


Cite this: *RSC Adv.*, 2020, 10, 29114

Received 7th July 2020

Accepted 27th July 2020

DOI: 10.1039/d0ra05921h

rsc.li/rsc-advances

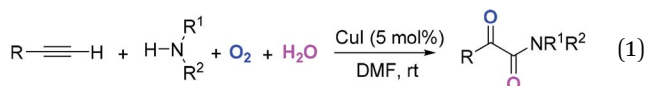
Copper-catalyzed synthesis of α -ketoamides using water and dioxygen as the oxygen source†

Yuanyuan Xiao,^a Zijuan Yi,^b Xianrong Yu^b and Fang Xiao^{id}*^a

The reaction employing H_2O and O_2 as the co-oxygen source in the catalytic synthesis of α -ketoamides is described. This copper-catalyzed reaction is carried out in a tandem manner constituted by the hydroamination of alkyne, hydration of vinyl–Cu complex and subsequent oxidation. Isotope labeling and radical capture experiments reveal that the oxygen atom of α -ketone at α -ketoamides derives from O_2 and the oxygen atom of amide group originates from H_2O .

Introduction

The introduction of oxygen atoms into organic molecules to construct oxygenated compounds is one of the most fundamental subjects in organic chemistry. From a “green and sustainable chemistry” perspective, water and dioxygen are the most environmentally benign and cost-effective oxygen-containing reagents.¹ Consequently, employing them as oxygen sources offers appealing access to oxygen-containing organic compounds.^{2,3} Herein, the example of direct utilization of H_2O and O_2 as the co-oxygen source to assemble α -ketoamides is reported. Isotope labeling and radical capture experiments demonstrate that the oxygen atom of α -ketone at α -ketoamide derives from dioxygen and the oxygen atom of amide group originates from water (eqn (1)).



α -Ketoamides have attracted increasingly synthetic pursuit of chemists, as key structural motifs of many biologically active compounds and versatile building blocks.⁴ Various synthetic methods for the preparation of α -ketoamides have been developed over the past decades, such as amidation of α -ketoacids,⁵ oxidation of enamines,⁶ ynamines,⁷ arylacetamides⁸ and α -cyanoamides,⁹ Pd-catalyzed double carbonylative amination of aryl halides,¹⁰ and the oxidation of acyl cyanophosphoranes followed by amidation of the resulting α,β -diketone nitriles.¹¹ Most of these well established approaches toward α -ketoamides often

require toxic, expensive or preformed oxygen sources, such as SeO_2 , $\text{K}_2\text{Cr}_2\text{O}_7$, CO, TBHP, and O_3 . Thus, the development of direct incorporation oxygen atoms from clean and cheap oxygen sources into organic frameworks to construct α -ketoamides is highly desirable.¹² In 2010, Zhu reported the transformation of aldehydes with isocyanides to α -ketoamides using water as the oxygen source.¹³ Recently, various metal-catalyzed or metal-free methods for the oxidative synthesis of α -ketoamides from terminal alkynes,¹⁴ aryl acetaldehydes,¹⁵ ketones,¹⁶ 1-arylethanol,¹⁷ phenethyl alcohol derivatives,¹⁸ and ethylarenes¹⁹ have also been developed by using dioxygen as oxygen source. In 2019, Wei and co-workers reported the transformation of α -ketoacids with isocyanides to α -ketoamides using water as the oxygen source.²⁰

Multicomponent reaction has emerged as a powerful protocol to construct complex organic compounds.²¹ The present multicomponent reaction of copper-catalyzed direct oxidative transformation of alkynes and secondary amines to α -ketoamides is realized at room temperature without any ligand or additive, in which H_2O and O_2 were employed as the co-oxygen source (eqn (1)). Preliminary mechanistic studies suggest that this multicomponent reaction is performed in a tandem manner constituted by the hydroamination of alkyne, hydration of vinyl–Cu complex and subsequent oxidation with dioxygen. This methodology not only provides an interesting and attractive approach to α -ketoamides, but also allows an avenue to simultaneously introduce oxygen atoms from H_2O and O_2 into organic frameworks to access multi-oxygen containing compounds.

Results and discussion

During the course of investigation on transition-metal-catalyzed oxidative transformation of alkynes and secondary amines to α -ketoamides, we found CuBr can catalyze the reaction of phenylacetylene **1a** with piperidine **2a** to give the product **3aa** in presence of H_2O (2 equiv.) under O_2 without ligand or additive (Table 1, entry 1). Preliminary exploration showed that no **3aa** was detected when the reaction was performed in the absence of

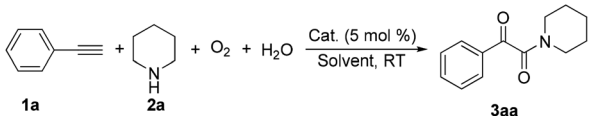
^aDepartment of Health Toxicology, Xiangya School of Public Health, Central South University, Changsha 410078, PR China. E-mail: fangxiao@csu.edu.cn

^bSchool of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan 411201, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra05921h



Table 1 Optimization of reaction conditions^a

			
Entry	Catalyst (mol%)	Solvent	3aa ^b (%)
1	CuBr	THF	21
2	CuBr	THF	0 ^c
3	CuBr	THF	0 ^d
4	CuBr ₂	THF	18
5	CuCl ₂	THF	15
6	CuCl	THF	14
7	Cu(OTf) ₂	THF	16
8	(CH ₃ CN) ₄ CuPF ₆	THF	21
9	CuI	THF	43
10	AgOTf	THF	0
11	RhCl ₃	THF	0
12	InCl ₃	THF	0
13	AlF ₃	THF	0
14	AuBr ₃	THF	Trace
15	—	THF	0
16	CuI	1,4-Dioxane	25
17	CuI	MeOH	0
18	CuI	EtOH	0
19	CuI	DME	45
20	CuI	DCE	32
21	CuI	Toluene	23
22	CuI	DMSO	34
23	CuI	DMF	71
24	CuI	DMF	46 ^e

^a Reaction conditions: **1a** (2 mmol), **2a** (0.5 mmol), catalyst (5 mol%), H₂O (2 equiv.), O₂ (balloon), solvent (0.5 mL), at room temperature, 12 h. ^b Isolated yields based on **2a**. ^c Under N₂. ^d Dry THF was used and 4 Å molecular sieve was added. ^e Under air.

O₂ or H₂O (Table 1, entries 2 and 3). These results suggested that H₂O might be served as the oxygen source of **3aa** and O₂ as the oxidant or both of them were used as the co-oxygen source. This interesting phenomenon prompted us to optimize the reaction conditions and disclose the accurate origination of the oxygen atoms of α -ketoamides.

Initially, the reaction of phenylacetylene **1a** with piperidine **2a** was performed to examine the catalytic activity of various transition metal complexes including Au, Ag, Cu, Rh, Ni, Pd, Al, Bi, and In salts in the presence of H₂O (2 equiv.) under the oxygen atmosphere. As shown in Table 1, among those metal catalysts examined (entries 4–14), CuI was found to be the best catalyst to catalyze the formation of α -ketoamide **3aa**. No conversion was observed in the absence of catalyst (entry 15). The screening of solvents indicated that DMF was the optimal reaction medium (entries 16–23). This reaction could also proceed smoothly under the air atmosphere (entry 24).

With the optimized conditions in hand, the scope of this new reaction was investigated (Table 2). Generally, the reaction tolerated electron-donating (*para*-, *meta*-, and *ortho*-substituted) and electron-withdrawing groups at the aromatic ring of alkynes (Table 2, entries 1–5). It was found that the reaction

Table 2 Copper-catalyzed synthesis of α -ketoamides^a

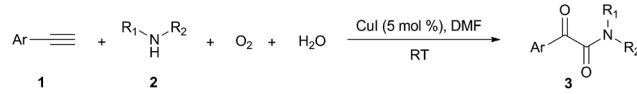
				
Entry	Alkyne (1)	Amine (2)	Product (3)	Yield ^b (%)
1	1a	2a	3aa	71
2	1b	2a	3ba	72
3	1c	2a	3ca	61
4	1d	2a	3da	60
5	1e	2a	3ea	56
6	1f	2a	3fa	64
7	1g	2a	3ga	57
8	1a	2b	3ab	65
9	1a	2c	3ac	56
10	1a	2d	3ad	64
11	1b	2c	3bc	65
12	1b	2d	3bd	62
13	1c	2c	3cc	63
14	1c	2d	3cd	60
15	1d	2c	3dc	61



Table 2 (Contd.)

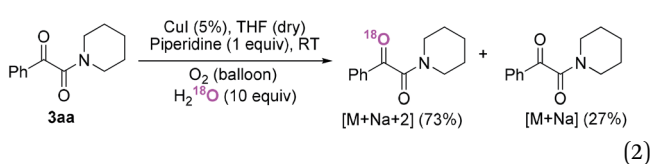
$\text{Ar}-\text{C}\equiv\text{C}-\text{H} + \text{R}_1\text{NHR}_2 + \text{O}_2 + \text{H}_2\text{O} \xrightarrow[\text{RT}]{\text{CuI (5 mol %), DMF}} \text{Ar}-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{NR}_1\text{R}_2$				
Entry	Alkyne (1)	Amine (2)	Product (3)	Yield ^b (%)
16	1d	2d	3dd	60
17	1a	2e	3ae	52
18	1a	2f	3af	63

^a Reaction conditions: **1** (2 mmol), **2** (0.5 mmol), CuI (5 mol%), H₂O (2 equiv.), O₂ (balloon), DMF (0.5 mL), rt, 12–48 h. ^b Isolated yields.

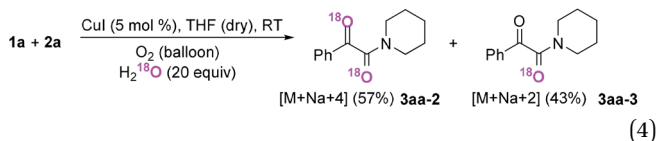
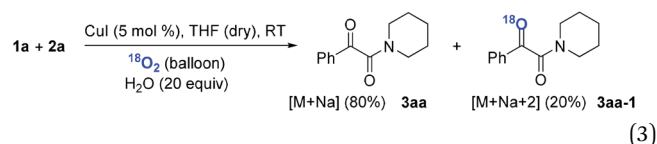
efficiency was affected by the steric effect. The more sterically demanding substrates such as *ortho*-methyl or chloro substituted arylalkynes demonstrated slightly lower activities (Table 2, entries 1–5). The present method can also apply to alkynes connected with naphthalene rings (Table 2, entries 6 and 7). The scope of amines was also examined, and both cyclic amines and linear amines were suitable substrates for this process. Cyclic amines such as piperidine, morpholine, 4-substituted piperidines, and pyrrolidine reacted with phenylacetylene or substituted phenylacetylenes to generate the corresponding products in moderate to good yields (Table 2, entries 1 and 8–17). The reaction of di-*n*-butylamine with **1a** afforded α -ketoamide in moderate yield (Table 2, entry 18).

Isotope labeling and radical capture experiments were performed to elucidate the origination of the oxygen atoms of α -ketoamide. Results of these experiments demonstrate the oxygen atom of amide group originates from H₂O and the oxygen atom of α -ketone at α -ketoamide derives from dioxygen.

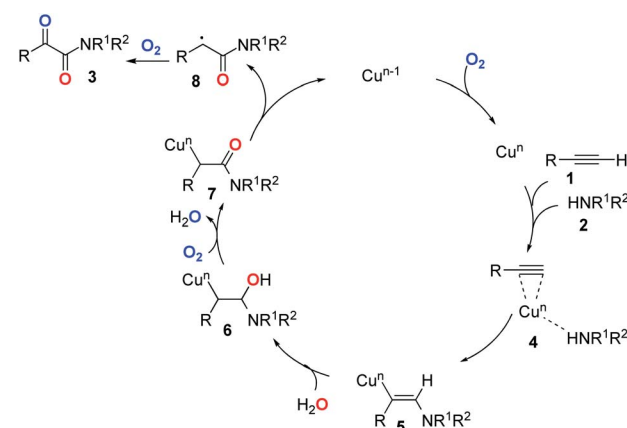
Firstly, the α -ketone group at α -ketoamide is more electrophilic than a ketone due to the electron-withdrawing effect of the amide group, thus it is possible for oxygen atom exchange with water *via* a hemiketal intermediate, while the amide group of α -ketoamide is stable. Indeed, as illustrated in eqn (2), when **3aa** was stirred with CuI, piperidine, and H₂¹⁸O (10 equiv.) under oxygen atmosphere in THF,²² 73% singly ¹⁸O-labeled, 27% unlabeled product were obtained and no doubly ¹⁸O-labeled α -ketoamide was detected (see HRMS in ESI†).



Subsequently, when the reaction of **1a** and **2a** was conducted in the presence of H₂O (20 equiv.) under ¹⁸O₂, 80% unlabeled (**3aa**, eqn (3)) and 20% singly ¹⁸O-labeled product (**3aa-1**, eqn (3)) were detected (see HRMS in ESI†). If the oxygen atom of amide group originates from ¹⁸O₂, unlabeled product would not be observed *via* oxygen exchange with H₂O. The existence of 80% unlabeled product (**3aa**, eqn (3)) demonstrated that the oxygen atom of amide group originated from H₂O. Further control experiment showed that 57% doubly ¹⁸O-labeled (**3aa-2**, eqn (4)) and 43% singly ¹⁸O-labeled product (**3aa-3**, eqn (4)) were detected when the reaction of **1a** and **2a** was performed in the presence of H₂¹⁸O (20 equiv.) under O₂ (see HRMS in ESI†). This result also revealed the oxygen atom of amide group derived from H₂O (eqn (4)).



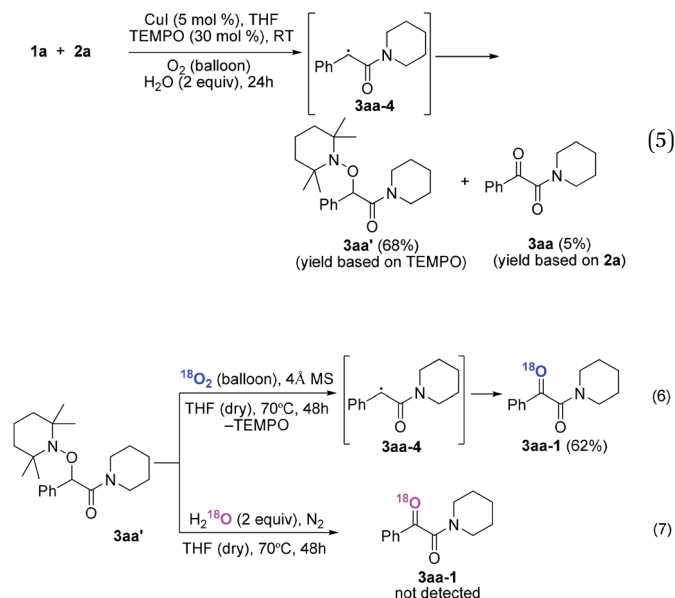
Radical capture experiments revealed that the oxygen atom of α -ketone at α -ketoamides derived from O₂, which also indicated the possible mechanism of this transformation. As shown in eqn (5), TEMPO, a well known radical-capturing species, can remarkably suppress the formation of α -ketoamide **3aa**.²³ When TEMPO (30 mol%) was added to the reaction system of **1a** and **2a**, 69% TEMPO-trapped compound **3aa'** (isolated yield based on TEMPO) was obtained and only 4% of **3aa** (isolated yield based on **2a**) was detected. Furthermore, owing to the thermal instability of the covalent bond between TEMPO and the carbon free radical intermediate **3aa-4** that was easily oxidized by dioxygen to form carbonyl compounds,^{24,25} the transformation



Scheme 1 Plausible reaction pathway.



of **3aa'** to singly ^{18}O -labeled α -ketoamide and TEMPO was observed in the presence of $^{18}\text{O}_2$ at 70 °C (**3aa-1**, eqn (6)). Meanwhile, no conversion of **3aa'** to **3aa-1** was detected in the presence of H_2^{18}O under N_2 (eqn (7)). These results suggested that the carbonyl oxygen atom of α -ketone at α -ketoamide **3aa** derived from molecular oxygen *via* a radical oxidation process.



Based on the above experiments and previous reports,^{26–28} we proposed a postulated reaction pathway for this transformation as outlined in Scheme 1. Firstly, the complex **4** was formed by the reaction of the Cu species with alkyne **1** and amine **2**. Then, the migration of amine to the triple bond led to the formation of the vinyl-Cu intermediate **5**. Next, **5** underwent hydration to give **6**. Subsequently, **7** was formed through the oxidation of **6** with dioxygen. Finally, the reductive elimination of the copper species of **7**²⁷ followed by double oxidation with dioxygen would deliver the desired product **3**.^{2,28}

Conclusions

In summary, we have successfully developed a tandem copper catalyzed approach to α -ketoamides from terminal alkynes, secondary amines, dioxygen, and water at room temperature without ligand or additive, in which O_2 and H_2O were used as the co-oxygen source of α -ketoamides. The present method opens a new window to construct complicated oxygen-containing compounds. Further studies of the detailed mechanism of this process and its application are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Scientific Research Fund of Hunan Provincial Education Department (18A192).

Notes and references

- (a) N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725–2750; (b) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329–2363.
- (a) Q. Liu, L. Wang, H. Yue, J.-S. Li, Z. Luo and W. Wei, *Green Chem.*, 2019, **21**, 1609–1613; (b) Z. Cao, Q. Zhu, Y.-W. Lin and W.-M. He, *Chin. Chem. Lett.*, 2019, **30**, 2132–2138; (c) W. Wei, P. Bao, H. Yue, S. Liu, L. Wang, Y. Li and D. Yang, *Org. Lett.*, 2018, **20**, 5291–5295.
- (a) L.-Y. Xie, Y. Duan, L.-H. Lu, Y.-J. Li, S. Peng, C. Wu, K.-J. Liu, Z. Wang and W.-M. He, *ACS Sustainable Chem. Eng.*, 2017, **5**, 10407–10412; (b) K.-J. Liu, T.-Y. Zeng, J.-L. Zeng, S.-F. Gong, J.-Y. He, Y.-W. Lin, J.-X. Tan, Z. Cao and W.-M. He, *Chin. Chem. Lett.*, 2019, **30**, 2304–2308; (c) K.-J. Liu, J.-H. Deng, J. Yang, S.-F. Gong, Y.-W. Lin, J.-Y. He, Z. Cao and W.-M. He, *Green Chem.*, 2020, **22**, 433–438; (d) L. Wang, Y. Zhang, M. Zhang, P. Bao, X. Lv, H.-G. Liu, X. Zhao, J.-S. Li, Z. Luo and W. Wei, *Tetrahedron Lett.*, 2019, **60**, 1845–1848; (e) K.-J. Liu, J.-H. Deng, T.-Y. Zeng, X.-J. Chen, Y. Huang, Z. Cao, Y.-W. Lin and W.-M. He, *Chin. Chem. Lett.*, 2020, **31**, 1868–1872.
- (a) G. Kokotos, D. A. Six, V. Loukas, T. Smith, V. Constantinou-Kokotou, D. Hadjipavlou-Litina, S. Kotsovolou, A. Chiou, C. C. Beltzner and E. A. Dennis, *J. Med. Chem.*, 2004, **47**, 3615–3628; (b) F. G. Njoroge, K. X. Chen, N.-Y. Shih and J. J. Piwinski, *Acc. Chem. Res.*, 2008, **41**, 50–59; (c) D. Tomita, K. Yamatsugu, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 6946–6948; (d) F. R. Bou-Hamdan and J. L. Leighton, *Angew. Chem., Int. Ed.*, 2009, **48**, 2403–2406; (e) A. Natarajan, K. Wang, V. Ramamurthy, J. R. Scheffer and B. Patrick, *Org. Lett.*, 2002, **4**, 1443–1446; (f) Y.-X. Jia, D. Katayev and E. P. Kündig, *Chem. Commun.*, 2010, **46**, 130–132.
- (a) R. P. Singh and J. M. Shreeve, *J. Org. Chem.*, 2003, **68**, 6063–6065; (b) A. Papanikos, J. Rademann and M. Meldal, *J. Am. Chem. Soc.*, 2001, **123**, 2176–2181; (c) A. Chiou, T. Markidis, V. Constantinou-Kokotou, R. Verger and G. Kokotos, *Org. Lett.*, 2000, **2**, 347–350.
- (a) Y.-H. Chen, Y.-H. Zhang, H.-J. Zhang, D.-Z. Liu, M. Gu, J.-Y. Li, F. Wu, X.-Z. Zhu, J. Li and F.-J. Nan, *J. Med. Chem.*, 2006, **49**, 1613–1623; (b) M. Sassatelli, F. Bouchikhi, S. Messaoudi, F. Anizon, E. Debiton, C. Barthomeuf, M. Prudhomme and P. Moreau, *Eur. J. Med. Chem.*, 2006, **41**, 88–100.
- (a) Z. F. Al-Rashid, W. L. Johnson, R. P. Hsung, Y. Wei, P.-Y. Yao, R. Liu and K. Zhao, *J. Org. Chem.*, 2008, **73**, 8780–8784; (b) P. Müller and J. Godoy, *Tetrahedron Lett.*, 1982, **23**, 3661–3664.
- B. Song, S. Wang, C. Sun, H. Deng and B. Xu, *Tetrahedron Lett.*, 2007, **48**, 8982–8986.
- J. Zhu, H. Wong, Z. Zhang, Z. Yin, J. F. Kadow, N. A. Meanwell and T. Wang, *Tetrahedron Lett.*, 2005, **46**, 3587–3589.
- (a) F. Ozawa, H. Soyama, H. Yanagihara, I. Aoyama, H. Takino, K. Izawa, T. Yamamoto and A. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 3235–3245; (b) E. R. Murphy,



- J. R. Martinelli, N. Zaborenko, S. L. Buchwald and K. F. Jensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1734–1737; (c) L. Huang, F. Ozawa and A. Yamamoto, *Organometallics*, 1990, **9**, 2603–2611.
- 11 H. H. Wasserman and A. K. Petersen, *J. Org. Chem.*, 1997, **62**, 8972–8973.
- 12 D. Kumar, S. R. Vemula and G. R. Cook, *ACS Catal.*, 2016, **6**, 4920–4945.
- 13 M. Bouma, G. Masson and J. Zhu, *J. Org. Chem.*, 2010, **75**, 2748–2751.
- 14 (a) C. Zhang and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 28–29; (b) A. Sagadevan, A. Ragupathi, C.-C. Lin, J. R. Hwu and K. C. Hwang, *Green Chem.*, 2015, **17**, 1113–1119; (c) M. Kumar, S. Devari, A. Kumar, S. Sultan, Q. N. Ahmed, M. Rizvi and B. A. Shah, *Asian J. Org. Chem.*, 2015, **4**, 438–441; (d) K. Sun, G. Li, Y. Li, J. Yu, Q. Zhao, Z. Zhang and G. Zhang, *Adv. Synth. Catal.*, 2020, **362**, 1947–1954.
- 15 C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 11088–11092.
- 16 (a) F.-T. Du and J.-X. Ji, *Chem. Sci.*, 2012, **3**, 460–465; (b) J. Zhang, Y. Wei, S. Lin, F. Liang and P. Liu, *Org. Biomol. Chem.*, 2012, **10**, 9237–9242; (c) M. Zhou and Q. Song, *Synthesis*, 2014, **46**, 1853–1858.
- 17 S. Guo, Z. Fang, Z. Yang, C. Liu, Z. Dai, L. Zhao and K. Guo, *RSC Adv.*, 2016, **6**, 1503–1507.
- 18 N. Sharma, S. S. Kotha, N. Lahiri and G. Sekar, *Synthesis*, 2015, **47**, 726–736.
- 19 F. Liu, K. Zhang, Y. Liu, S. Chen, Y. Chen, D. Zhang, C. Lin and B. Wang, *RSC Adv.*, 2017, **7**, 7158–7162.
- 20 Y. Lv, P. Bao, H. Yue, J.-S. Li and W. Wei, *Green Chem.*, 2019, **21**, 6051–6055.
- 21 (a) H. G. O. Alvim, J. R. Correa, J. F. Assumpção, W. A. da Silva, M. O. Rodrigues, J. L. de Macedo, M. Fioramonte, F. C. Gozzo, C. C. Gatto and B. A. D. Neto, *J. Org. Chem.*, 2018, **83**, 4044–4053; (b) D. Zhu, Y. Yao, R. Zhao, Y. Liu and L. Shi, *Chem.-Eur. J.*, 2018, **24**, 4805–4809; (c) P. Kumari, R. Bharti and T. Parvin, *Mol. Diversity*, 2019, **23**, 205–213; (d) L. Zeng, B. Huang, Y. Shen and S. Cui, *Org. Lett.*, 2018, **20**, 3460–3464; (e) G.-L. Wu and Q. P. Wu, *Adv. Synth. Catal.*, 2018, **360**, 1949–1953; (f) K. Sun, Y. Li, R. Feng, S. Mu, X. Wang and B. Zhang, *J. Org. Chem.*, 2020, **85**, 1001–1008.
- 22 Water in DMF is very difficult to remove, thus we use THF instead of DMF.
- 23 (a) A. L. J. Beckwith, V. W. Bowry and K. U. Ingold, *J. Am. Chem. Soc.*, 1992, **114**, 4983–4992; (b) C. Aliaga, J. M. Juárez-Ruiz, J. C. Scaiano and A. Aspée, *Org. Lett.*, 2008, **10**, 2147–2150; (c) M. R. Heinrich, A. Wetzel and M. Kirschstein, *Org. Lett.*, 2007, **9**, 3833–3835; (d) A. D. Allen, B. Cheng, M. H. Fenwick, B. Givehchi, H. Henry-Riyad, V. A. Nikolaev, E. A. Shikhova, D. Tahmassebi, T. T. Tidwell and S. Wang, *J. Org. Chem.*, 2001, **66**, 2611–2617.
- 24 M. V. Ciriano, H.-G. Korth, W. B. van Scheppingen and P. Mulder, *J. Am. Chem. Soc.*, 1999, **121**, 6375–6381.
- 25 F. Recupero and C. Punta, *Chem. Rev.*, 2007, **107**, 3800–3842.
- 26 G. Huerta and L. Fomina, *J. Mol. Struct.: THEOCHEM*, 2006, **761**, 107–112.
- 27 S. Murata, K. Suzuki, M. Miura and M. Nomura, *J. Chem. Soc., Perkin Trans. 1*, 1990, 361–365.
- 28 Y. Usuki, X. Peng, B. Gülgeze, S. Manyem and J. Aubé, *ARKIVOC*, 2006, (iv), 189–199.

