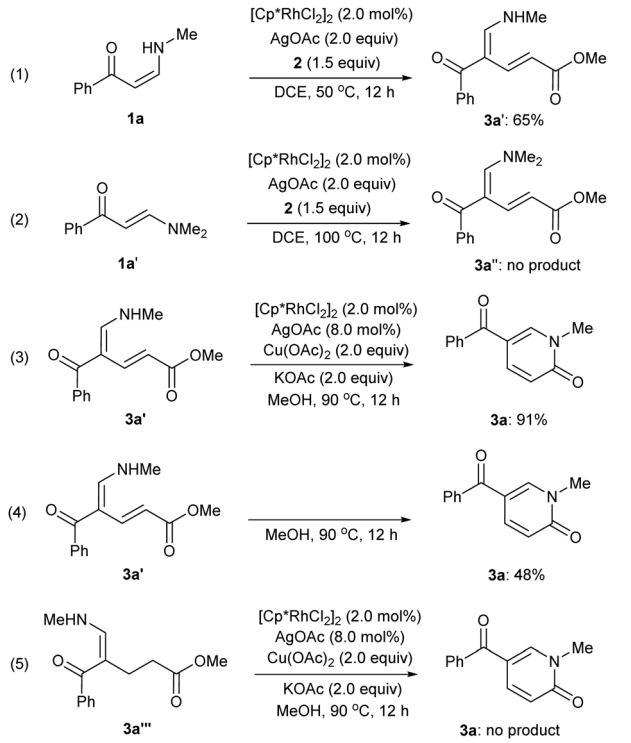


[a] Reaction conditions: enaminone **1a** (0.2 mmol, 1.0 equiv.), methyl acrylate **2** (0.3 mmol, 1.5 equiv.), $Cu(OAc)_2$ (0.4 mmol, 2.0 equiv.), KOAc (0.4 mmol, 2.0 equiv.), MeOH (1.0 mL), $[Cp^*RhCl_2]_2$ (2.0 mol%), AgOAc (8.0 mol%), 90 °C, and 12 h. [b] Isolated yields. [c] $[Cp^*RhCl_2]_2$ (0.2 mol%) and AgOAc (0.8 mol%) on a 2.0 mmol scale. [d] $[Cp^*RhCl_2]_2$ (5.0 mol%) and AgOAc (20 mol%). [e] 36 h.

ESI,† for more details) were conducted, which helped to clarify the intermediates and their transformation processes. As shown in Scheme 3, two thirds of (*Z*)-**1a** can be converted to (*E*)-**1a** in CD_3OD at 90 °C in 3 h in the absence of the rhodium catalyst. Whereas, in the $[Cp^*RhCl_2]_2$ and AgOAc catalytic system, the hydrogen of (*Z*)-**1a** at the α-position can be almost completely deuterated according to ^1H NMR detection. This C–H/C–D exchange supports a reversible activation by the rhodium catalyst. On the other hand, alkenylation of the *N*-methyl enaminone **1a** can provide diene **3a′** in good yield by using modified conditions to reduce aminolysis cyclization (Scheme 4, eqn (1)), while no coupling product **3a″** was obtained with *N*,*N*-dimethyl enaminone **1a′** (Scheme 4, eqn (2)). These results imply that the amino functionality with the N–H bond was deprotonated and then coordinated to the rhodium catalyst as a directing group for C–H bond activation to form the reactive four-membered rhodacycle intermediate, which further reacted with acrylate to realize the cross-coupling reaction. Next, the reaction pattern of forming C–C and C–N bonds in a one-step manner was evaluated to

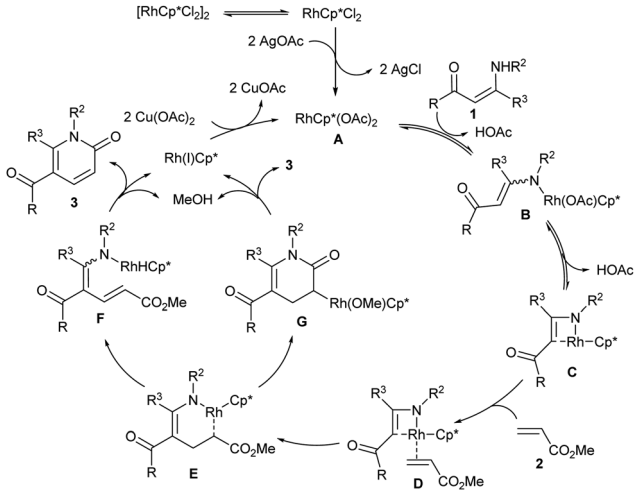


Scheme 3 Deuterium-labeling experiments detected by ^{1}H NMR. (a) (*Z*)-**1a** (0.1 mmol), CD_3OD, 90 °C, and 3 h; (b) (*Z*)-**1a** (0.1 mmol), $[Cp^*RhCl_2]_2$ (2.0 mol%), AgOAc (8 mol%), CD_3OD, 90 °C, and 3 h.



Scheme 4 Control experiments.

determine the possible process by designing control experiments. When diene intermediate **3a**′ was subjected to standard conditions, the reaction proceeded smoothly, affording the cyclization product **3a** in 91% yield (Scheme 4, eqn (3)). However, without the rhodium catalyst, the desired product **3a** was obtained in 48% yield. Maybe the rhodium species after N–H deprotonation helps to promote the aminolysis cyclization (Scheme 4, eqn (4)). In contrast, no product **3a** was detected in the cyclization experiment of **3a**′′′ by Michael addition (Scheme 4, eqn (5)). These observations also suggested that this [3+3] annulation involves β-hydride elimination after coordination and migratory insertion of a four-membered rhodacycle species with acrylate.



Scheme 5 Mechanistic hypothesis.

A plausible mechanism of our formal [3+3] annulation reaction by Rh^{III}-catalyzed C–H activation is presented in Scheme 5 on the basis of the mechanistic study (See ESI,† for more details) and the relevant literature.[12] Briefly, the reaction starts by anion exchange forming the reactive rhodium acetate species **A**, which activates (*Z*)-*N*-substituted enaminone **1** by successive N–H deprotonation and C–H bond activation leading to the *E* configuration species **B** and rhodacycle complex **C**. After that, coordination and migratory insertion of methyl acrylate form a new six-membered rhodacycle intermediate **E**, which undergoes β-hydride elimination to afford a Rh^{III} hydride species **F**. Subsequent intramolecular aminolysis reaction of the ester and reductive elimination provide the target product **3** and Rh(I)Cp*. Here, we also do not rule out that the intermediate **G** is generated by aminolysis cyclization before β-hydride elimination. Finally, the resulting Rh^{I} complex is further oxidized by $Cu(OAc)_2$ to regenerate Rh^{III} acetate species **A** to complete the catalytic cycle.

In summary, we have accomplished the synthesis of *N*-substituted 2-pyridones through the Rh^{III}-catalyzed formal [3+3] annulation of enaminones with acrylates. A plausible mechanism involving C–C coupling *via* C–H bond functionalization and subsequent aminolysis cyclization was proposed through control and deuterated experiments. Further investigations on the practical applications of this method, especially in the synthesis of drug candidates, are underway.

We gratefully acknowledge Northwestern Polytechnical University, the Fundamental Research Funds for the Central Universities (31020200QD046), the Natural Science Foundation of Jiangsu Province (BK20171463), the grant of MOE-Tier 1 (M4012045.110 RG12/18-(S)), Nanjing Tech University, and Nanyang Technological University for the generous financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) G. Mehta and V. Singh, *Chem. Rev.*, 1999, **99**, 881–930; (*b*) P. Hajek, H. McRobbie and K. Myers, *Thorax*, 2013, **68**, 1037–1042; (*c*) J. A. D. Good, M. Kulén, J. Silver, K. S. Krishnan, W. Bahnan, C. Núñez-Otero, I. Nilsson, E. Wede, E. Groot, Å. Gylfe, S. Bergström and F. Almqvist, *J. Med. Chem.*, 2017, **60**, 9393–9399; (*d*) P. Dubruel, L. Dekie and E. Schacht, *Biomacromolecules*, 2003, **4**, 1168–1176; (*e*) E. D. Silva, A. S. Geiermann, M. I. Mitova, P. Kuegler, J. W. Blunt, A. L. J. Cole and M. H. G. Munro, *J. Nat. Prod.*, 2009, **72**, 477–479; (*f*) J. Han, C. Liu, L. Li, H. Zhou, L. Liu, L. Bao, Q. Chen, F. Song, L. Zhang, E. Li, L. Liu, Y. Pei, C. Jin, Y. Xue, W. Yin, Y. Ma and H. Liu, *J. Org. Chem.*, 2017, **82**, 11474–11486.

2 (*a*) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139–165; (*b*) S. T. Harrison, M. S. Poslusney, J. J. Mulhearn, Z. Zhao, N. R. Kett, J. W. Schubert, J. Y. Melamed, T. J. Allison, S. B. Patel, J. M. Sanders, S. Sharma, R. F. Smith, D. L. Hall, R. G. Robinson, N. A. Sachs, P. H. Hutson, S. E. Wolkenberg and J. C. Barrow, *ACS Med. Chem. Lett.*, 2015, **6**, 318–323; (*c*) S. Hibi, K. Ueno, S. Nagato, K. Kawano, K. Ito, Y. Norimine, O. Takenaka, T. Hanada and M. Yonaga, *J. Med. Chem.*, 2012, **55**, 10584–10600; (*d*) V. Krishnamurti, S. B. Munoz, X. Ispizua-Rodriguez, J. Vickerman, T. Mathew and G. K. S. Prakash, *Chem. Commun.*, 2018, **54**, 10574–10577.

3 (*a*) J. Diesel, A. M. Finogenova and N. Cramer, *J. Am. Chem. Soc.*, 2018, **140**, 4489–4493; (*b*) Y. Nakao, H. Idei, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.*, 2009, **131**, 15996–15997; (*c*) D. M. Dalton, K. M. Oberg, R. T. Yu, E. E. Lee, S. Perreault, M. E. Oinen, M. L. Pease, G. Malik and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 15717–15728; (*d*) R. K. Friedman and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 10775–10782; (*e*) Y. Su, M. Zhao, K. Han, G. Song and X. Li, *Org. Lett.*, 2010, **12**, 5462–5465; (*f*) A. Nakatani, K. Hirano, T. Satoh and M. Miura, *Chem. – Eur. J.*, 2013, **19**, 7691–7695; (*g*) M. Torres, S. Gil and M. Parra, *Curr. Org. Chem.*, 2005, **9**, 1757–1779; (*h*) A. Brossi, *The Alkaloids: Chemistry and Pharmacology*, Elsevier, 1993, vol. 43, pp. 119–183; (*i*) S. W. Pelletier, *Alkaloids: Chemical and Biological Perspectives*, Wiley, New York, 1983, vol. 1, pp. 1–31; (*j*) S. W. Pelletier, *Alkaloids: Chemical and Biological Perspectives*, Wiley, New York, 1987, vol. 5, pp. 1–54.

4 (*a*) R. Odani, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2014, **53**, 10784–10788; (*b*) Y. Jin, L. Ou, H. Yang and H. Fu, *J. Am. Chem. Soc.*, 2017, **139**, 14237–14243; (*c*) T. Katsina, K. E. Papoulidou and A. L. Zografos, *Org. Lett.*, 2019, **21**, 8110–8115; (*d*) Y. Li, F. Xie and X. Li, *J. Org. Chem.*, 2016, **81**, 715–722; (*e*) K. Hirano and M. Miura, *Chem. Sci.*, 2018, **9**, 22–32.

5 (*a*) A. R. Healy, M. I. Vizcaino, J. M. Crawford and S. B. Herzon, *J. Am. Chem. Soc.*, 2016, **138**, 5426–5432; (*b*) A. R. Healy and S. B. Herzon, *J. Am. Chem. Soc.*, 2017, **139**, 14817–14824; (*c*) Z. Zhang, S. Fang, Q. Liu and G. Zhang, *J. Org. Chem.*, 2012, **77**, 7665–7670; (*d*) H. Imase, T. Suda, Y. Shibata, K. Noguchi, M. Hirano and K. Tanaka, *Org. Lett.*, 2009, **11**, 1805–1808; (*e*) H. Imase, K. Noguchi, M. Hirano and K. Tanaka, *Org. Lett.*, 2008, **10**, 3563–3566.

6 (*a*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449–6457; (*b*) R. T. Yu and T. Rovis, *J. Am. Chem. Soc.*, 2006, **128**, 2782–2783; (*c*) L. V. R. Boňaga, H.-C. Zhang, A. F. Moretto, H. Ye, D. A. Gauthier, J. Li, G. C. Leo and B. E. S. Maryanoff, *J. Am. Chem. Soc.*, 2005, **127**, 3473–3485; (*d*) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama and K. Itoh, *J. Am. Chem. Soc.*, 2005, **127**, 605–613; (*e*) H. A. Duong, M. J. Cross and J. Louie, *J. Am. Chem. Soc.*, 2004, **126**, 11438–11439; (*f*) L. Ackermann, A. V. Lygin and N. Hofmann, *Org. Lett.*, 2011, **13**, 3278–3281; (*g*) M. Fujii, T. Nishimura, T. Koshiba, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2013, **15**, 232–234; (*h*) Y. Komine and K. Tanaka, *Org. Lett.*, 2010, **12**, 1312–1315.

7 R. Ferraccioli, D. Carenzi, E. Motti and M. Catellani, *J. Am. Chem. Soc.*, 2006, **128**, 722–723.

8 (*a*) H. Tinnermann, C. Wille and M. Alcarazo, *Angew. Chem., Int. Ed.*, 2014, **53**, 8732–8736; (*b*) Y. Q. Fang, M. M. Bio, K. B. Hansen, M. S. Potter and A. Clausen, *J. Am. Chem. Soc.*, 2010, **132**, 15525–15527; (*c*) Y. Chen, F. Wang, A. Jia and X. Li, *Chem. Sci.*, 2012, **3**, 3231–3236; (*d*) J. Hillenbrand, W. S. Ham and T. Ritter, *Org. Lett.*, 2019, **21**, 5363–5367; (*e*) G. N. Vaidya, A. Khan, H. Verma, S. Kumar and D. Kumar, *J. Org. Chem.*, 2019, **84**, 3004–3010.

9 (*a*) Y. H. Xu, Y. K. Chok and T. P. Loh, *Chem. Sci.*, 2011, **2**, 1822–1825; (*b*) T. Besset, N. Kuhl, F. W. Patureau and F. Glorius, *Chem. – Eur. J.*, 2011, **17**, 7167–7171; (*c*) Y.-Y. Yu, M. J. Niphakis and G. I. Georg, *Org. Lett.*, 2011, **13**, 5932–5935; (*d*) M. Li, L. Li and H. Ge, *Adv. Synth. Catal.*, 2010, **352**, 2445–2449.

10 (*a*) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 17440–17443; (*b*) J. Chen, P. Guo, J. Zhang, J. Rong, W. Sun, Y. Jiang and T. P. Loh, *Angew. Chem., Int. Ed.*, 2019, **58**, 12674–12679; (*c*) S. Zhou, J. Wang, L. Wang, C. Song, K. Chen and J. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 9384–9388; (*d*) S. Zhou, B. W. Yan, S. X. Fan, J. S. Tian and T. P. Loh, *Org. Lett.*, 2018, **20**, 3975–3979.

11 Z. Lv, C. Sheng, T. Wang, Y. Zhang, J. Liu, J. Feng, H. Sun, H. Zhong, C. Niu and K. Li, *J. Med. Chem.*, 2010, **53**, 660–668.

12 (*a*) B. Jiang, M. Z. Shu, S. L. Yun, H. Xu and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2018, **57**, 555–559; (*b*) S. Jambu, R. Sivasakthikumaran and M. Jeganmohan, *Org. Lett.*, 2019, **21**, 1320–1324; (*c*) T. Zhou, Y. Wang, B. Li and B. Wang, *Org. Lett.*, 2016, **18**, 5066–5069.

