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Copper-catalyzed one-pot amine-alkylation of quinones with amines and alkanes†

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A copper-catalyzed one-pot amine-alkylation of quinones with amines and alkanes in the presence of di-*tert*-butyl peroxide (DTBP) was developed *via* a radical reaction process. Various alkanes and aromatic or aliphatic amines with diverse structures and electronic properties are suitable substrates, and the chirality of amines can be maintained for the transformation. This method has high step and atom economy for straightforward access to aminated and alkylated quinones from readily available starting materials.

Introduction

Quinones play significant roles in developing pharmaceuticals and functional materials and act as building blocks in total synthesis.[1] Owing to their unique structure and electron transport properties, quinone derivatives exhibit a wide range of biological and pharmacological activities in biological systems.[2] It is worth noting that amino and alkyl substituted quinones display good biological activity, including antibacterial, antibiotic and antitumor activities (Fig. 1).[3] Therefore, the development of novel, simple and efficient methods to synthesize amine and alkyl substituted quinones is of great significance. Generally, the methods for synthesizing amine and alkyl substituted quinones are rarely described, and there are two main methods: (i) the treatment of 1,4-naphthoquinones, *via* sequential amination and alkylation of the quinones, to form amine and alkyl substituted quinones[4] and (ii) the direct amination reaction of methyl substituted quinones with amines also yields amine and alkyl substituted quinones.[5] Regrettably, these ways required multistep reaction procedures and the substrate scope was very restricted. Therefore, developing high atom economy and more facile methods for the synthesis of amine and alkyl substituted quinones from quinones in a one-pot fashion is highly desirable.

Recently, due to its excellent features, such as high step economy and atom economy, the difunctionalization of alkenes *via* a radical pathway is used for the construction of polyfunctionalized molecules.[6] Meanwhile, significant progress has been achieved in a plethora of alkene difunctionalizations, such as carbo-, oxy-, halo-, cyano-, azido-, and amine-alkylation.[7] In contrast, although there have been many reports on monofunctionalization of quinones, such as alkyl-, aryl-, alkynyl-, and trifluoromethylation,[8] reports on one-pot difunctionalization of quinones have been very rare. In 2002, Theodorakis and co-workers reported alkylation and thioetherification of quinones by photochemical decarboxylation of thiocarbonyl derivatives (Scheme 1a).[9] In 2019, the group of Chen developed a copper-catalyzed one-pot three-component thioamination of 1,4-naphthoquinone with thiols and amines (Scheme 1b).[10] Despite the significant development, as far as we know, the direct amine-alkylation of quinones in a one-pot manner has not yet been reported. Inspired by these results and our group's continuous interest in the functionalization of quinones,[11] we envisage the synthesis of amines and alkyl-substituted quinones in a one-step manner from quinones with amines and alkanes *via* a radical process. Herein, we report for

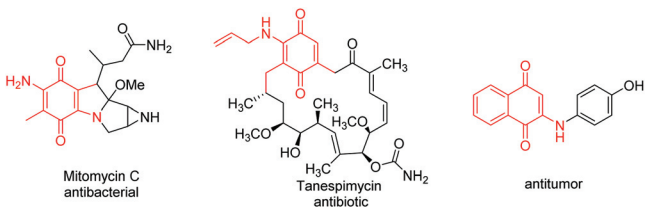

Fig. 1 Amine-alkyl substituted quinones with biological and pharmacological activities.

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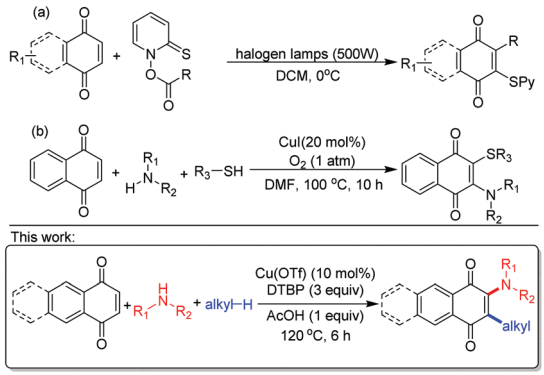
‡These authors contributed equally to this work.



Scheme 1 The one-pot difunctionalization of quinones.

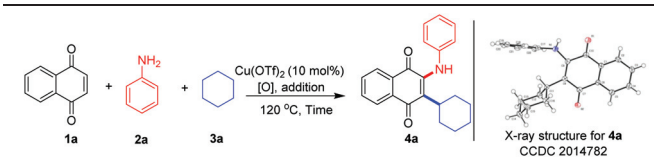
the first time a copper-catalyzed one-pot amine-alkylation of quinones with amines and alkanes in the presence of DTBP.

Results and discussion

Initially, we selected 1,4-naphthoquinone **1a** as a model substrate, aniline **2a** as an amination reagent, and cyclohexane **3a** as an alkylation reagent to evaluate our hypothesis (Table 1, as well as Tables S1–S6 in the ESI†). Fortunately, in the presence of DTBP (2 equiv.), **1a** was converted to the amine-alkylated 1,4-naphthoquinone **4a** in 46% yield with a 10 mol% loading of $Cu(OTf)_2$ in a sealed tube at 120 °C for 20 hours in cyclohexane (entry 1). Subsequently, the oxidant was screened. DTBP was proved to be more efficient than others, such as *tert*-butyl-hydroperoxide (TBHP), *tert*-butyl-peroxybenzoate (TBPB), dicumyl peroxide (DCP), and benzoyl peroxide (BPO) (entries 2–5). To our delight, when acetic acid was added, the yield of product **4a** was increased to 52% (entries 6–8). The reaction time was crucial for the present reaction, and 76% yield was obtained when it was reduced from 20 h to 6 h (entries 9–11). This is probably because too short reaction time will lead to incomplete reaction, while too long reaction time will increase by-products. Finally, the reaction could afford **4a** in 83% yield using 3 equiv. of DTBP (entry 12).

With the optimized reaction conditions in hand, we began to evaluate the feasibility of the reaction by studying the performance of various amines that bear diverse substituent groups (Table 2). Gratifyingly, anilines with various substituents, such as halide, alkyl, ether, thioether, acyl and ester groups, at the *para*-, *meta*- or *ortho*-position on the aryl ring, were suitable for this transformation, and the corresponding products were obtained in moderate to good yields (**4a–p**, 37–83%). The result indicated that aniline with electron-donating substituents exhibited more reactivity than those with electron-withdrawing substituents and no obvious steric effects of anilines were observed for this reaction. The disubstituted aniline with diverse electronic properties smoothly afforded the desired products (**4q–u**, 39–78%). Notably, by adding an electron donating group, the nitro substituted products **4t** and **4u** were successfully obtained in 42% and 39% yields, respectively. For **4v**, addition of excess catalyst was necessary for this reaction (**4v**, 38%). Moreover, although the yield of aliphatic amines is lower than that of aromatic amines, the corres-

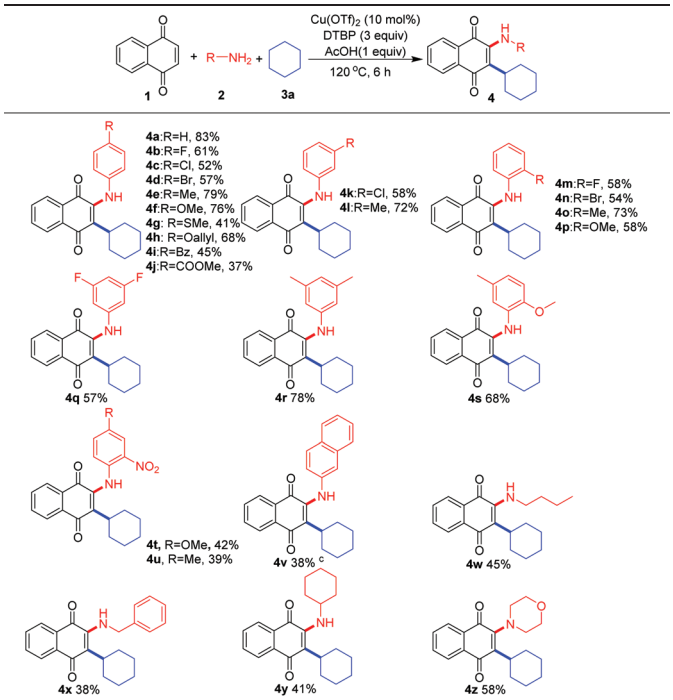
Table 1 Optimization of reaction conditions[a]



Entry	Oxidant (2 equiv.)	Addition (1 equiv.)	Time (h)	Yield[b] (%)
1	DTBP	—	20	46
2	TBPB	—	20	Trace
3	BPO	—	20	Trace
4	DCP	—	20	38
5	TBHP	—	20	Trace
6	DTBP	AcOH	20	52
7	DTBP	TFA	20	Trace
8	DTBP	$TsOH·H_2O$	20	48
9	DTBP	AcOH	4	44
10	DTBP	AcOH	6	76
11	DTBP	AcOH	8	64
12[c]	DTBP	AcOH	6	83

[a] Reaction conditions: 1,4-Naphthoquinone (0.30 mmol), aniline (1.2 equiv.), $Cu(OTf)_2$ (10 mol%), oxidant (2 equiv.), additive (1 equiv.), and cyclohexane (2 ml) as the solvent, 120 °C, sealed tube, and 6 h. [b] Isolated yields. [c] DTBP 3 equiv.

Table 2 Substrate scope for amines[a,b]

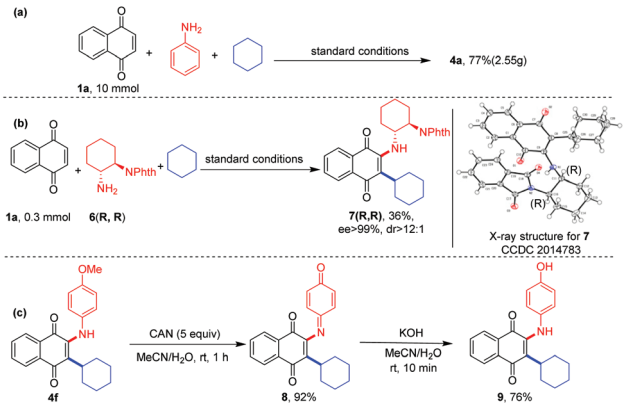


[a] Reaction conditions: 1,4-Naphthoquinone (0.30 mmol), amine (1.2 equiv.), $Cu(OTf)_2$ (10 mol%), DTBP (3 equiv.), additive (1 equiv.), and cyclohexane (2 ml) as the solvent, 120 °C, sealed tube, and 6 h. [b] Isolated yields. [c] $Cu(OTf)_2$ (30 mol%).

ponding product was also obtained. Primary aliphatic amines such as butylamine, benzylamine, and cyclohexylamine were suitable substrates under standard reaction conditions, while the corresponding products were furnished in acceptable yields (**4w–y**, 38–45%). Morpholine also reacted successfully with 1,4-naphthoquinone and cyclohexane to give the desired product **4z** in 58% yield.

To further extend the utility of this amine-alkylation reaction, we have also investigated the substrate scope of alkanes and quinones (Table 3). Cyclopentane, cycloheptane and cyclooctane also worked well, providing the desired products in moderate yields (**5a–c**, 68–74%). To our excitement, this amine-alkylation reaction was not limited to cycloalkanes. Benzylic hydrocarbons and chain alkanes were also suitable substrates with a slight change of the reaction conditions. Different electronic property substituents on toluene have a greater impact on this reaction, and toluenes with electron-withdrawing substituents exhibited more reactivity than those with the electron-donating substituents (**5d–f**, 55–70%). Hexane also took part in the amine-alkylation reaction, leading to the 2- and 3-functionalized products **5g** (2 : 1) in total 74% yield. For quinones, 1,4-anthraquinones are suitable substrates under the standard conditions while the desired products were obtained in 42% yield (**5h**). Unfortunately, hydroxyl substituted 1,4-naphthoquinones are not suitable substrates under the standard conditions (**5i**).

Furthermore, the scale-up of the reaction was performed to reveal the applicability of this method. When 1,4-naphthoquinone **1a** was scaled up by 10 mmol, **4a** was isolated in 77% yield (Scheme 2a). Moreover, when a chiral diamine was used

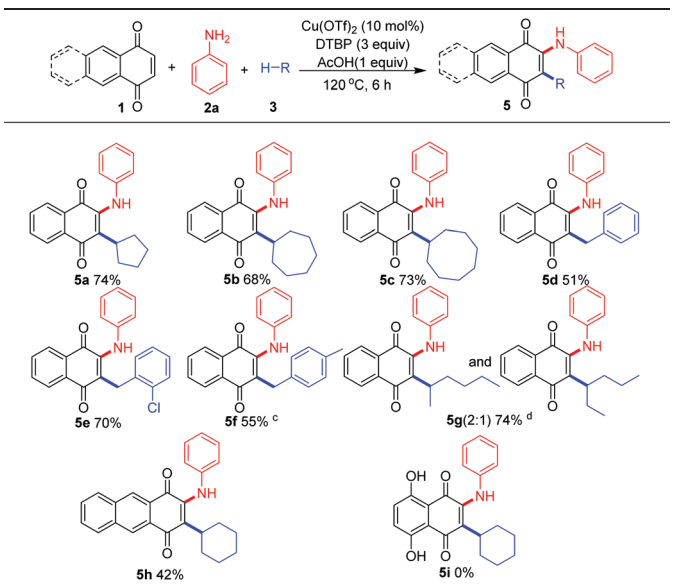


Scheme 2 The scale-up reaction and synthetic applications.

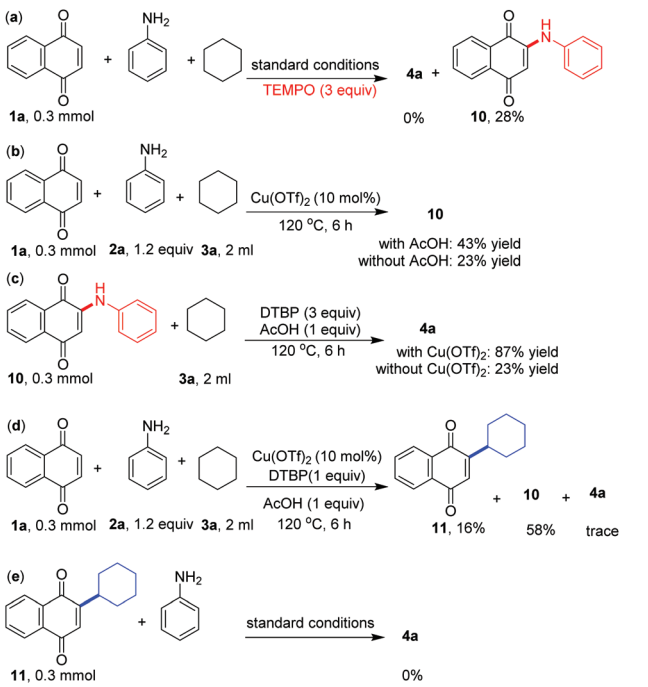
for the protocol, the product **6** was also successfully obtained, and it was found that the chirality was maintained by single crystal diffraction (Scheme 2b). This also provides a new method for the synthesis of new chiral catalysts or ligands with a quinoid structure. Finally, we hope to obtain amino and alkyl substituted quinones *via* CAN deprotection of the PMP group.[12] Interestingly, the compound **4f** produced an oxidation product **8** in 92% yield. Furthermore, the compound **8** could provide the compound **9** in 76% yield, which is an analogue of phenylamino naphthoquinone with antitumor activity (Scheme 2c).

In order to further investigate the mechanism of the amine-alkylation reaction, several control experiments were carried out as shown in Scheme 3. The model reaction only afforded

Table 3 Substrate scope of alkanes and quinones[a,b]



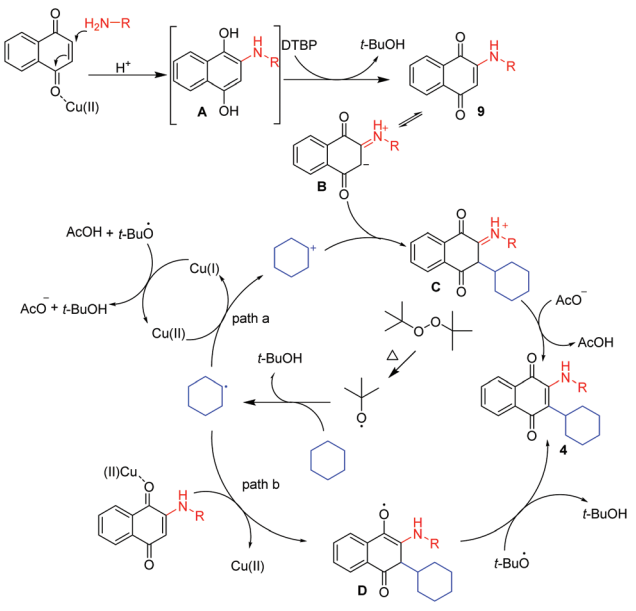
[a] Reaction conditions: 1,4-Naphthoquinone (0.30 mmol), amine (1.2 equiv.), $Cu(OTf)_2$ (10 mol%), DTBP (3 equiv.), additive (1 equiv.), and cyclohexane (2 ml) as the solvent, 120 °C, sealed tube, and 6 h. [b] Isolated yields. [c] DTBP (5 equiv.), 12 h. [d] DTBP (5 equiv.), determined by ^1H NMR spectra.



Scheme 3 Control experiment.

the aminated product **10** with the addition of 3 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), which suggests that the amine-alkyl reaction involves a step-by-step reaction and a radical process (Scheme 3a). The reaction of model compounds **1a**, **2a** and cyclohexane **3a** generated the aminated product **10** in 43% yield without DTBP, while the aminated product was obtained in only 23% yield without DTBP and AcOH, which means that AcOH can promote the amination reaction (Scheme 3b). Subsequently, **4a** was obtained in 87% yield with the reaction of compound **10** and cyclohexane **3a** under the standard conditions, while the yield of **4a** was decreased from 87% to 26% in the absence of copper salt (Scheme 3c). This showed that copper played an important role in this transformation. When the amount of oxidant was reduced to 1 equiv., the reaction generated compound **10** in 68% yield, alkylated product **11** in 16% yield and trace amounts of **4a**, respectively (Scheme 3d). Moreover, the reaction of compounds **11** and **2a** did not give **4a** under standard conditions (Scheme 3e). These results showed that the intermediate was compound **10** instead of compound **11** in this amino-alkylation reaction.

Based on the control experiment results and previous literature,[4,10,13] a possible reaction mechanism is proposed in Scheme 4. First, in the presence of protons, amine reacted with 1,4-naphthoquinone activated by Cu(II) to give the intermediate **A**, which was immediately oxidized to compound **9** by DTBP. Meanwhile, the *tert*-butyl radical generated by the thermal cracking of DTBP abstracts a proton from cyclohexane to form a cyclohexyl radical. On the one hand, the cyclohexyl radical generated a cyclohexyl carbocation and regenerated Cu (I) *via* a SET process with Cu(II). Thereafter, the reaction of the cyclohexyl carbocation with intermediate **B** formed by the rearrangement of **9** generates intermediate **C**, and the product **4** is obtained after deprotonation and rearrangement of intermediate **C** (**path a**). On the other hand, the cyclohexyl radical could react with compound **9** activated by Cu(II) to give the intermediate **D**. Subsequently, the intermediate **D** is oxidized by the *tert*-butoxy radical to form the product **4** (**path b**).



Scheme 4 Possible mechanisms.

Conclusions

In conclusion, a novel and efficient strategy for amine-alkylation of quinones with amines and alkanes has been described. The reaction had excellent functional group tolerance, and various aromatic or aliphatic amines and alkanes or benzylic hydrocarbons were suitable substrates for the reaction. Meanwhile, the chirality of the reactant was also maintained in this transformation. Finally, we proposed a possible radical pathway for the reaction based on the results from control experiments.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

1 (*a*) E. L. Bonifazi, C. Ríos-Luci, J. M. Padrón and R. I. Misico, *Bioorg. Med. Chem.*, 2010, **18**, 2621–2630; (*b*) K. R. Prasad, K. S. Babu, P. U. Rani and J. M. Rao, *Med. Chem. Res.*, 2012, **21**, 578–583; (*c*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (*d*) J. Lee, H. S. Mei and J. K. Snyder, *J. Org. Chem.*, 1990, **55**, 5013–5016; (*e*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115.

2 (*a*) J. E. Klare, G. S. Tulevski, K. A. White and C. Nuckolls, *J. Am. Chem. Soc.*, 2003, **125**, 6030–6031; (*b*) B. Nowicka and J. Kruk, *Biochim. Biophys. Acta*, 2010, **1797**, 1587–1605; (*c*) A. K. Jordão, J. Novais, H. M. dos Santos Jú and V. F. Ferreira, *Eur. J. Med. Chem.*, 2013, **63**, 196–201; (*d*) P. Petrangolini, A. Alessandrini and P. Facci, *J. Phys. Chem. C*, 2013, **117**, 17451–17461.

3 (*a*) J. Benites, J. A. Valderrama, P. B. Calderon and J. Verrax, *Eur. J. Med. Chem.*, 2010, **45**, 6052–6057; (*b*) R. Domalaon, D. Ammeter, G. G. Zhanel and F. Schweizer, *Front. Microbiol.*, 2019, **10**, 1556; (*c*) M. A. Dimopoulos, C. S. Mitsiades, K. C. Anderson and P. G. Richardson, *Clin. Lymphoma, Myeloma Leuk.*, 2011, **11**, 17–22.

4 (*a*) C. D. S. Lisboa, V. G. Santos, M. N. Eberlin and S. J. Garden, *J. Org. Chem.*, 2011, **76**, 5264–5273;

(*b*) Q.-J. Wang, B. Wang, H.-C. Guo and C. Zhang, *J. Org. Chem.*, 2019, **84**, 1006–1014; (*c*) Y. Shangguan, F.-Z. Yang, Y.-M. Xiao and C. Zhang, *J. Org. Chem.*, 2019, **84**, 10649–10657; (*d*) K. Kobayashi, M. Suzuki, H. Sakurai and H. Suginorne, *J. Chem. Soc., Perkin Trans. 1*, 1994, **8**, 1009–1104.

5 (*a*) U. Sharma, D. Katoch, A. Thakur and A. Gulati, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2013, **52**, 1431–1440; (*b*) Y.-Y. Ding, F. Tang, Z.-C. Tu and J.-C. Zhang, *Bioorg. Chem.*, 2019, **89**, 102870.

6 (*a*) G. Qiu, L. Lai, J. Wu and J. Cheng, *Chem. Commun.*, 2018, **54**, 10405–10414; (*b*) T. Courant and G. Masson, *J. Org. Chem.*, 2016, **81**, 6945–6952; (*c*) T. Koike and M. Akita, *Chem*, 2018, **4**, 409–437; (*d*) X.-W. Lan, N.-X. Wang and Y. Xing, *Eur. J. Org. Chem.*, 2017, 5821–5851; (*e*) G. S. Sauer and S. Lin, *ACS Catal.*, 2018, **8**, 5175–5187; (*f*) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294–8308.

7 (*a*) J. Terao, K. Saito, N. Kambe and N. Sonoda, *J. Am. Chem. Soc.*, 1998, **120**, 11822–11823; (*b*) T. Ishii, K. Ota, K. Nagao and H. Ohmiya, *J. Am. Chem. Soc.*, 2019, **141**, 14073–14077; (*c*) J. L. Schwarz, H.-M. Huang, T. O. Paulisch and F. Glorius, *ACS Catal.*, 2020, **10**, 1621–1627; (*d*) Y.-J. Zhang and D.-Y. Zhang, *J. Org. Chem.*, 2020, **85**, 3213–3223; (*e*) M. Lux and M. Klussmann, *Org. Lett.*, 2020, **22**, 3697–3701; (*f*) W.-J. Jian, L. Ge, Y.-H. Jiao and H.-L. Bao, *Angew. Chem., Int. Ed.*, 2017, **56**, 3650–3654; (*g*) L. Ge, Y.-J. Li, W.-J. Jian and H.-L. Bao, *Chem. – Eur. J.*, 2017, **23**, 11767–111770; (*h*) Y.-X. Li, Q.-Q. Wang and L. Yang, *Org. Biomol. Chem.*, 2017, **15**, 1338–1342; (*i*) C.-G. Li, Q. Xie, Y.-F. Liang and H.-J. Xu, *Org. Lett.*, 2019, **21**, 8496–8500; (*j*) W.-B. Du, L.-X. Tian, X.-G. She and S.-C. Tang, *Org. Lett.*, 2014, **16**, 2470–2473; (*k*) Z.-Q. Liu and D. Liu, *J. Org. Chem.*, 2017, **82**, 1649–1656; (*l*) Z.-J. Hang, Z.-J. Li and Z.-Q. Liu, *Org. Lett.*, 2014, **16**, 3648–3651; (*m*) W.-X. Sha, L.-L. Deng, H.-B. Mei and J.-L. Han, *ACS Catal.*, 2018, **8**, 7489–7494; (*n*) M. Israr, H.-G. Xiong, Y.-J. Li and H.-L. Bao, *Adv. Synth. Catal.*, 2020, **362**, 2211–2215; (*o*) W.-Y. Li, Q.-Q. Wang and L. Yang, *Org. Biomol. Chem.*, 2017, **15**, 9987–9991; (*p*) H.-G. Xiong, N. Ramkumar, X.-H. Zhang and H.-L. Bao, *Nat. Commun.*, 2019, **10**, 122; (*q*) Y.-Y. Liu, X.-H. Yang, S.-L. Luo and J.-H. Li, *Nat. Commun.*, 2016, **8**, 14720; (*r*) B. Qian, S.-W. Chen, X.-H. Zhang and H.-L. Bao, *J. Am. Chem. Soc.*, 2017, **139**, 13076–13082; (*s*) G.-H. Pan, Y.-X. Xie and J.-H. Li, *Adv. Synth. Catal.*, 2017, **359**, 2564–2570.

8 (*a*) Y. Fujiwara, V. Domingo, M. Del Bel and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 3292–3295; (*b*) A. Ilangovan, S. Saravanakumar and S. Malayappasamy, *Org. Lett.*, 2013, **15**, 4968–4971; (*c*) Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui and G. A. Molander, *J. Am. Chem. Soc.*, 2017, **139**, 12251–12258; (*d*) D. L. R. Sutherland, C. L. Oates and A.-L. Lee, *Org. Lett.*, 2018, **20**, 6863–6667; (*e*) J. Wang, S. Wang, J. Zhang and X. Q. Yu, *Chem. Commun.*, 2012, **48**, 11769–11771; (*f*) P. Patil, A. Nimonkar and K. G. Akamanchi, *J. Org. Chem.*, 2014, **79**, 2331–2336; (*g*) S. E. Walker, J. A. Jordan-Hore, S. A. Macgregor and A.-L. Lee, *Angew. Chem., Int. Ed.*, 2014, **53**, 13876–13879; (*h*) M. Youngtaek, J. Yujeong, K. Daehyuk and H. Sungwoo, *Org. Biomol. Chem.*, 2015, **13**, 3918–3923; (*i*) C. Schiel, M. Oelgemöller, J. Ortner and J. Mattay, *Green Chem.*, 2001, **3**, 224–228; (*j*) P. A. Waske, J. Mattay and M. Oelgemoller, *Tetrahedron Lett.*, 2006, **47**, 1329–1332; (*k*) N. O. Ilchenko, P. G. Janson and K. J. Szabó, *Chem. Commun.*, 2013, **49**, 6614–6616; (*l*) X. Wang, Y.-X. Ye, Y. Zhang and J.-B. Wang, *Org. Lett.*, 2013, **15**, 3730–3733; (*m*) C. Li, K. Zhang, X.-H. Xu and F.-L. Qing, *Tetrahedron Lett.*, 2015, **56**, 6273–6275.

9 T.-T. Ling, E. Poupon, E. J. Rueden and E. A. Theodorakis, *J. Am. Chem. Soc.*, 2002, **124**, 12261–12267.

10 F.-L. Zeng, X.-L. Chen, Y.-F. Zhao and B. Yu, *Org. Chem. Front.*, 2019, **6**, 1476–1480.

11 (*a*) B.-R. Ai, X.-L. Chen and J.-Y. Wang, *Synthesis*, 2017, **49**, 4017–4024; (*b*) Y. Dong, X.-L. Chen and J.-Y. Wang, *Tetrahedron Lett.*, 2018, **59**, 3620–3623; (*c*) X.-L. Chen, Y. Dong, X.-M. Zhang and J.-Y. Wang, *Synlett*, 2019, **30**, 615–619; (*d*) Y. Dong, J. Yang, X.-M. Zhang and J.-Y. Wang, *RSC Adv.*, 2019, **9**, 27588–27592; (*e*) J. Yang, Y. Dong, Y. Wang and J.-Y. Wang, *Tetrahedron*, 2019, **75**, 130729; (*f*) Y. Dong, H. Zhang, J. Yang and J.-Y. Wang, *ACS Omega*, 2019, **4**, 21567–21577; (*g*) Y. Dong, J. Yang, X.-M. Zhang and J.-Y. Wang, *Org. Lett.*, 2020, **22**, 5151–5156.

12 G.-L. Li, Y.-X. Liang and J. C. Antilla, *J. Am. Chem. Soc.*, 2007, **129**, 5830–5831.

13 (*a*) H.-B. Peng, J.-T. Yu, H.-T. Yang and J. Cheng, *J. Org. Chem.*, 2014, **79**, 9847–9853; (*b*) E. R. Baral, S. H. Kim and Y. R. Lee, *Asian J. Org. Chem.*, 2016, **5**, 1134–1141; (*c*) H.-L. Zhang, Z.-X. Gu, P. Xu, Y.-X. Cheng and C.-J. Zhu, *Chem. Commun.*, 2016, **52**, 477–480; (*d*) A. Samzadeh-Kermani, *New J. Chem.*, 2018, **42**, 4766–4772.

