RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2022, **12**, 24232

Cu(I)-catalyzed cross-coupling of primary amines with 2,2′-dibromo-1,1′-biphenyl for the synthesis of polysubstituted carbazole†

Yan-Ning Niu, *[a] Yan Qiao,[b] Ke-Yu Wang,[a] Bai-Xue Sha[a] and Gao-Qiang Li[b]

Received 27th May 2022
Accepted 12th August 2022

DOI: 10.1039/d2ra03323b

rsc.li/rsc-advances

A Cu(I)-catalyzed cross-coupling of primary amines with 2,2′-dibromo-1,1′-biphenyl for the synthesis of polysubstituted carbazole has been achieved. This protocol provides an efficient strategy for the synthesis of carbazole using cheap copper catalysts with diamine ligand, and it provides convenient access to a series of carbazole derivatives in moderate yields.

1. Introduction

Carbazole is an important organic nitrogen-containing heterocyclic skeleton, which is extensively applied as a building block in natural products,[1] dyes[2] and pharmaceuticals.[3] As shown in Fig. 1, some representative bioactive molecules possessing carbazole moieties are listed. For example, murrayafoline A has strong antifungal and antitumor properties.[4] Celiptium, as a potent DNA intercalator and topoisomerase II inhibitor, has been used as a medicine for the treatment of breast cancer.[5] Clausenaquinone A showed an effective inhibitory activity on platelet aggregation as well as cytotoxicity in RPMI-7951, HCT-8 and TE671 tumor cells.[6] Calothrixin A and calothrixin B, carbazole quinone alkaloids, are novel DNA topoisomerase inhibitors, which have excellent effects on anti-tumor cells.[7] Curaxin 137 (CBLC137) is an effective inducer of apoptosis. It is toxic for proliferating various tumor cells and pancreatic cancer stem cells.[8] Carbazole and its derivatives are also used in the synthesis of photoelectric functional materials.[9] For these reasons, the synthesis of carbazole using simple substrates and methodologies is still an active research field. Recently, some novel organic synthesis strategies for the construction of carbazoles have been reported.[10]

The traditional approaches for the construction of the carbazole rings were to use the Buchwald–Hartwig C–N cross-coupling reaction.[11] In 2003, the Nozaki group firstly presented the synthesis of carbazole with double N–H arylation of primary amides *via* the $[Pa_2(dba)_3]/^tBu_3P/^tBuONa$ system.[12] Later, Chida *et al.* revealed the *N*-arylation protocol *via* the $[Pa_2(dba)_3]$/dialkylphosphinobiaryls/^{t}BuONa system, and further applied it to the synthesis of murrayafoline A.[13] In 2010, Zhou and co-workers developed the $[Pa_2(dba)_3]/(^tBu)_2P{=}N{-}P(^iBuNCH_2CH_2)_3N/^tBuONa$ system for the synthesis of carbazole under mild conditions.[14] However, the need for expensive Pd catalysts and the frequent use of expensive phosphine ligands are the drawbacks of these methods. Recently, copper catalysts have become popular and have been widely used to synthesize carbazole.[15] In 2010, Liao and coworkers developed a convenient Cu-catalyzed double C–N bond-forming reaction using 2,2-diiodobiphenyl and *p*-methylaniline for the synthesis of carbazole.[15b] However, only one example was reported, and the cheaper 2,2-dibromobiphenyl was not used in this reaction. Although Do and coworkers reported dibromide substrates using CuI/proline system for the synthesis of carbazole,[15c] the reaction requires higher temperatures and a strong base. Therefore, it is necessary to develop a new system for the synthesis of carbazole to use the cheaper 2,2-dibromobiphenyl as substrates in the copper-catalyzed C–N coupling reaction under mild conditions. Compared to palladium, copper catalyst has the advantages of low price and low toxicity, and it can be suitable for industrial-scale production. The Ullmann-type coupling reaction between aryl halides and nitrogen-based

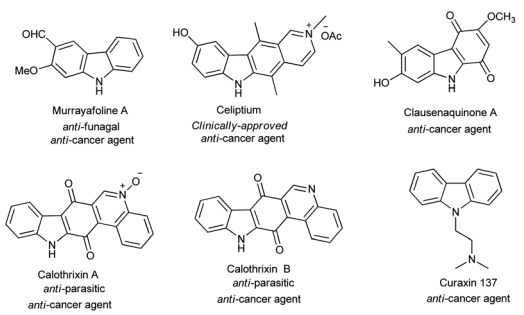


Fig. 1 Biologically active carbazole derivatives.

[a]*Department of Teaching and Research, Nanjing Forestry University, Huaian, Jiangsu, 223003, People's Republic of China. E-mail: zjsnyn@163.com*

[b]*Key Laboratory of Macromolecular Science of Shanxi Province, School of Chemistry and Chemical Engineering, Shanxi Normal University, Xi'an, Shanxi 710062, People's Republic of China*

† Electronic supplementary information (ESI) available. See https://doi.org/10.1039/d2ra03323b

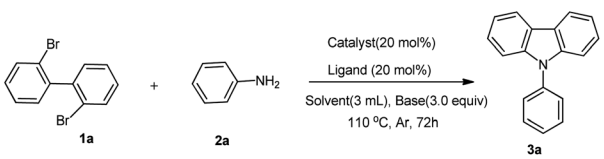
nucleophiles has also been used for the synthesis of carbazoles.[16,17] However, these methods usually suffer from several disadvantages, such as the need to use stoichiometric copper catalysts and the high reaction temperatures (normally above 150 °C).[17] In order to solve these problems, special ligands need to be designed to promote these coupling reactions. In this scenario, it is highly desirable to develop a simple, efficient and practical approach to the synthesis of carbazole derivatives using cheap Cu catalysts and ligands under mild conditions.

The efficient construction of functional nitrogen-containing heterocycles in a simple way is an important task in synthetic chemistry and some new synthetic strategies have been reported continuously.[18] As a continuation of our long-term interest in the synthesis of heterocyclic compounds,[19] in this study, we present a simple methodology for the synthesis of *N*-arylcarbazoles using substituted 2,2′-dihalobiphenyl and aromatic primary amine *via* the copper-catalyzed cross-coupling reaction.

2. Results and discussion

In our initial investigation, 2,2′-dibromo-1,1′-biphenyl **1a** and aniline **2a** were chosen as the model substrates in the presence of CuI (20 mol%), DMEDA (*N*,*N*′-dimethylethylenediamines) (20 mol%) and K_2CO_3 (3 equiv.) at 110 °C in 3 mL DMF for 72 h (Table 1, entry 1). To our disappointment, the required product **3a** was not obtained. Other solvents such as THF, DMSO and toluene were screened and to our delight, the desired product **3a** was obtained, in toluene with small polarity, in 64% yield (Table 1, entries 2–4). Changing base to Cs_2CO_3, ^{t}BuOK, DABCO, DBU and Et_3N failed to improve the yield of the product **3a** (Table 1, entries 5–9). Other Cu catalysts such as CuCl, CuBr, $Cu(OTf)_2$ and Cu powder were also investigated for this cross-coupling reaction but no better results were observed (Table 1, entries 10–13). The effects of ligands in the cross-coupling reaction were then evaluated. The results showed that double *N*-chelated ligands played a significant role in the formation of carbazole; other ligands such as TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), EDA (ethylenediamines) and 4,4′-dimethyl-2,2′-dipyridine only obtained lower yields, and PPh_3 gave no desired product (Table 1, entries 4 and 14–17). On decreasing the temperature to 80 °C, only 26% yield was isolated (Table 1, entry 18). By raising the reaction temperature to 140 °C, the *N*-phenylcarbazole **3a** was obtained in 60% yield (Table 1, entry 19). On decreasing **2a** to 2 equiv., the lower yield was observed (Table 1, entry 20). When the catalyst loading was decreased to 10 mol%, the yield of **3a** was decreased to 45%

Table 1 Optimization of the reaction conditions[a]

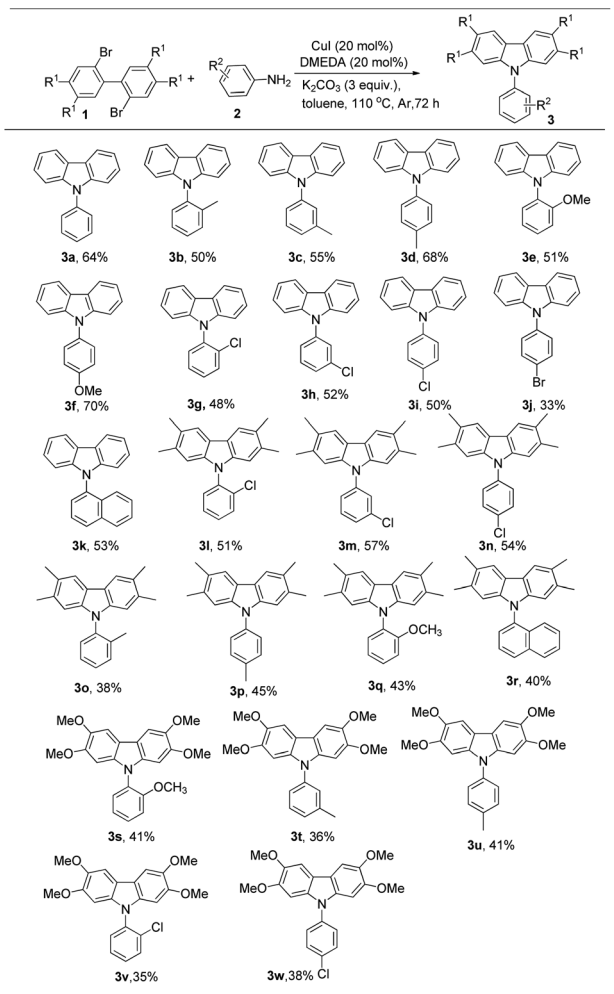


Entry	Catalyst	Solvent	Base	Ligand	Temperature (°C)	Yield **3a**[b] (%)
1	CuI	DMF	K_2CO_3	DMEDA	110	0
2	CuI	DMSO	K_2CO_3	DMEDA	110	0
3	CuI	THF	K_2CO_3	DMEDA	110	0
4	CuI	Toluene	K_2CO_3	DMEDA	110	64
5	CuI	Toluene	$CsCO_3$	DMEDA	110	13
6	CuI	Toluene	^{t}BuOK	DMEDA	110	22
7	CuI	Toluene	DABCO	DMEDA	110	0
8	CuI	Toluene	DBU	DMEDA	110	0
9	CuI	Toluene	Et_3N	DMEDA	110	0
10	CuCI	Toluene	K_2CO_3	DMEDA	110	45
11	CuBr	Toluene	K_2CO_3	DMEDA	110	24
12	$Cu(OTf)_2$	Toluene	K_2CO_3	DMEDA	110	47
13	Cu	Toluene	K_2CO_3	DMEDA	110	48
14	CuI	Toluene	K_2CO_3	TMEDA	110	19
15	CuI	Toluene	K_2CO_3	EDA	110	34
16	CuI	Toluene	K_2CO_3	Ph_3P	110	0
17	CuI	Toluene	$CsCO_3$	4,4′-Dimethyl-2,2′-dipyridine	110	21
18	CuI	Toluene	K_2CO_3	DMEDA	80	26
19	CuI	Toluene	K_2CO_3	DMEDA	140	60
20	CuI	Toluene	K_2CO_3	DMEDA	110	46[c]
21	CuI (10%)	Toluene	K_2CO_3	DMEDA	110	45

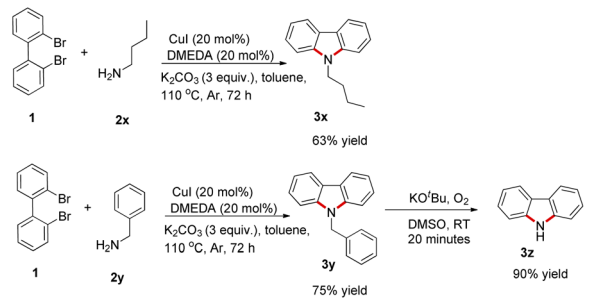
[a] Reaction conditions: **1a** (1 equiv., 0.2 mmol), **2a** (3 equiv., 0.6 mmol), catalyst (20 mol% without other declaration), ligand (20 mol%), base (3 equiv.), solvent (3.0 mL), the reaction was carried out at 110 °C, under an Ar atmosphere in a sealed tube for 72 h. [b] Isolated yield. [c] 0.4 mmol **2a** (2 equiv.) was used.

(Table 1, entry 21). Thus, the optimized reaction conditions chosen for all subsequent coupling reactions are as follows: 0.2 mmol of 2,2′-dibromo-1,1′-biphenyl, 0.6 mmol aniline, and 0.04 mmol CuI, 0.04 mmol DMEDA and 3 equiv. K_2CO_3 in 3 mL toluene, stirred at 110 °C, under the Ar atmosphere in a sealed tube for 72 h.

With the optimized reaction conditions, the scope of this coupling reaction was examined and the results are summarized in Scheme 1. Firstly, a series of functional groups were tolerated in different positions of arylamine in this reaction, such as $-CH_3$, $-OCH_3$, –Br and –Cl substituents on arylamine. When introducing the electron-donating groups, such as $-CH_3$ and $-OCH_3$ on the arylamine, the desired carbazoles were obtained in 50–70% yields (Scheme 1, **3b–3f**). When bearing electron-withdrawing groups on arylamine, it slightly hindered the reaction (Scheme 1, **3g–3j**). It should be noted that relatively lower yields were observed when *ortho*-substituted aromatic amines were used, and this might be due to steric hindrance (Scheme 1, **3b**, **3e** and **3j**). Naphthylamine was also compatible with this coupling reaction, and the desired product **3k** was obtained in 53% yield (Scheme 1, **3k**). We continued to elucidate the scope of this reaction by replacing the hydrogen atom



Scheme 1 The scope of the coupling reaction.

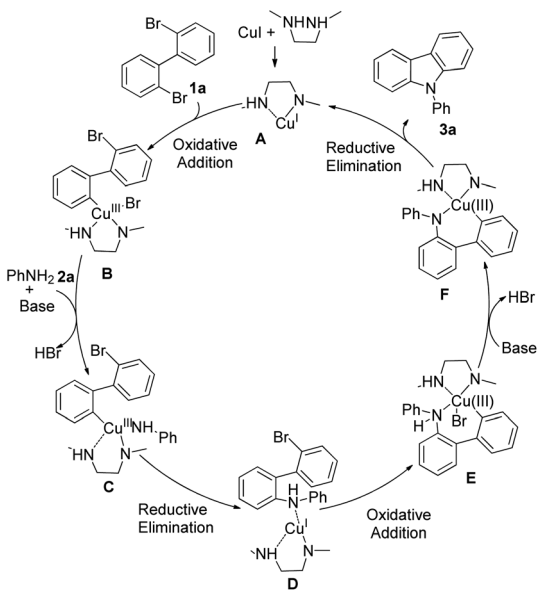


Scheme 2 Cu(I)-catalyzed cross-coupling of aliphatic amines with 2,2′-dibromo-1,1′-biphenyl for the synthesis of substituted carbazole.

at the R^1 position with $-CH_3$ and $-OCH_3$ groups (Scheme 1, **3l–3w**). The results showed that strong electron-donating substituents on 2,2′-dibromo-1,1′-biphenyl gave lower yields (Scheme 1, **3s–3w**). To further confirm the applicability of this reaction, a gram-scale reaction of **1a** (1.56 g, 5.0 mmol) with **2a** (1.40 g, 15 mmol) was carried out under the standard conditions, providing the corresponding product **3a** in 54% yield (0.66 g).

To further expand the scope of this reaction, butylamine and benzylamine, which were also compatible with this reaction, were investigated and the corresponding carbazoles were obtained in 63% and 75% yields, respectively. In the presence of oxygen, *N*-benzylcarbazole reacted with ^{t}BuOK in DMSO to quickly remove benzyl groups to obtain carbazole in 90% yield (Scheme 2). This result is consistent with that reported in the literature.[20]

The possible mechanism of this copper-catalyzed cross-coupling reaction for the synthesis of carbazole is proposed in Scheme 3. Firstly, DMEDA combined with CuI to form **A**, which subsequently reacted with 2,2′-dibromobiphenyl *via* oxidative addition to form intermediate **B**. Then, the aniline, as a nucleophile, attacked **B** to produce **C**, in which HBr was also lost in



Scheme 3 A plausible mechanism for the formation of **3a**.

the presence of base. The intermediate **D** was formed by reductive elimination. Subsequently, a similar oxidative addition occurred to give intermediate **E**, and then another HBr was lost with base. Finally, the desired product **3a** was obtained with another reductive elimination, and Cu catalyst **A** was regenerated.

3. Conclusions

In summary, we have developed a one-pot method, *via* Cu-catalyzed coupling of primary amines with 2,2′-dibromo-1,1′-biphenyl, for the synthesis of polysubstituted carbazole. This reaction provides a simple and facile route to the straightforward synthesis of polysubstituted carbazole in moderate yields. Further synthetic applications are ongoing in our laboratory.

Author contributions

The design of this protocol was carried out by Y.-N. Niu and G.-Q. Li. The manuscript was written through contributions of Y.-N. Niu. The empirical data were acquired by Y.-N. Niu and Y. Qiao. K.-Y. Wang and B.-X. Sha participated in the modification of the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge the financial support of this work by National Natural Science Foundation of China (22171108) and Natural Science Research Projects in Huai'an (HAB202065).

References

1 (*a*) A. W. Schmidt, K. R. Reddy and H. J. Knölker, *Chem. Rev.*, 2012, **112**, 3193; (*b*) C. M. Miller and F. O. McCarthy, *RSC Adv.*, 2012, **2**, 8883.

2 J. Yin, Y. Ma, G. Li, M. Peng and W. Lin, *Coord. Chem. Rev.*, 2020, **412**, 213257.

3 (*a*) S. Issa, A. Prandina, N. Bedel, P. Rongved, S. Yous, M. Le Borgne and Z. Bouaziz, *J. Enzyme Inhib. Med. Chem.*, 2019, **34**, 1321; (*b*) D. Zhu, M. Chen, M. Li, B. Luo, Y. Zhao, P. Huang, F. Xue, S. Rapposelli, R. Pi and S. Wen, *Eur. J. Med. Chem.*, 2013, **68**, 81; (*c*) A. D. Favia, D. Habrant, R. Scarpelli, M. Migliore, C. Albani, S. M. Bertozzi, M. Dionisi, G. Tarozzo, D. Piomelli, A. Cavalli and M. De Vivo, *J. Med. Chem.*, 2012, **55**, 8807; (*d*) C. Alayrac, D. Schollmeyer and B. Witulski, *Chem. Commun.*, 2009, 1464.

4 (*a*) C. Börger, O. Kataeva and H. J. Knölker, *Org. Biomol. Chem.*, 2012, **10**, 7269; (*b*) V. Humne, Y. Dangat, K. Vanka and P. Lokhande, *Org. Biomol. Chem.*, 2014, **12**, 4832.

5 (*a*) N. C. Garbett and D. E. Graves, *Curr. Med. Chem.: Anti-Infect. Agents*, 2004, **4**, 149; (*b*) C. M. Miller and F. O. McCarthy, *RSC Adv.*, 2012, **2**, 8883; (*c*) C. M. Miller, E. C. O'Sullivan, K. J. Devine and F. O. McCarthy, *Org. Biomol. Chem.*, 2012, **10**, 7912.

6 T. S. Wu, S. C. Huang, P. L. Wu and K. H. Lee, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 23958.

7 (*a*) S. Lee, K.-H. Kim and C.-H. Cheon, *Org. Lett.*, 2017, **19**, 2785; (*b*) J. Guo, I. N. C. Kiran, J. S. Gao, R. S. Reddy and Y. He, *Tetrahedron Lett.*, 2016, **57**, 3481; (*c*) S. A. Kaliyaperumal, S. Banerjee and U. K. S. Kumar, *Org. Biomol. Chem.*, 2014, **12**, 6105–6113; (*d*) N. Ramkumar and R. Nagarajan, *J. Org. Chem.*, 2013, **78**, 2802.

8 S. M. Thomas, A. Purmal, M. Pollastri and K. Mensa-Wilmot, *Sci. Rep.*, 2016, **6**, 32083.

9 (*a*) B. Xu, E. Sheibani, P. Liu, J. Zhang, H. Tian, N. Vlachopoulos, G. Boschloo, L. Kloo, A. Hagfeldt and L. Sun, *Adv. Mater.*, 2014, **26**, 6629; (*b*) S. Kumar and Y.-T. Tao, *J. Org. Chem.*, 2015, **80**, 5066.

10 (*a*) K. Takamatsu, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2014, **16**, 2892; (*b*) B. J. Stokes, B. Jovanović, H. Dong, K. J. Richert, R. D. Riell and T. G. Driver, *J. Org. Chem.*, 2009, **74**, 3225; (*c*) T. L. Guo, Q. B. Jiang, F. Huang, J. P. Chen and Z. K. Yu, *Org. Chem. Front.*, 2014, **1**, 707; (*d*) T. Gensch, M. Rönnefahrt, R. Czerwonka, A. Jäger, O. Kataeva, I. Bauer and H.-J. Knölker, *Chem.–Eur. J.*, 2012, **18**, 770; (*e*) S. Maiti, T. K. Achar and P. Mal, *Org. Lett.*, 2017, **19**, 2006.

11 (*a*) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27; (*b*) J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534; (*c*) D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338.

12 (*a*) A. Kuwahara, K. Nakano and K. Nozaki, *J. Org. Chem.*, 2005, **70**, 413; (*b*) K. Nozaki, K. Takahashi, K. Nakano, T. Hiyama, H. Tang, M. Fujiki, S. Yamaguchi and K. Tamao, *Angew. Chem., Int. Ed.*, 2003, **42**, 2051.

13 T. Kitawaki, Y. Hayashi, A. Ueno and N. Chida, *Tetrahedron*, 2006, **62**, 6792.

14 Y. Zhou and J. Verkade, *Adv. Synth. Catal.*, 2010, **352**, 616.

15 (*a*) M. J. James, R. E. Clubley, K. Y. Palate, T. J. Procter, A. C. Wyton, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Org. Lett.*, 2015, **17**, 4372; (*b*) Q. Liao, L. Zhang, F. Wang, S. Li and C. Xi, *Eur. J. Org. Chem.*, 2010, 5426; (*c*) H. N. Do, N. M. Quan, B. V. Phuc, D. V. Tinh, N. Q. Tien, T. T. T Nga, V. T Nguyen, T. Q. Huang, T. T. Dang and P. Langer, *Synlett*, 2021, **32**, 611.

16 (*a*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*b*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954; (*c*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (*d*) D. Zhu, Q. Liu, B. Luo, M. Chen, R. Pi, P. Huang and S. Wen, *Adv. Synth. Catal.*, 2013, **355**, 2172.

17 (*a*) F. Bellina, C. Calandri, S. Cauteruccio and R. Ross, *Eur. J. Org. Chem.*, 2007, 2147; (*b*) J. K. Kwon, J. H. Cho, Y.-S. Ryu, S. H. Oh and E. K. Yum, *Tetrahedron*, 2011, **67**, 4820.

18 For selected papers: (*a*) Z.-L. Wu, J.-Y. Chen, X.-Z. Tian, W.-T. Ouyang, Z.-T. Zhang and W.-M. He, *Chin. Chem. Lett.*, 2022, **33**, 1501; (*b*) Y. Wu, J.-Y. Chen, J. Ning, X. Jiang, J. Deng, Y. Deng, R. Xu and W.-M. He, *Green Chem.*, 2021, **23**, 3950; (*c*) J.-Y. Chen, H.-Y. Wu, Q.-W. Gui, S.-S. Yan,

J. Deng, Y.-W. Lin, Z. Cao and W.-M. He, *Chin. J. Catal.*, 2021, **42**, 1445; (*d*) Q.-W. Gui, F. Teng, Z.-C. Li, Z.-Y. Xiong, X.-F. Jin, Y.-W. Lin, Z. Cao and W.-M. He, *Chin. Chem. Lett.*, 2021, **32**, 1907; (*e*) Y. Wan, Q. Liu, H. Wu, Z. Zhang and G. Zhang, *Org. Chem. Front.*, 2022, **9**, 1634; (*f*) Y. Shan, L. Su, Z. Zhao and D. Chen, *Adv. Synth. Catal.*, 2021, **363**, 906; (*g*) L. Tang, Y. Ouyang, K. Sun and B. Yu, *RSC Adv.*, 2022, **12**, 19736.

19 (*a*) X.-F. Xia and Y.-N. Niu, *Org. Biomol. Chem.*, 2022, **20**, 282; (*b*) Q. Huang, M. Zhao, Y. Yang, Y.-N. Niu and X.-F. Xia, *Org. Chem. Front.*, 2021, **8**, 5988; (*c*) Y.-N. Niu, X.-F. Xia and Y. Yuan, *Synlett*, 2018, **29**, 617; (*d*) X.-F. Xia, L.-L. Zhang, X.-R. Song, Y.-N. Niu, X.-Y. Liu and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 1410.

20 A. A. Haddach, A. Kelleman and M. V. Deaton-Rewolinski, *Tetrahedron Lett.*, 2002, **43**, 399.