



Cite this: *RSC Adv.*, 2020, 10, 6351

Ru(II)-catalyzed C6-selective C–H acylmethylation of pyridones using sulfoxonium ylides as carbene precursors†

Yangjie Fu,^{ab} Zhaohui Wang,^{ab} Qiyu Zhang,^{ab} Zhiyu Li,^a Hong Liu,^{ab} Xiaoling Bi^{*a} and Jiang Wang^{id}^{*b}

Received 20th December 2019

Accepted 27th January 2020

DOI: 10.1039/c9ra10749e

rsc.li/rsc-advances

In this study, we describe a method using sulfoxonium ylides as carbene precursors to achieve C6-selective acylmethylation of pyridones catalyzed by a ruthenium(II) complex. This approach featured mild reaction conditions, moderate to excellent yields, high step economy, and had excellent functional group tolerance with good site selectivity. Besides, gram-scale preparation, synthetic utility, and mechanistic studies were conducted. It offers a direct and efficient way to synthesize pyridone derivatives.

1 Introduction

Pyridone is exhibited as a privilege scaffold in a large range of biological active agents, attracting much attention from medicinal chemists (Fig. 1).¹ Consequently, how to achieve the late stage functionalization of pyridone has attracted intensive attention.

Traditionally, the direct alkylation of pyridone was usually afforded by pre-functionalization with a halogen followed by transition-metal catalyzed coupling reactions. Recently, the direct C–H functionalization strategy to form C–C or C–X bonds has become a more effective and reliable synthetic route.² Transition-metal-promoted C3 (ref. 3) and C5 (ref. 4) positions of 2-pyridones have been probed exhaustively owing to the sufficient electron density of C–H bonds in these positions. However, only limited examples have been reported on the direct C–H bond functionalization on C6 position of pyridone.⁵ For instance, Cramer and collaborators described the synthesis of 1,6-annulated 2-pyridones by selective intramolecular nickel catalyzed cyclization.^{5c} Afterwards, more C–H functionalization at C6 position of pyridone mediated by transition-metal have been reported.⁶ Miura and colleagues exploited selective C6 borylation of pyridone with bis(pinacolato)diboron *via* rhodium catalyzed C–H bond activation. The synthetic utility has been extended by subsequent Suzuki–Miyaura cross-coupling to form new C–C bonds and after removal of the directing group, the C6-

arylated NH-pyridone has been afforded.^{6c} At the same time, our group has successively reported the rhodium or cobalt-catalyzed, C6-selective C–H alkylation, arylation, and amidation of pyridones by using potassium trifluoroborates or oxazolones (Scheme 1a and b).^{6d,6h}

Transition-metal-catalyzed C–H functionalization is based on carbene migratory insertion to achieve the transformation. In transition-metal-catalyzed C–H functionalization, α -diazo carbonyls are commonly used as carbene precursor.^{7,8} Samanta and colleagues disclosed a rhodium-mediated C6-selective alkylation of 2-pyridones employing α -diazocarbonyl derivatives (Scheme 1c).^{7c} However, there are still some limitations of diazo compounds serving as a carbene precursor, such as the potential explosiveness due to the evolution of nitrogen gas. To overcome these problems, other carbene surrogates were explored, such as cyclopropenes,⁹ hydrazones,¹⁰ ketone-functionalized enynes,¹¹ triazoles,¹² and sulfoxonium ylides. Sulfoxonium ylides have been reported to be employed in industry, and are more safe alternatives to diazo compounds.¹³ And recently, Barday and co-workers developed the cross-coupling reactions of α -carbonyl sulfoxonium ylides with arenes and heteroarenes using (Cp* RhCl_2)₂ as the catalyst (Scheme 1d).^{13d}

^aJiangsu Key Laboratory of Drug Design and Optimization, Department of Medicinal Chemistry, China Pharmaceutical University, 24 Tongjiyaxiang, Nanjing 210009, China. E-mail: bxl@163.com

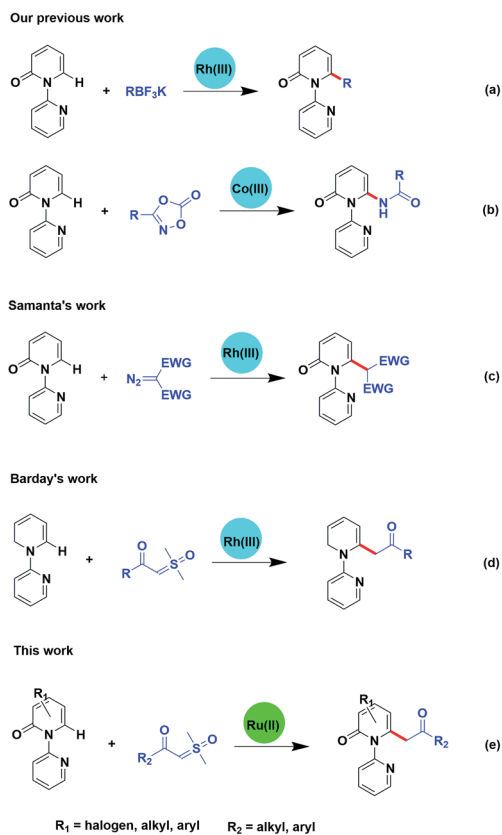
^bState Key Laboratory of Drug Research, Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China. E-mail: jwang@simm.ac.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra10749e



Fig. 1 Pharmaceuticals containing a C6-alkylated pyridone core structure.





- ✓ Cost-effective ruthenium catalyst
- ✓ External-oxidant free
- ✓ Good to excellent yields
- ✓ Wide function-group tolerance
- ✓ Mild conditions and simple operation

Scheme 1 C6-selective C–H functionalization of pyridones.

Instead of using the noble metals such as rhodium and iridium, to date, more examples on direct C–H bond functionalization catalysed by ruthenium, a cost-effective transition-metal, has attracted attention and been developed. Herein, we reveal ruthenium(II)-catalyzed C6-selective direct acylmethylation of pyridones using sulfoxonium ylides (Scheme 1e).

2 Results and discussion

Based on the precedent reported research, 2-pyridone (**1a**) and α -benzoyl sulfoxonium ylide (**2a**) were selected to probe the reaction conditions for transition-metal catalyzed acylmethylation of pyridone (Table 1). Initially, the coupling reaction between substrate **1a** (0.4 mmol) and **2a** (0.8 mmol) was triggered by a screen of various transition metal complexes. Ruthenium(II) (5 mol%), cobalt(III) (5 mol%), and rhodium(III) (5 mol%) were independently investigated in the presence of AgSbF₆ (10 mol%) in hexafluoroisopropanol (HFIP) and the mixture was stirred at 60 °C under an argon atmosphere for 24 h. The results indicated that [Ru(*p*-cymene)Cl₂]₂ was the optimal catalyst (Table 1, entries 1–3). Additionally, if replacing the [Ru(*p*-cymene)Cl₂]₂ with [RuCl(*p*-cymene)((*S*)-binap)]Cl, Ru(PPh₃)₃Cl₂, or RuCl[(*R,R*)-Tsdpen](*p*-cymene), the yield of **3aa**

Table 1 Optimization of the reaction conditions^a

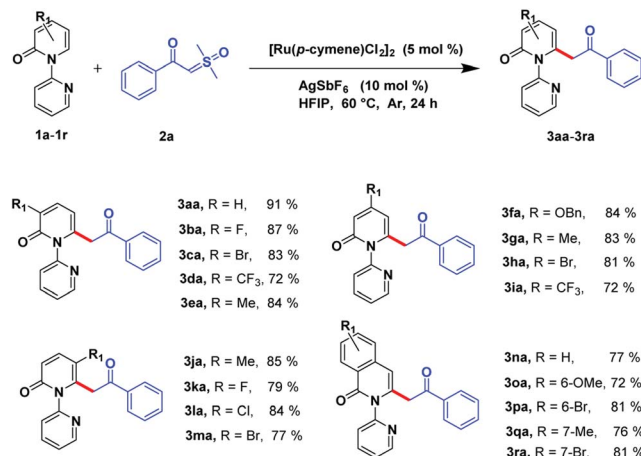
Entry	Cat. ^b	Ag salt	Solvent	Yield ^c (%)
1	A	AgSbF ₆	HFIP	13
2	B	AgSbF ₆	HFIP	49
3	C	AgSbF ₆	HFIP	91
4	D	AgSbF ₆	HFIP	31
5	E	AgSbF ₆	HFIP	16
6	F	AgSbF ₆	HFIP	63
7	C	AgSbF ₆	DCE	22
8	C	AgSbF ₆	MeCN	13
9	C	AgSbF ₆	Dioxane	21
10	C	AgSbF ₆	CH ₃ OH	12
11	C	AgSbF ₆	CH ₃ CH ₂ OH	64
12	C	AgNTf ₂	HFIP	84
13	C	AgOTf	HFIP	78
14	C	Ag(OAc) ₂	HFIP	Trace
15 ^d	C	AgSbF ₆	HFIP	84
16 ^e	C	AgSbF ₆	HFIP	82
17 ^f	C	AgSbF ₆	HFIP	91
18 ^g	C	AgSbF ₆	HFIP	67
19 ^h	C	AgSbF ₆	HFIP	76
20	—	AgSbF ₆	HFIP	N.R.
21	C	—	HFIP	N.R.

^a Reaction conditions: compound **1a** (0.4 mmol), compound **2a** (0.8 mmol), cat. (5 mol%), Ag salt (10 mol%) in solvent (3 mL) at 60 °C for 24 h, under Ar atmosphere. N.R. = no reaction. ^b Catalyst A = [Cp*Co(CO)I₂], catalyst B = (Cp*RhCl₂)₂, catalyst C = [Ru(*p*-cymene)Cl₂]₂, catalyst D = [RuCl(*p*-cymene)((*S*)-binap)]Cl, catalyst E = Ru(PPh₃)₃Cl₂, catalyst F = RuCl[(*R,R*)-Tsdpen](*p*-cymene). ^c Isolated yield. ^d Cat. (2.5 mol%). ^e Ag salt (5 mol%). ^f At 90 °C. ^g At 40 °C. ^h At air condition.

was decreased (Table 1, entries 4–6). Solvent was subsequently examined and results demonstrated that **3aa** could be obtained in a higher yield in HFIP than in others including 1,2-dichloroethane (DCE), acetonitrile, dioxane, methanol, and ethanol (Table 1, entries 7–11). Changing the additive from AgSbF₆ to AgNTf₂, AgOTf, or Ag(OAc)₂ could diminish the yield of **3aa** (Table 1, entries 12–14). The yield slightly decreased caused by the reduction of [Ru(*p*-cymene)Cl₂]₂ and AgSbF₆ (Table 1, entries 15 and 16). Whilst when the reaction was conducted at 90 °C, **3aa** could also be attained in 91% yield which was no more discrepancy with conducting at 60 °C (Table 1, entry 15). However, decreasing the temperature to 40 °C, the yield was reduced to 67% (Table 1, entry 16). The reaction could also be carried out in air with 76% yield (Table 1, entry 17), but without ruthenium(II) complex or Ag(I) additive, the reaction was no longer proceeded (Table 1, entries 18 and 19).

With the optimized reaction conditions obtained, we investigated the substrate scope of pyridones **1a–1r** (Scheme 2). The results showed that C3 substituted of 2-pyridones can sustain multiple functional groups, including electron-withdrawing groups or electron-donating groups, and even halogens to afford the desirable products in good to moderate yields





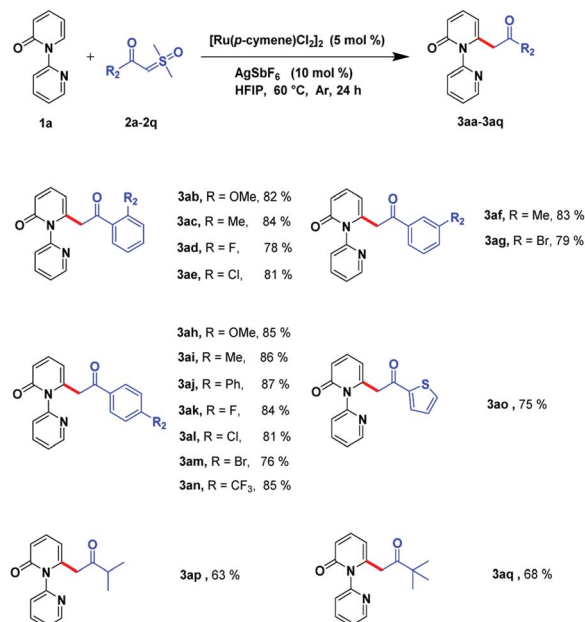
Scheme 2 Substrate scope of pyridions.^{a,b} ^a Reaction conditions: compound **1a–1r** (0.4 mmol), compound **2a** (0.8 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol%), and AgSbF₆ (10 mol%) in HFIP (3 mL) at 60 °C, under Ar in 24 h. ^b Isolated yield.

(**3ba–3ea**, 72–87%). Substituents installed on the C4 position of pyridones can be processed smoothly by obtaining the desired products in good to moderate yields (**3fa–3ia**, 72–84%). Satisfyingly, although suffering from steric hindrance for the C5-substituted 2-pyridones, the desired compounds could be afforded in considerable yields (**3ja–3ma**, 77–85%). Moreover, this transformation was also compatible to isoquinolinones by attaining target molecules in good to excellent yields (**3na–3ra**, 72–81%).

Next, we investigated the scope of sulfoxonium ylides. The acylmethylation proposal was suitable for various kinds of α -benzoyl sulfoxonium ylides (Scheme 3). It can be tolerated by electron-donating groups, such as CH₃ and OMe, and can be processed smoothly even if electron-withdrawing groups, such as CF₃, or halogens (F, Cl, and Br), are incorporated in the derivatives. Different positions such as the *ortho*-, *meta*-, and *para*-of the phenyl ring can favorably afford the relevant products (**3ab–3an**) in high yields (76–86%). Gratifyingly, this reaction could also be carried out with heterocyclic compounds such as thiophene and the corresponding product (**3ao**) was detected in 75% yield. The sulfoxonium ylides can also bear some alkyl substrates and the relevant products could be detected in acceptable yields (**3ap–3aq**, 63–68%).

To indicate the synthetic utility of this strategy for the approach to C6-acylmethylation piperidin-2-one, gram-scale synthesis of compound **3aa** was conducted and the product was obtained in 89% yield (Scheme 4a). Furthermore, hydrogenation of **3aa** was examined to form **4aa** in 69% yield (Scheme 4b).

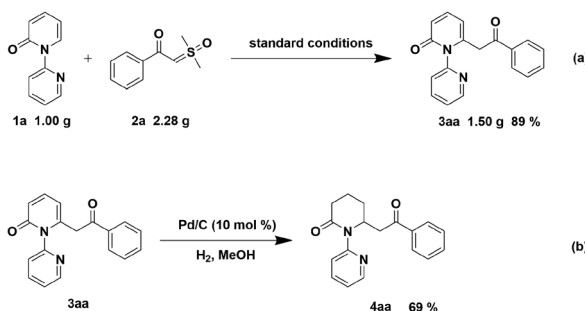
In order to investigate the preliminary mechanism, a series of experiments were designed and performed. Firstly, a hydrogen–deuterium (H/D) exchange experiment was conducted to gain insight into the C–H cleavage, when 2-pyridone (**1a**) was examined in the optimized condition with the presence of CD₃OD and no deuterium exchange was observed. It demonstrate the irreversible of C–H bond cleavage catalyzed by



Scheme 3 Substrate scope of sulfoxonium ylides.^{a,b} ^a Reaction conditions: compound **1a** (0.4 mmol), compound **2a–2q** (0.8 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol%), and AgSbF₆ (10 mol%) in HFIP (3 mL) at 60 °C, under Ar in 24 h. ^b Isolated yield.

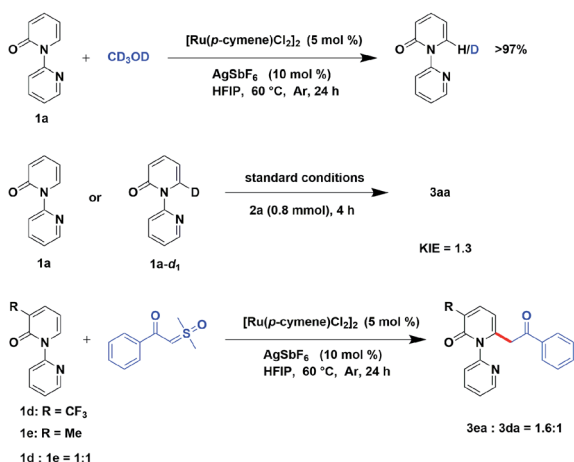
ruthenium. Furthermore, the kinetic isotope effect (KIE) experiment was conducted, employing [D₁]-**1a** as substrate, illustrated a KIE of 1.3, indicated that the rate-limited step was not the division of the C–H bond. Additionally, an intermolecular competition reaction between 3-(trifluoromethyl)-2*H*-[1,2'-bipyridin]-2-one (**1d**) and 3-methyl-2*H*-[1,2'-bipyridin]-2-one (**1e**) with compound **2a** were carried out in one sealed tube. Finally, it gave a higher yield of **3ea** than **3da**, revealing that the electron-donating substrate has faster reaction rate (Scheme 5).

On the basis of the preliminary experimental results, a plausible acylmethylation catalytic cycle is proposed (Scheme 6). The reactive Ru(II) complex was first formed after ligand exchange of [Ru(*p*-cymene)Cl₂]₂ with AgSbF₆, followed by a *ortho* C–H bond activation of pyridone. This process is assisted by the DG, pyridine motif and generate intermediate **A**. There is a ligand exchange among **2a** and intermediate **A**, which affords the intermediate **B**. With the leaving of DMSO,

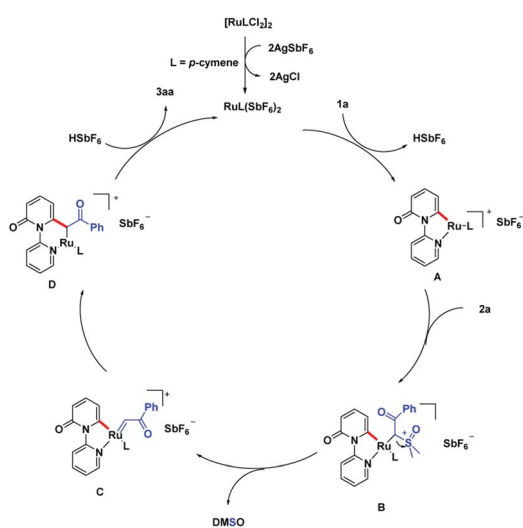


Scheme 4 Gram-scale synthesis and synthetic transformation of compound **3aa**.





Scheme 5 Mechanism study experiments.



Scheme 6 Proposed reaction mechanism.

ruthenium carbene intermediate **C** is produced. Migratory insertion of ruthenium-carbene generate intermediate **D**. Eventually, the intermediate **D** transfer the protonation, produce the product **3aa** and liberate the active Ru-catalyst.

3 Conclusions

In summary, we achieved the ruthenium(II)-catalyzed C6-selective C–H acylmethylation of pyridones employing sulfoxonium ylides. This new transformation is achieved using the excellent role of the Ru(II) catalyst ($[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$), and allows the synthesis of various C6-acylmethylated 2-pyridone derivatives. Besides, this approach features mild reaction conditions, moderate to excellent yields and high step economy. Furthermore, mechanistic study experiments were conducted to reveal the catalytic transformation cycle. It offers a direct and efficient way to synthesize pyridone derivatives and will be important to medicinal chemists.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation (81620108027, 21632008, and 21877118) and supported by grants from Science and Technology Commission of Shanghai Municipality (17431903100 and 18431907100).

References

- (a) A. Hueber, P. Esser and K. Heimann, *Exp. Eye Res.*, 1998, **67**, 530–533; (b) T. Brunin, L. Legentil and H. Pierre, *Tetrahedron*, 2006, **62**, 3959–3968; (c) H. Zhou, T. Shen, Y. Luo, L. Liu, W. Chen and B. Xu, *Int. J. Cancer*, 2010, **127**, 2467–2477; (d) R. Paola, E. Mazzon and I. Paterniti, *Eur. J. Pharmacol.*, 2011, **650**, 612–620; (e) P. Blier and J. Pharmacol., *Exp. Ther.*, 2014, **351**, 585–595; (f) M. Ma, Q. Ren and C. Yang, *Psychopharmacology*, 2017, **234**, 525–533.
- (a) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013–1025; (b) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345; (c) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362–3374; (d) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814–825; (e) J. J. Mousseau and A. B. Charette, *Acc. Chem. Res.*, 2013, **46**, 412–424; (f) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2015, **115**, 1622–1651; (g) L. Yang and H. M. Huang, *Chem. Rev.*, 2015, **115**, 3468–3517; (h) C. Bruneau and P. H. Dixneuf, *Top. Organomet. Chem.*, 2016, **55**, 137–188; (i) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachaland and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576; (j) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900–2936.
- (a) A. Nakatani, K. Hirano, T. Satoh and M. Miura, *Chem.–Eur. J.*, 2013, **19**, 7691–7695; (b) E. E. Anagnostaki, A. D. Fotiadou, V. Demertzidou and A. L. Zografos, *Chem. Commun.*, 2014, **50**, 6879–6882; (c) A. Nakatani, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2014, **79**, 1377–1385; (d) A. Modak, S. Rana and D. Maiti, *J. Org. Chem.*, 2015, **80**, 296–303; (e) A. Najib, S. Tabuchi, K. Hirano and M. Miura, *Heterocycles*, 2016, **92**, 1187–1203; (f) P. Chauhan, M. Ravi, S. Singh, P. Prajapati and P. P. Yadav, *RSC Adv.*, 2016, **6**, 109–118.
- (a) T. Itahara and F. Ouseto, *Synthesis*, 1984, **1984**, 488–489; (b) Y. Y. Chen, F. Wang, A. Q. Jia and X. W. Li, *Chem. Sci.*, 2012, **3**, 3231–3236; (c) Y. Li, F. Xie and X. Li, *J. Org. Chem.*, 2016, **81**, 715–722; (d) S. Maity, D. Das, S. Sarkar and R. Samanta, *Org. Lett.*, 2018, **20**, 5167–5171.
- (a) R. Tamura, Y. Yamada, Y. Nakao and T. Hiayama, *Angew. Chem., Int. Ed.*, 2012, **51**, 5679–5682; (b) Y. Cao, H. Xing, Q. Yang, Z. Li, T. Chen, Z. Bao and Q. Ren, *Ind. Eng. Chem. Res.*, 2014, **53**, 10784–10790; (c) P. A. Donets and N. Cramer, *Angew. Chem., Int. Ed.*, 2015, **54**, 633–637; (d) A. Biswas, D. Giri, D. Das, A. De, S. K. Patra and



- R. Samanta, *J. Org. Chem.*, 2017, **82**, 10989–10996; (e) K. Hirano and M. Miura, *Chem. Sci.*, 2018, **9**, 22–32.
- 6 (a) R. Odani, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2014, **53**, 10784–10788; (b) Y. Li, F. Xie and X. Li, *J. Org. Chem.*, 2016, **81**, 715–722; (c) W. Miura, K. Hirano and M. Miura, *Org. Lett.*, 2016, **18**, 3742–3745; (d) P. F. Peng, J. Wang, H. L. Jiang and H. Liu, *Org. Lett.*, 2016, **18**, 5376–5379; (e) K. A. Kumar, P. Kannaboina and P. Das, *Org. Biomol. Chem.*, 2017, **15**, 5457–5461; (f) D. Das, P. Poddar, S. Maity and R. Samanta, *J. Org. Chem.*, 2017, **82**, 3612–3621; (g) W. Miura, K. Hirano and M. Miura, *J. Org. Chem.*, 2017, **82**, 5337–5344; (h) F. Gao, X. Han, C. P. Li, L. J. Liu, Z. Q. Cong and H. Liu, *RSC Adv.*, 2018, **8**, 32659–32663; (i) D. Das and R. Samanta, *Adv. Synth. Catal.*, 2018, **360**, 379–384.
- 7 (a) J. Barluenga, P. Moriel, C. Valdés and F. Aznar, *Angew. Chem., Int. Ed.*, 2007, **46**, 5587–5590; (b) M. Roche, A. Hamze, O. Provot, J.-D. Brion and M. Alami, *J. Org. Chem.*, 2013, **78**, 445–454; (c) D. Das, A. Biswas, U. Karmakar, S. Chand and R. Samanta, *J. Org. Chem.*, 2016, **81**, 842–848; (d) Y. Xia, D. Qiu and J. Wang, *Chem. Rev.*, 2017, **117**, 13810–13828; (e) M. Paraja, R. Barroso, M. P. Cabal and C. Valdés, *Adv. Synth. Catal.*, 2017, **359**, 1058–1062.
- 8 (a) E. Brachet, A. Hamze, J.-F. Peyrat, J.-D. Brion and M. Alami, *Org. Lett.*, 2010, **12**, 4042–4045; (b) B. Tréguier, M. Lawson, G. Bernadat, J. Bignon, J. Dubois, J. D. Brion, M. Alami and A. Hamze, *ACS Comb. Sci.*, 2014, **16**, 702–710; (c) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert and F. Glorius, *Angew. Chem., Int. Ed.*, 2015, **54**, 4508–4511; (d) P. K. Patel, J. P. Dalvadi and K. H. Chikhalia, *Tetrahedron Lett.*, 2015, **56**, 6585–6589; (e) Y. Zhou, F. Ye, X. Wang, S. Xu, Y. Zhang and J. Wang, *J. Org. Chem.*, 2015, **80**, 6109–6118; (f) Y. Xia, F. Hu, Y. Xia, Z. Liu, F. Ye, Y. Zhang and J. Wang, *Synthesis*, 2017, **49**, 1073–1086; (g) S. Qu and C. J. Cramer, *J. Org. Chem.*, 2017, **82**, 1195–1204; (h) X. Hu, X. Chen, Y. Shao, H. Xie, Y. Deng, Z. Ke, H. Jiang and W. Zeng, *ACS Catal.*, 2018, **8**, 1308–1312.
- 9 (a) H. Zhang, K. Wang, B. Wang, H. Yi, F. Hu, C. Li, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 13234–13238; (b) L. Dian and I. Marek, *Angew. Chem., Int. Ed.*, 2018, **57**, 3682–3686.
- 10 (a) Q. Xiao, Y. Zhang and J. Wang, *Acc. Chem. Res.*, 2013, **46**, 236–247; (b) A. P. Jadhav, D. Ray, V. U. B. Rao and R. P. Singh, *Eur. J. Org. Chem.*, 2016, **2016**, 2369–2394.
- 11 S. Y. Hong, J. Jeong and S. Chang, *Angew. Chem., Int. Ed.*, 2017, **56**, 2408–2412.
- 12 (a) N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi and V. V. Fokin, *J. Am. Chem. Soc.*, 2012, **134**, 14670–14673; (b) H. M. L. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151–5162; (c) Y. Wang, X. Lei and Y. Tang, *Synlett*, 2015, **26**, 2051–2059; (d) V. Helan, A. V. Gulevich and V. Gevorgyan, *Chem. Sci.*, 2015, **6**, 1928–1931; (e) W. H. Jeon, J.-Y. Son, J. E. Kim and P. H. Lee, *Org. Lett.*, 2016, **18**, 3498–3501; (f) Y. Jiang, R. Sun, X.-Y. Tang and M. Shi, *Chem.-Eur. J.*, 2016, **22**, 17910–17924.
- 13 (a) F. Wang, L. Jin, L. Kong and X. Li, *Org. Lett.*, 2017, **19**, 1812–1815; (b) Y. Xu, X. Zhou, G. Zheng and X. Li, *Org. Lett.*, 2017, **56**, 13117–13121; (c) J. Vaitla, A. Bayer and K. H. Hopmann, *Angew. Chem., Int. Ed.*, 2017, **56**, 4277–4281; (d) M. Barday and C. Janot, *Angew. Chem., Int. Ed.*, 2017, **56**, 13117–13121; (e) J. Zhu, S. Sun and J. Cheng, *Tetrahedron Lett.*, 2018, **59**, 2284–2287; (f) Y. Xu, G. Zheng, X. Yang and X. Li, *Chem. Commun.*, 2018, **54**, 670–673; (g) Y. Wu, Z. Chen, Y. Yang, W. Zhu and B. Zhou, *J. Am. Chem. Soc.*, 2018, **140**, 42–45.

