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COMMUNICATION

Synthesis of Pyrazolo[1,5-*c*]quinazoline Derivatives through Copper-Catalyzed Domino Reaction of *o*-Alkenyl Aromatic Isocyanides with Diazo Compounds

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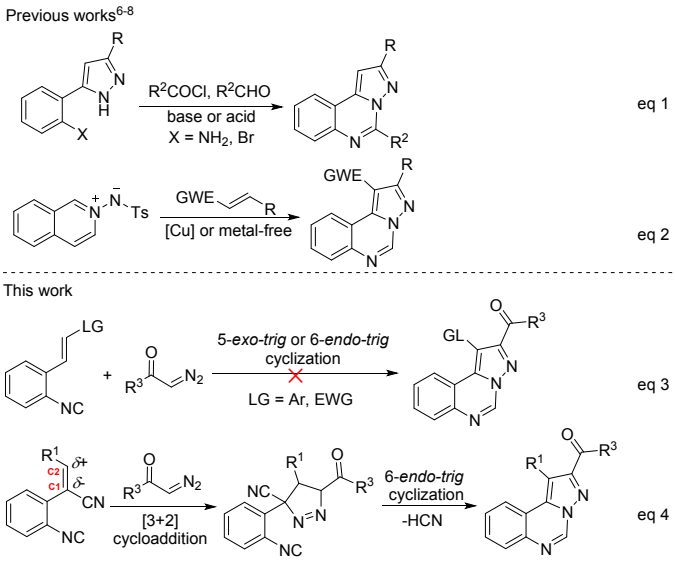
A novel copper-catalyzed domino reaction between *o*-alkenyl aromatic isocyanides and diazo compounds has been developed under mild reaction conditions. Various *o*-alkenyl aromatic isocyanides were prepared from readily available reactants. The reaction provides a general and efficient method for synthesis of pyrazolo[1,5-*c*]quinazolines by the formation of two rings and three new bonds in single step from readily available acyclic starting materials. A mechanism involving tandem (3+2) cyclization/elimination/intramolecular aza-addition sequence was proposed.

N-fused heterocycle scaffolds are frequently found in a large number of nature products, pharmaceuticals and bioactive compounds.[1] Among them, the pyrazolo[1,5-*c*]quinazoline derivatives have been used as AMPA and kainate receptor, adenosine receptor, Gly/NMDA receptor and excitatory amino acid antagonists,[2] potent IκB kinase and phosphodiesterase 10A inhibitors,[3] EGFR inhibitor,[4] and potential vaccinia virus inhibitors.[5] Consequently, many methods for the construction of pyrazolo[1,5-*c*]quinazolines have been reported in recent decades.[6-8] These methods generally follow two typical modes: (i) middle pyrimidine construction via the condensation of prior functionalized pyrazoles with acyl chorides or aldehydes (Scheme 1, eqn (1)),[6-7] and (ii) pyrazol ring construction via the (3+2) cycloaddition reaction between prior functionalized quinazolines and alkenes (Scheme 1, eqn (2)).[8] Recently, double annulation strategy with the formation of two rings by a domino reaction has emerged as a promising and step-economical strategy to improve the synthetic efficiency of pyrazolo[1, 5-*c*]quinazolines. For example, Fu and co-workers reported a one-pot two-step method for the synthesis of pyrazolo[1,5-*c*]quinazoline derivatives.[9] Sawant's group developed a four-component reaction (2-azidobenzaldehydes, isocyanides, sulfonyl hydrazides and alkynes/alkenes) through a one-pot tricyclic Pd(II)/Ag(I) relay catalysis.[4] Despite these successes, the development of efficient and general methods to achieve pyrazolo[1,5-*c*]quinazoline derivatives from readily available acyclic starting materials remains highly desirable.

Isocyanides are highly valuable building blocks that have been extensively applied in organic chemistry.[10] In particular, *o*-alkenyl aromatic isocyanides have been well-established for the construction of benzo-fused heterocycles via 5-*exo* or 6-*endo* cyclization.[11-13] Through the retrosynthetic analyses of molecular architecture of the pyrazolo[1,5-*c*]quinazoline, the key step in the synthesis of such a scaffold boils down to the construction of a pyrazole or pyrimidine ring. As part of our ongoing research on isocyanides[14] and diazo compounds,[15] recently, we developed (3+2) cyclization reactions of diazo

Scheme 1. Strategies for the synthesis of pyrazolo[1,5-*c*]quinazoline derivatives.



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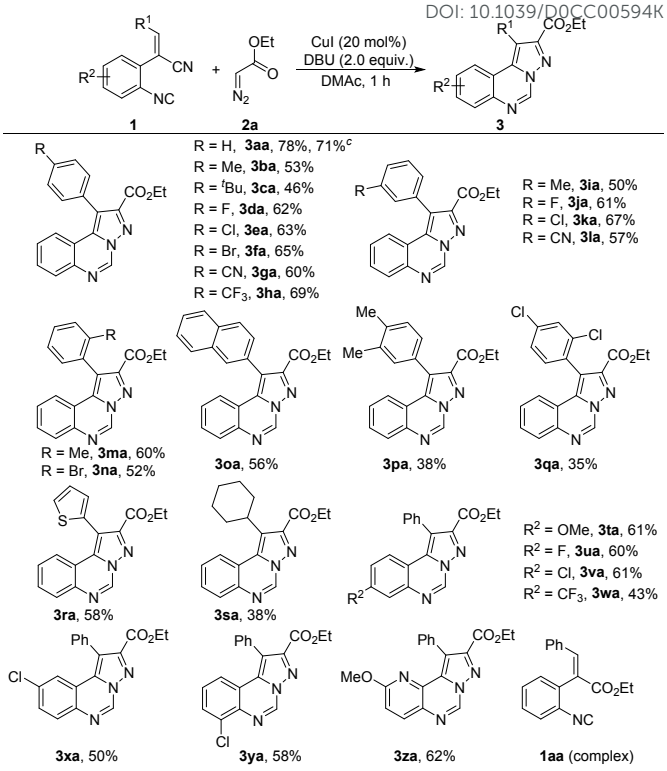
compounds with alkenes,[15e] active methylene compounds,[15f] or isocyanides[15h] for the construction of pyrazole or imidazoline skeleton. A strategy can thus be envisioned to fulfill this synthetic target by taking advantage of diazo compounds that delivers a proximal nucleophilic nitrogen upon (3+2) cyclization. For this purpose, *o*-alkenyl aromatic isocyanides were identified as bifunctional reagents via a transannulation strategy. However, in these reactions, no desired product was obtained (Scheme 1, eqn (3)). We hypothesized that the introduction of electron-drawing group (*e.g.* cyano) on C1 position of *o*-vinyl group in aromatic isocyanides, as the nucleophilic carbon is turned into an electrophile carbon in the *o*-alkenyl aromatic isocyanides (Scheme 1, eqn (4)). This transformation represents an umpolung of the substrates, which could electronically match diazo compounds, leading to synthesis of pyrazolo[1, 5-*c*]quinazoline scaffold via a tandem (3+2) cyclization/elimination/intramolecular aza-addition process. Herein, we developed the preparation of a variety of functionalized *o*-alkenyl aromatic isocyanides (for more details, see Scheme S1 of the SI) and their double annulation with diazo compounds for the efficient construction of pyrazolo[1,5-*c*]quinazoline derivatives in a single operation under mild reaction conditions.

At the outset, the reaction of *o*-alkenyl aromatic isocyanide **1a** with ethyl 2-diazoacetate (EDA) **2a** was investigated to optimize the reaction conditions (see Table S1 of the SI). When a solution of isocyanide **1a** (0.2 mmol), EDA **2a** (0.3 mmol), and DBU (0.5 equiv.) in DMAc was stirred at room temperature in air in the presence of CuI (20 mol%) for 1h, the desired pyrazolo[1,5-*c*]quinazolines **3aa** could be isolated in 16% yield (entry 1). Encouraged by the above result, we then screened with different amount of DBU (entries 2-4). The results revealed that the use of 2 equiv. of DBU delivered the best yields compared to 1.5 or 3.0 equiv. of DBU. When the reaction was performed under nitrogen, the product **3aa** was isolated in 66% yield (entry 5). Further increasing the amount of EDA **2a** to 2 equiv. gave equally optimal yield (entry 6). However, a slightly lower yield was isolated when the reaction temperature was raised up to 40 °C (entry 7). When the CuI loading was decreased to 10 mol%, the product **3aa** was isolated in 68% yield (entry 8). Screening of copper catalysts revealed that CuI exhibited the highest activity (entries 9-14). Next, Ag_2CO_3 and AgOAc were found to be much less effective as compared to CuI (entries 15-16). To improve the reaction outcomes, we next screened different bases and solvents, DBU and DMAc were proven to be the best choice (see Table S2 of the SI).

With the optimal conditions in hand, the scope and generality with respect to isocyanides were examined, and the results are summarized in Scheme 2. Generally, a variety of isocyanides (**1a**-**1t**) were successfully converted to the corresponding pyrazolo[1,5-*c*]quinazolines in moderate to good yields. The electronic effects exerted by the aryl group (R^1 = Ar) had a marginal impact on the reaction efficiency. Substrates bearing either electron-donating or electron-withdrawing group at the different positions of the phenyl ring all proceeded smoothly with EDA **2a** in 46-78% yields (**3aa**-**3na**). The molecular structure of **3aa** was unambiguously confirmed by X-ray crystallography (CCDC 1973902). Moreover, the isocyanides **1o**-**1q** derived from β-naphthaldehyde and di-substituted arene aldehydes were

Scheme 2. Substrate Scope of *o*-vinyl aromatic isocyanides[a,b]

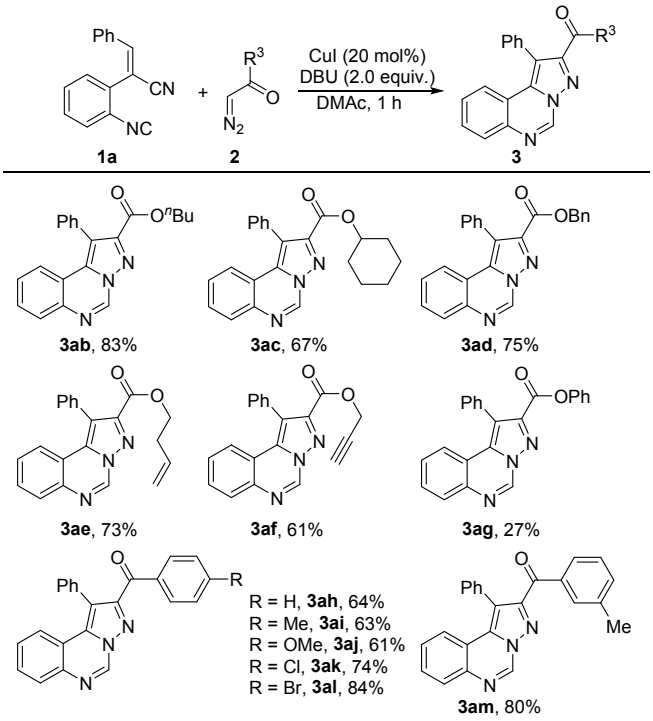


[a] Reactions were carried out using **1** (0.2 mmol), **2a** (0.3 mmol), CuI (20 mol%), DBU (0.4 mmol) and in DMAc (1 mL) at room temperature for 1 h under air. [b] Isolated yield. [c] Reaction was performed with 5 mmol of **1a**.

also viable for this transformation. Besides the arene aldehydes, thiophene aldehyde has been proved to be compatible, and afforded the desired product in 58% yield (**3ra**). Notably, the reaction between **1s** and **2a** also afforded the desired product **3sa**, albeit in a low yield. Substrates **1t**-**1y** bearing methoxy, fluroro, chloro, and trifluoromethyl at different position of the phenyl ring also proceeded well in this domino reaction, and pyrazolo[1,5-*c*]quinazoline **3ta**-**3ya** were isolated in moderate to good yields. Notably, the arene substrate could be smoothly extended to a pyridine ring in 62% yield (**3za**). A substrate **1aa** has been also utilized for this reaction, unfortunately the desired product could not be detected in the reaction mixture. A gram-scale reaction of **1a** and **2a** was carried out and a 71% isolated yield was obtained.

We next evaluated the diversity of this tandem transformation with respect to diazo compounds, and the results are shown in Scheme 3. A series of α-diazocarbonyl compounds **2** could react with **1a** to afford the corresponding pyrazolo[1,5-*c*]quinazolines **3ab**-**3am** in 27-84% yields. It is noteworthy that the α-diazo esters with terminal alkenyl or alkynyl group was also compatible, and furnished the desired products **3ae** and **3af** in 73% and 61% yields, respectively. In contrast to these efficient cyclization reactions, reaction of **1a** and **2g** with lower efficiency under the standard conditions. In addition, the cyclization system could be extended to other diazoacetophenones (**2h**-**2m**), delivering the desired products in good to high yields (**3ah**-**3am**). The above results indicate that

Scheme 3. Scope of Diazo Compounds[a,b]



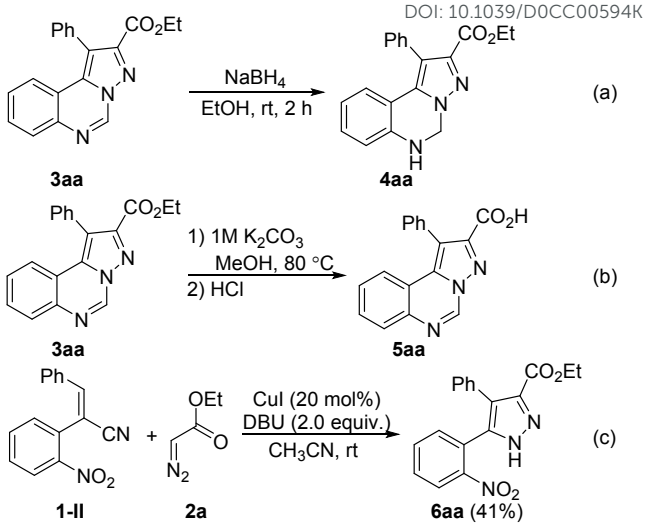
[a] Reactions were carried out using **1a** (0.2 mmol), **2** (0.3 mmol), CuI (20 mol%), DBU (0.4 mmol) and in DMAc (1 mL) at room temperature for 1 h under air. [b] Isolated yield.

the tandem reaction tolerates a wide scope of *o*-alkenyl aromatic isocyanides and diazo compounds.

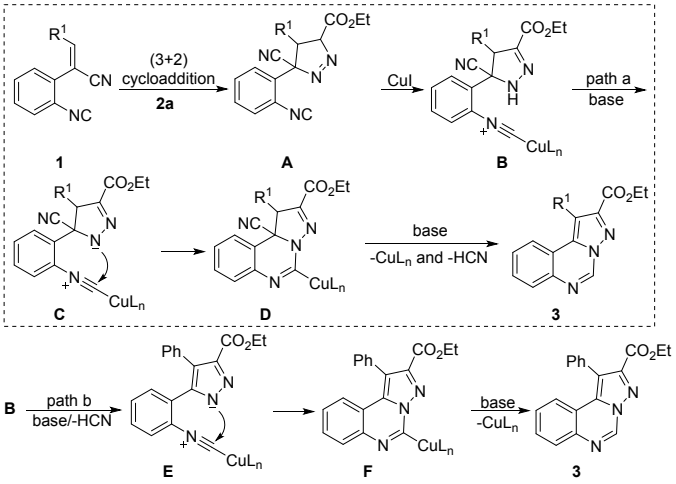
we next investigated the synthetic applications of the product **3aa**. For example, the product **3aa** could be reduced with $NaBH_4$ in EtOH to yield 5,6-dihydropyrazolo[1,5-*c*]quinazoline **4aa** (Scheme 4, eqn (a)), which have been used as antagonists for a biological targets.[16] The product **3aa** can be also hydrolyzed to the corresponding acid **5aa** by simple aqueous K_2CO_3 and acid treatment (Scheme 4, eqn (b)). To get some insights into the reaction mechanism, the reaction of the substrate **1-II** with **2a** was investigated under the standard condition (Scheme 4, eqn (c)). The non-productive intermediate (3+2) cycloadduct **6aa** was isolated in 41% yield, indicating that the (3+2) cycloaddition might be involved in this reaction.

Base on the above results and the related reports,[13,15] a plausible mechanism for this tandem reaction was proposed (Scheme 5). Initially, the (3+2) cycloaddition reaction of **1** with **2a** produces 1-pyrazoline intermediate **A**, which was converted to intermediate **B** via the coordination of CuI to isocyanide moiety and isomerization in the presence of a base.[17] Thereafter, there are two possible pathways for the pyrazolo[1,5-*c*]quinazolines formation. Cyclization involving intramolecular nucleophilic attack resulted in the formation of intermediate **D** in the presence of base. Then, the final product basic conditions (Scheme 5, path a). Another pathway involves the elimination of HCN to generate 1-pyrazole intermediate **E**, which undergoes intramolecular nucleophilic attack to afford intermediate **F**. Further elimination of the CuL_n from intermediate **F** gives the desired product **3** (Scheme 5, path b).

Scheme 4. Transformation of **3aa** and control experiment.



Scheme 5. Proposed mechanism for formation of **3**.



Conclusions

In summary, a series of *o*-alkenyl aromatic isocyanides were prepared from readily accessible starting materials and their double annulation with diazo compounds. This reaction provides a general and highly efficient method for the one-pot synthesis of pyrazolo[1,5-*c*]quinazolines from acyclic starting materials. Two rings and three new bonds were created through a copper-catalyzed domino reaction involving (3+2) cyclization/elimination/intramolecular aza-addition sequence. This protocol shows its attractive features such as synthetic simplicity, a broad substrate scope, and excellent functional group compatibility under mild reaction conditions. Moreover, the reaction can be also carried out on a gram scale with satisfactory yield, which opens up the possibility in practical applications.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) S. B. Mhaske and N. P. Argade, *Tetrahedron* 2006, **62**, 9787-9826; (b) L. M. Blair and J. Sperry, *J. Nat. Prod.* 2013, **76**, 794-812; (c) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.* 2014, **57**, 10257-10274; (d) U. H. F. Bunz, *Acc. Chem. Res.* 2015, **48**, 1676-1686.

2 (a) F. Varano, D. Catarzi, V. Colotta, G. Filacchioni, A. Galli, C. Costagli and V. Carlà, *J. Med. Chem*. 2002, **45**, 1035-1044; (b) F. Varano, D. Catarzi, V. Colotta, F. R. Calabri, O. Lenzi, G. Filacchioni, A. Galli, C. Costagli, F. Deflorian and S. Moro, *Bioorg. Med. Chem*. 2005, **13**, 5536-5549; (c) F. Varano, D. Catarzi, V. Colotta, O. Lenzi, G. Filacchioni, A. Galli and C. Costagli, *Bioorg. Med. Chem.* 2008, **16**, 617-2626; (d) F. Varano, D. Catarzi, V. Colotta, O. Lenzi, G. Filacchioni, A. Galli and C. Costagli, *Bioorg. Med. Chem.* 2008, **16**, 2617-2626; (e) D. Catarzi, V. Colotta, F. Varano, D. Poli, L. Squarcialupi, G. Filacchioni, K. Varani, F. Vincenzi, P. A. Borea, D. Dal Ben, C. Lambertucci and G. Cristalli, *Bioorg. Med. Chem.* 2013, **21**, 283-294.

3 (a) F. Beaulieu, C. Ouellet, E. H. Ruediger, M. Belema, Y. Qiu, X. Yang, J. Banville, J. R. Burke, K. R. Gregor and J. F. MacMaster, *Biorg. Med Chem. Lett.* 2007, **17**, 1233-1237; (b) B. Asproni, G. Murineddu, A. Pau, G. A. Pinna, M. Langgård, C. T. Christoffersen, J. Nielsen and J. Kehler, *Bioorg. Med. Chem.* 2011, **19**, 642-649.

4 D. M. Sawant, S. Sharma, R. S. Pathare, G. Joshi, S. Kalra, S. Sukanya, A. K. Maurya, R. K. Metre, V. K. Agnihotri, S. Khan, R. Kumar and R. T. Pardasani, *Chem. Commun.* 2018, **54**, 11530-11533.

5 M. Nuth, L. Huang, Y. L. Saw, N. Schormann, D. Chattopadhyay and R. P. Ricciardi, *J. Med. Chem*. 2011, **54**, 3260-3267.

6 (a) S. Guo, J. Wang, X. Fan, X. Zhang and D. Guo, *J. Org. Chem.* 2013, **78**, 3262-3270; (b) D. Kumar and R. Kumar, *Tetrahedron Lett.* 2014, **55**, 2679-2683.

7 (a) G. DeStevens, A. Halamandaris, M. Bernier and H. M. Blatter, *J. Org. Chem.* 1963, **28**, 1336-1339; (b) M. Janjić, R. Prebil, U. Grošelj, D. Kralj, Č. Malavašič, A. Golobič, K. Stare, G. Dahmann, B. Stanovnik and J. Svete, *Helv. Chim. Acta.* 2011, **94**, 1703-1717.

8 (a) T. Wang, A. Shao, H. Feng, S. Yang, M. Gao, J. Tian and A. Lei, *Tetrahedron*, 2015, **71**, 4473-4477; (b) H. Feng, T. Wang, S. Chen, Y. Huang, W. Yu, Y. Huang and F. Xiong, *RSC Adv.* 2016, **6**, 95774-95779.

9 X. Yang, Y. Jin, H. Liu, Y. Jiang and H. Fu, *RSC Adv*. 2012, **2**, 11061-11066.

10 For recent reviews, see: (a) Isocyanide Chemistry Applications in Synthesis and Materials Science (Ed.: V. Nenajdenko,), Wiley-VCH, Weinheim, 2012; (b) A. V. Lygin and A. D. Meijere, *Angew. Chem. Int. Ed*. 2010, **49**, 9094-9124; (c) S. Lang, *Chem. Soc. Rev.* 2013, **42**, 4867-4880; (d) G. Qiu, Q. Ding and J. Wu, *Chem. Soc. Rev.* 2013, **42**, 5257-5269; (e) V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin and V. Yu. Kukushkin, *Chem. Rev.* 2015, **115**, 2698-2779; (f) B. Zhang and A. Studer, *Chem. Soc. Rev.* 2015, **44**, 3505-3521; (g) M. Giustiniano, A. Basso, V. Mercalli, A. Massarotti, E. Novellino, G. C. Tron and J. Zhu, *Chem. Soc. Rev.* 2017, **46**, 1295-1357; (h) B. Song and B. Xu, *Chem. Soc. Rev.* 2017, **46**, 1103-1123.

11 (a) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang and S. Yu, *Angew. Chem. Int. Ed.* 2013, **52**, 13289-13292; (b) D. Leifert, A. Studer, *Angew. Chem. Int. Ed.* 2016, **55**, 11660-11663; (c) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, *Angew. Chem. Int. Ed.* 2016, **55**, 2743-2747; (d) D. Li, T. Mao, J. Huang and Q. Zhu, *Org. Lett.* 2017, **19**, 3223-3226; (e) Y. Liu, X.-L. Chen, K. Sun, X.-Y. Li, F.-L. Zeng, X.-C. Liu, L.-B. Qu, Y.-F. Zhao and B. Yu, *Org. Lett.* 2019, **21**, 4019-4024.

12 (a) T. Mitamura, K. Iwata, A. Ogawa, *J. Org. Chem.* 2011, **76**, 3880-3887; (b) B. Zhang and A. Studer, *Org. Lett.* 2014, **16**, 1216-1219; (c) C. J. Evoniuk, M. Ly and I. V. Alabugin, *Chem. Commun.* 2015, **51**, 12831-12834; (d) Y.-C. Yuan, H.-L. Liu, X.-B. Hu, Y. Wei and M. Shi, *Chem. - Eur. J.* 2016, **22**, 13059-13063; (e) C. J. Evoniuk, G. D. P. Gomes, M. Ly, F. D. White and I. V. Alabugin, *J. Org. Chem.* 2017, **82**, 4265-4278; (f) C. H. Wang, Y. H. Li and S. D. Yang, *Org. Lett.* 2018, **20**, 2382-2385; (g) A. Vidyasagar, J. Shi, P. Kreitmeier and O. Reiser, *Org. Lett.* 2018, **20**, 6984-6989.

13 (a) Y. Fang, S.-Y. Wang, X.-B. Shen and S.-J. Ji, *Org. Chem. Front.* 2015, **2**, 1338-1341; (b) Z. Hu, H. Yuan, Y. Men, Q. Liu, J. Zhang and X. Xu, *Angew. Chem. Int. Ed.* 2016, **55**, 7077-7080; (c) Z. Y. Hu, J. H. Dong, Y. Men, Y. F. Li and X. X. Xu, *Chem. Commun.* 2017, **53**, 1739-1742; (d) J. Cai, Z. Hu, Y. Li, J. Liu and X. Xu, *Adv. Synth. Catal.* 2018, **360**, 3595-3600; (e) Z. Hu, J. Dong, Z. Li, B. Yuan, R. Wei and X. Xu, *Org. Lett.* 2018, **20**, 6750-6754; (f) Y. Men, Z. Hu, J. Dong, X. Xu and B. Tang, *Org. Lett*. 2018, **20**, 5348-5352; (g) L. Bao, J. Liu, L. Xu, Z. Hu and X. Xu, *Adv. Synth. Catal.* 2018, **360**, 1870-1875.

14 (a) H. Wang, Y.-L. Zhao, C.-Q. Ren, A. Diallo and Q. Liu, *Chem. Commun*. 2011, **47**, 12316-12318; (b) X.-B. Bu, Z. Wang, Y.-H. Wang, T. Jiang, L. Zhang and Y.-L. Zhao, *Eur. J. Org. Chem*. 2017, **2017**, 1132-1138; (c) X.-B. Bu, Z.-X. Zhang, Q.-Q. Peng, X. Xu and Y.-L. Zhao, *J. Org. Chem*. 2019, **84**, 53-59; (d) L. Zhang, T. Liu, Y. M. Wang, J. Chen and Y. L. Zhao, *Org. Lett.* 2019, **21**, 2973-2977.

15 (a) S. Wawzonek and C.E. Morreal, *J. Am. Chem. Soc.* 1960, **82**, 439-441; (b) W. I. Awad and A. H. Lawrence, *Tetrahedron* 1970, **26**, 5959-5967; (c) J. Elzinga, H. Hogeveen and E. P. Schudde, *J. Org. Chem.* 1980, **45**, 4337-4338; (d) L. L. Rodina, S. A. Karavaeva, Vs.V. Nikolaev and V. V. Dubitskii, *Russ. J. Org. Chem.* 2001, **37**, 214-216; (e) H. Wang, Y.-L. Zhao, L. Li, Z.-W. Zhang and Q. Liu, *Adv. Synth. Catal.* 2013, **355**, 1540-1544; (f) L. Li, J.-J. Chen, Y.-J. Li, X.-B. Bu, Q. Liu and Y.-L. Zhao, *Angew. Chem. Int. Ed*. 2015, **54**, 12107-12111; (g) Y.-J. Li, X. Li, S.-X. Zhang, Y.-L. Zhao and Q. Liu, *Chem. Commun*. 2015, **51**, 11564-11567; (h) X.-B. Bu, Y. Yu, B. Li, L. Zhang, J.-J. Chen and Y.-L. Zhao, *Adv. Synth. Catal*. 2017, **359**, 351-356; (i) X.-B. Bu, Z. Wang, X.-D. Wang, X.-H. Meng and Y.-L. Zhao, *Adv. Synth. Catal*. 2018, **360**, 2945-2951; (j) L. Zhang, J.-J. Chen, S.-S. Liu, Y.-X. Liang and Y.-L. Zhao, *Adv. Synth. Catal*. 2018, **360**, 2172-2177.

16 H.-T. Tang, K. Xiong, R.-H. Li Z.-C. Ding and Z.-P. Zhan, *Org. Lett.* 2015, **17**, 326-329.

17 (a) C. Kanazawa, S. Kamijo and Y. Yamamoto, *J. Am. Chem. Soc.* 2006, **128**, 10662-10663; (b) Q. Cai, F. Zhou, T. Xu, L. Fu and K. Ding, *Org. Lett.* 2011, **13**, 340-343.

