## PAPER

Check for updates

# Rh(III)-catalyzed synthesis of dibenzo[b,d]pyran-6-ones from aryl ketone O-acetyl oximes and quinones via C−H activation and C−C bond cleavage†

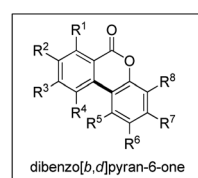Wei Yang, [ID] *[ab] Haonan Zhang,[a] Yu Liu,*[ab] Cuiman Tang,[a] Xiaohui Xu[a] and Jiaqi Liu[a]

A redox-neutral synthesis of dibenzo[b,d]pyran-6-ones from aryl ketone O-acetyl oximes and quinones has been realized via Rh(III)-catalyzed cascade C−H activation annulation. A possible Rh(III)−Rh(V)−Rh(III) mechanism involving an unprecedented β-C elimination step was proposed.

The dibenzo[b,d]pyran-6-one is one of the most important structural motifs widely present in natural products with pharmacological relevance,[1] such as gut microbiota metabolites urolithins (1–4) that show anti-inflammatory, antiglycative and neuroprotective effects,[2–4] and the extracts of an endophytic fungus *Cephalosporium acremonium* IFB-E007 (5–7) that have pronounced anticancer activities.[5] In addition, the related heterocyclic structure benzo[d]naphtho[1,2-b]pyran-6-one is found in some bactericidal and antitumor natural products including gilvocarcins[6,7] (8–10) chrysomycins,[8,9] (11–13), *etc.* (Fig. 1). Therefore, a number of approaches to access dibenzo [b,d]pyran-6-ones have been developed *via* the intra- or inter-molecular biaryl formation as the key step.[10] However, many of these methodologies require multi-step reactions, and the development of new efficient synthetic methods, especially those easy one-step reactions that are still of great interest.

In the past decade, transition-metal-catalyzed C−H bond activation has proven to be a powerful tool in organic syntheses[11] and several methods for the synthesis of dibenzo [b,d]pyran-6-ones *via* C−H activation have been reported.[12] Actually, in 2015, our group reported Rh(III)-catalyzed synthesis of dibenzo[b,d]pyran-6-ones from N-methoxybenzamides and quinones through C−H activation annulation.[13] Interestingly, we obtained the same products using aryl ketone O-acetyl oximes as substrates to react with quinones under Rh(III)-cata-lyzed conditions in this work. Rh(III)-catalyzed C−H activation using ketoximes as substrates has been developed for synthesis of various substituted heterocycles.[14] Compared to the previous reports, this reaction undergoes a novel mechanism involving an unexpected C−C bond cleavage, which is attractive.
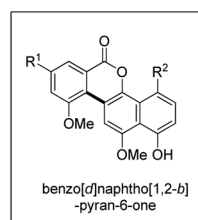
Moreover, our study demonstrated that solvent is vital to these reactions. In 2018, we reported Rh(III)-catalyzed annulation of aryl ketone O-acetyl oximes with quinones to synthesize 6H-benzo[c]chromenes with acetone as a co-solvent.[15] Herein, we described Rh(III)-catalyzed synthesis of dibenzo[b,d]pyran-6-ones using the same substrates without acetone (Scheme 1).

Initially, the reaction of acetophenone O-acetyl oxime 1a with benzoquinone 2a was employed to optimize the reaction conditions (Table 1). When the reaction was conducted in the presence of [Cp*RhCl₂]₂ (2.5 mol%), AgSbF₆ (10 mol%) and PivOH (100 mol%) in MeOH at 50 °C for 12 h, 2-hydroxy-6H-dibenzo[b,d]pyran-6-one 3a was obtained in 12% yield (Table 1, entry 1). Elevating the reaction temperature led to a higher yield of 3a (Table 1, entries 1–4). Solvent screening (Table 1, entries 4–9) revealed that reaction in MeOH gave a higher yield of 3a (Table 1, entry 4). Among the additives tested, benzoic acid was the most favorable with respect to product yield (Table 1, entries

*School of Chemical Engineering, Northeast Electric Power University, Jilin 132012, China. E-mail: yangw467@163.com; greatliudy123@163.com*

*Gongqing Institute of Science and Technology, Gongqing 332020, China*

**urolithins**:
**1**: R¹, R³, R⁴, R⁵, R⁶, R⁸ = H; R², R⁷ = OH
**2**: R¹, R⁴, R⁵, R⁶, R⁸ = H; R², R³, R⁷ = OH
**3**: R¹, R³, R⁵, R⁶, R⁸ = H; R², R⁴, R⁷ = OH
**4**: R¹, R⁵, R⁶, R⁸ = H; R², R³, R⁴, R⁷ = OH

**extracts of *C. acremonium* IFB-E007**:
**5**: R¹ = OH, R², R⁴, R⁶ = H; R³, R⁷, R⁸ = OMe; R⁵ = Me
**6**: R¹ = OH, R², R⁴, R⁶ = H; R³, R⁷ = OMe; R⁵ = Me
**7**: R¹, R⁷ = OH, R², R⁴, R⁶, R⁸ = H; R³ = OMe; R⁵ = Me

dibenzo[b,d]pyran-6-one

benzo[d]naphtho[1,2-b]-pyran-6-one

**gilvocarcins**:
**8**: R¹ = Me; R² = A
**9**: R¹ = Et; R² = A
**10**: R¹ = vinyl; R² = A

**chrysomycins**:
**11**: R¹ = vinyl; R² = B
**12**: R¹ = Me; R² = B
**13**: R¹ = Et; R² = B
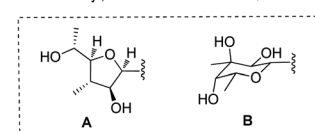
Fig. 1  Selected representative natural products.

**our prior work**

in 2015: reactions of *N*-methoxybenzamides with quinones
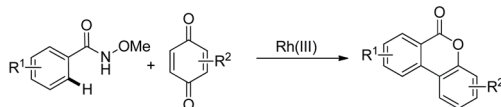
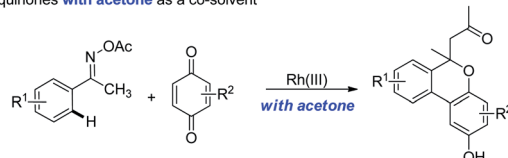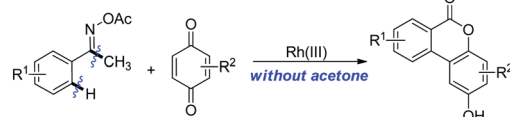in 2018: reactions of aryl ketone *O*-acyloximes with quinones **with acetone as a co-solvent**

**this work**

the same products: **aryl ketone *O*-acetyl oximes** as substrates **VS** our prior work in 2015

the same substrates: **without acetone** as solvent **VS** our prior work in 2018

**Scheme 1** Rh(III)-catalyzed divergent C–H activation annulation with quinones.
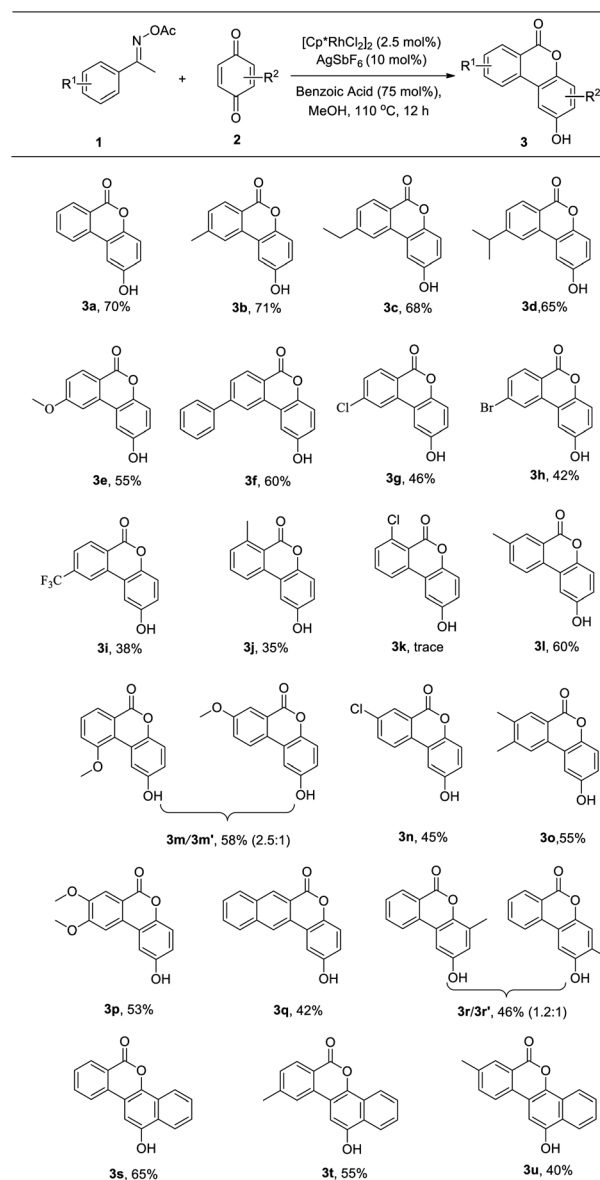
**Table 1** Optimization of the reaction conditions[a]

| Entry | Additive | Solvent | Temp °C | Yield[b] (%) |
|---|---|---|---|---|
| 1 | PivOH | MeOH | 50 | 12 |
| 2 | PivOH | MeOH | 70 | 20 |
| 3 | PivOH | MeOH | 90 | 36 |
| 4 | PivOH | MeOH | 110 | 43 |
| 5 | PivOH | EtOH | 110 | 26 |
| 6 | PivOH | DMF | 110 | 37 |
| 7 | PivOH | THF | 110 | 16 |
| 8 | PivOH | HFIP | 110 | 0 |
| 9 | PivOH | Acetone | 110 | Trace |
| 10 | HOAc | MeOH | 110 | Trace |
| 11 | Benzoic acid | MeOH | 110 | 50 |
| 12[c] | Benzoic acid | MeOH | 110 | 70 |
| 13[d] | Benzoic acid | MeOH | 110 | 63 |

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Cp*RhCl$_2$]$_2$ (2.5 mol%), additive (100 mol%), solvent (1 mL) for 12 h. [b] Isolated yields. [c] Benzoic acid (75 mol%) was added. [d] Benzoic acid (50 mol%) was added.

**Table 2** The reaction scope[a]

**3a**, 70%  **3b**, 71%  **3c**, 68%  **3d**, 65%

**3e**, 55%  **3f**, 60%  **3g**, 46%  **3h**, 42%

**3i**, 38%  **3j**, 35%  **3k**, trace  **3l**, 60%

**3m/3m′**, 58% (2.5:1)  **3n**, 45%  **3o**, 55%

**3p**, 53%  **3q**, 42%  **3r/3r′**, 46% (1.2:1)

**3s**, 65%  **3t**, 55%  **3u**, 40%

[a] Standard conditions.

4, 10 and 11). Decreasing the amount of benzoic acid to 75 mol% resulted in the best yield of **3a** (Table 1, entry 12).

Under the obtained optimum reaction conditions above (Table 1, entry 12), we surveyed the reaction scope (Table 2). First, the reactions of various aryl ketone *O*-acetyl oximes **1** with **2a** were examined. For acetophenone *O*-acetyl oximes, substrates with electron-donating groups or phenyl at the *para*-

position of aryl groups participated well in this reaction and the corresponding products were obtained in good yields (**3a**–**3f**). Substrates with halogens or strong electron-withdrawing group trifluoromethyl gave the products in lower yields (**3g**–**3i**). Substrate bearing the methyl or chlorine at the *meta*-position provided the desired products **3l** and **3n** with exclusive regio-selectivity toward the less-hindered site, whereas the *meta*-methoxy-substituted derivative gave a mixture of regioisomers (**3m**/**3m′** = 2.5 : 1), revealing that the nature of the substituent at the *meta*-position had an effect on the regioselectivity. 3,4-Disubstituted acetophenone *O*-acetyl oximes smoothly reacted to result the corresponding dibenzo[*b*,*d*]pyran-6-ones **3o** and **3p** in moderate yields. 2-Acetonaphthone *O*-acetyl oxime also produced the target product 2-hydroxy-6*H*-naphtho[2,3-*c*]

**Paper**
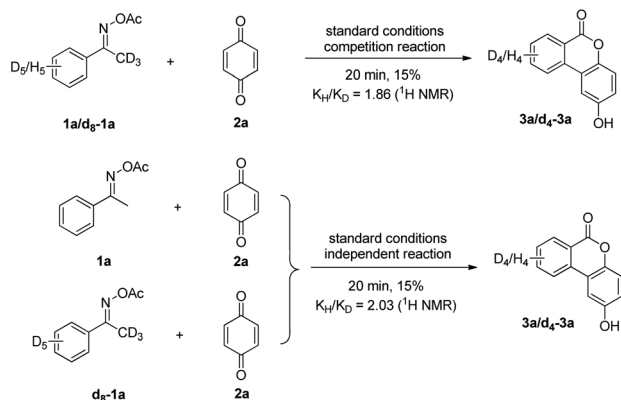
Scheme 2  Kinetic isotope effect experiments.



Scheme 3  Proposed mechanism.

chromen-6-one **3q**. Next, we examined the reactivity of quinone derivatives with **1a** under the established conditions. Methyl benzoquinone afforded the desired molecule in 46% yield with regioisomers (**3r**/**3r′**) in a ratio of approximately 1.2 : 1. The naphthoquinone could be also well tolerated, giving benzo[*d*]naphtho[1,2-*b*]pyran-6-one **3s** in 65% yield. Furthermore, *para*-methyl-substituted or *meta*-methyl-substituted acetophenone *O*-acetyl oximes also smoothly reacted with naphthoquinone to give the corresponding products **3t** or **3u**. Thus, several tetra-cyclic benzo[*d*]naphtho[1,2-*b*]pyran-6-ones were synthesized successfully.

To shed light on the reaction mechanism of this annulation, the reaction of acetophenone *O*-acetyl oxime **1a** with benzo-quinone **2a** under standard conditions was detected by GC-MS, and benzonitrile was observed (detected by GC-MS; see ESI†). This result suggested this reaction might undergo a β-C elimi-nation. Then, deuterium-labeling experiments were further carried out to gain some insights into the catalytic mechanism. A competition between protio and deutero **1a** showed a KIE value of 1.86 at early conversion. The KIE was further measured from two side-by-side reactions using protio and deutero **1a** with **2a** and a KIE value of 2.03 was observed (Scheme 2). These results demonstrated that the C–H bond cleavage process might be involved in the rate-determining step.

On the basis of our previous work, present observations and literature precedent,[11,13,15,16] a mechanistic pathway is proposed (Scheme 3, taking the reaction of substrate **1a** with benzoqui-none **2a** as an example). First, *O*-acetyl oxime **1a** reacts with the active Cp*Rh(III) species through directed C–H cleavage to form a five-membered rhodacycle intermediate **I**. Next, coordination of the benzoquinone affords intermediate **II**, which undergoes migratory insertion into the incipient Rh–C bond to form a seven-membered rhodacycle **III**. Protonolysis and aromatiza-tion deliver biaryl intermediate **IV**. Then, an oxidative addition of Rh(III) into the O–N bond is possible to produce the Rh(v) species **V**,[17] followed by β-C elimination to give the intermediate **VI**.[18] A subsequent intramolecular nucleophilic addition of intermediate **VI** delivers the intermediate **VII**, which undergoes hydrolysis to generate the final product **3a**.
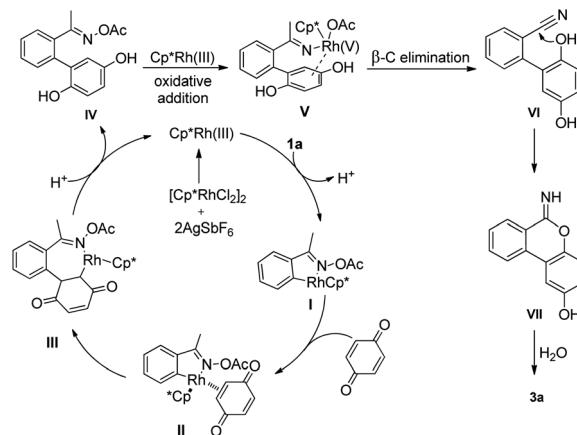
## Conclusions

In summary, we have developed a novel Rh(III)-catalyzed cascade C–H activation annulation with readily available and inexpen-sive substrates for the convenient and direct synthesis of dibenzo[*b*,*d*]pyran-6-ones. In this process, we proposed a possible Rh(III)–Rh(v)–Rh(III) pathway, which might undergo an unprecedented β-C elimination step. This is the first example of β-C elimination *via* Rh(III)-catalyzed C–H bond functionali-zation. Further studies into the detailed reaction mechanism is ongoing in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

## Notes and references

1 (*a*) J. M. Sayer, Y. Haruhiko, A. W. Wood, A. H. Conney and D. M. Jerina, *J. Am. Chem. Soc.*, 1982, **104**, 5562; (*b*) K. Koch, J. Podlech, E. Pfeiffer and M. J. Metzler, *Org. Chem.*, 2005, **70**, 3275; (*c*) W. Sun, L. D. Cama, E. T. Birzin, S. Warrier, L. Locco, R. Mosley, M. L. Hammond and S. P. Rohrer, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1468; (*d*) N. Tibrewal, P. Pahari, G. Wang, M. K. Kharel, C. Morris, T. Downey, Y. Hou, T. S. Bugni and J. Rohr, *J. Am. Chem. Soc.*, 2012, **134**, 18181; (*e*) J. S. Lazo, E. R. Sharlow, M. W. Epperly, A. Lira, S. Leimgruber, E. M. Skoda, P. Wipf and J. S. Greenberger, *J. Pharmacol. Exp. Ther.*, 2013, **347**, 669; (*f*) Z. Mao, W. Sun, L. Fu, H. Luo, D. Lai and L. Zhou, *Molecules*, 2014, **19**, 5088; (*g*) Y. L. Garazd and M. M. Garazd, *Chem. Nat. Compd.*, 2016, **52**, 1.

2 J. C. Espín, M. Larrosa, M. T. García-Conesa and F. T. Barberan, *J. Evidence-Based Complementary Altern. Med.*, 2013, **2013**, 15.

3 T. Yuan, H. Ma, W. Liu, D. B. Niesen, N. Shah, R. Crews, K. N. Rose and D. A. Vattem, *ACS Chem. Neurosci.*, 2016, **7**, 26.

4 J. P. Piwowarski, S. Granica, J. Stefanska and A. K. Kiss, *J. Nat. Prod.*, 2016, **79**, 3022.

5 H. W. Zhang, W. Y. Huang, Y. C. Song, J. R. Chen and R. X. Tan, *Helv. Chim. Acta*, 2005, **88**, 2861.

6 (*a*) S. Horii, H. Fukase, E. Mizuta, K. Hatano and K. Mizuno, *Chem. Pharm. Bull.*, 1980, **28**, 3601; (*b*) H. Nakano, Y. Matsuda, K. Ito, S. Ohkubo, M. Morimoto and F. Tomita, *J. Antibiot.*, 1981, **34**, 266.

7 (*a*) T. Matsumoto, T. Hosoya and K. Suzuki, *J. Am. Chem. Soc.*, 1992, **114**, 3568; (*b*) I. Takemura, K. Imura, T. Matsumoto and K. Suzuki, *Org. Lett.*, 2004, **6**, 2503; (*c*) P. R. Nandaluru and G. J. Bodwell, *J. Org. Chem.*, 2012, **77**, 8028.

8 (*a*) F. Strelitz, H. Flon and I. N. Asheshov, *J. Bacteriol.*, 1955, **69**, 280; (*b*) U. Weiss, K. Yoshihira, R. J. Highet, R. J. White and T. T. Wei, *J. Antibiot.*, 1982, **35**, 1194.

9 (*a*) I. R. Pottie, P. R. Nandaluru, W. L. Benoit, D. O. Miller, L. N. Dawe and G. J. Bodwell, *J. Org. Chem.*, 2011, **76**, 9015; (*b*) S. K. Jain, A. S. Pathania, R. Parshad, C. Raina, A. Ali, A. P. Gupta, M. Kushwaha, S. Aravinda, S. Bhushan, S. B. Bharate and R. A. Vishwakarma, *RSC Adv.*, 2013, **3**, 21046.

10 (*a*) W. R. Bowman, E. Mann and J. Parr, *J. Chem. Soc., Perkin Trans. 1*, 2000, **1**, 2991; (*b*) H. Abe, K. Nishioka, S. Takeda, M. Arai, Y. Takeuchi and T. Harayama, *Tetrahedron Lett.*, 2005, **46**, 3197; (*c*) N. Thasana, R. Worayuthakarn, P. Kradanrat, E. Hohn, L. Young and S. J. Ruchirawat, *Org. Chem.*, 2007, **72**, 9379; (*d*) M. E. Jung and D. A. Allen, *Org. Lett.*, 2009, **11**, 757; (*e*) K. Vishnumurthy and A. Makriyannis, *J. Comb. Chem.*, 2010, **12**, 664; (*f*) Y. Li, Y. J. Ding, J. Y. Wang, Y. M. Su and X. S. Wang, *Org. Lett.*, 2013, **15**, 2574; (*g*) S. Luo, F. X. Luo, X. S. Zhang and Z. J. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 10598; (*h*) H. N. Lv, P. F. Tu and Y. Jiang, *Mini-Rev. Med. Chem.*, 2014, **14**, 603.

11 For selected reviews, see:(*a*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (*b*) G. Rouquet and N. Chatani, *Angew. Chem., Int.*

*Ed.*, 2013, **52**, 11726; (*c*) F. Wang, S. Yu and X. Li, *Chem. Soc. Rev.*, 2016, **45**, 6462; (*d*) L. Liu and J. L. Zhang, *Youji Huaxue*, 2017, **37**, 1117; (*e*) T. H. L. Nguyen, N. Gigant and D. Joseph, *ACS Catal.*, 2018, **8**, 1546; (*f*) Y. Y. Xiang, C. Wang, Q. P. Ding and Y. Y. Peng, *Adv. Synth. Catal.*, 2019, **361**, 919; (*g*) S. Kumar, S. Nunewar, S. Oluguttula, S. Nanduri and V. Kanchupalli, *Org. Biomol. Chem.*, 2021, **19**, 1438.

12 (*a*) K. Inamoto, J. Kadokawa and Y. Kondo, *Org. Lett.*, 2013, **15**, 3962; (*b*) T. H. Lee, J. Jayakumar, C. H. Cheng and S. C. Chuang, *Chem. Commun.*, 2013, **49**, 11797; (*c*) K. Sasano, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.*, 2013, **135**, 10954; (*d*) F. Ji, X. Li, W. Wu and H. Jiang, *J. Org. Chem.*, 2014, **79**, 11246; (*e*) Y. Wang, J. Y. Gu and Z. J. Shi, *Org. Lett.*, 2017, **19**, 1326; (*f*) R. Chen and S. Cui, *Org. Lett.*, 2017, **19**, 4002; (*g*) L. Pan, J. Dong, D. Xie, Y. Li and Q. Liu, *Adv. Synth. Catal.*, 2018, **360**, 958; (*h*) Y. Dong, J. T. Yu, S. Sun and J. Cheng, *Chem. Commun.*, 2020, **56**, 6688.

13 W. Yang, S. Wang, Q. Zhang, Q. Liu and X. Xu, *Chem. Commun.*, 2015, **51**, 661.

14 (*a*) P. C. Too, S. H. Chua, S. H. Wong and S. Chiba, *J. Org. Chem.*, 2011, **76**, 6159; (*b*) H. Jiang, J. Yang, X. Tang and W. Wu, *J. Org. Chem.*, 2016, **81**, 2053; (*c*) H. Huang, J. Cai and G. J. Deng, *Org. Biomol. Chem.*, 2016, **14**, 1519; (*d*) V. Vinayagam, A. Mariappan, M. Jana and M. Jeganmohan, *J. Org. Chem.*, 2019, **84**, 15590; (*e*) N. Aravindan and M. Jeganmohan, *J. Org. Chem.*, 2021, **86**, 14826.

15 W. Yang, J. Wang, H. Wang, L. Li, Y. Guan, X. Xu and D. Yu, *Org. Biomol. Chem.*, 2018, **16**, 6865.

16 (*a*) L. Yang, B. Qian and H. Huang, *Chem. –Eur. J.*, 2012, **18**, 9511; (*b*) W. Yang, J. Sun, X. Xu, Q. Zhang and Q. Liu, *Chem. Commun.*, 2014, **50**, 4420; (*c*) Z. Qi and X. Li, *Chin. J. Catal.*, 2015, **36**, 48; (*d*) W. Yang, J. Wang, Z. Wei, Q. Zhang and X. Xu, *J. Org. Chem.*, 2016, **81**, 1675; (*e*) W. Yang, J. Dong, J. Wang and X. Xu, *Org. Lett.*, 2017, **19**, 616.

17 (*a*) W. Guo and Y. Xia, *J. Org. Chem.*, 2015, **80**, 8113; (*b*) Z. Zhou, M. Bian, L. Zhao, H. Gao, J. Huang, X. Liu, X. Yu, X. Li and W. Yi, *Org. Lett.*, 2018, **20**, 3892.

18 H. Li, M. L. Wang, Y. W. Liu, L. J. Li, H. Xu and H. X. Dai, *ACS Catal.*, 2022, **12**, 82.