RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 31101

ortho-Naphthoquinone-catalyzed aerobic oxidation of amines to fused pyrimidin-4(3*H*)-ones: a convergent synthetic route to bouchardatine and sildenafil†

Kyeongha Kim, Hun Young Kim and Kyungsoo Oh *

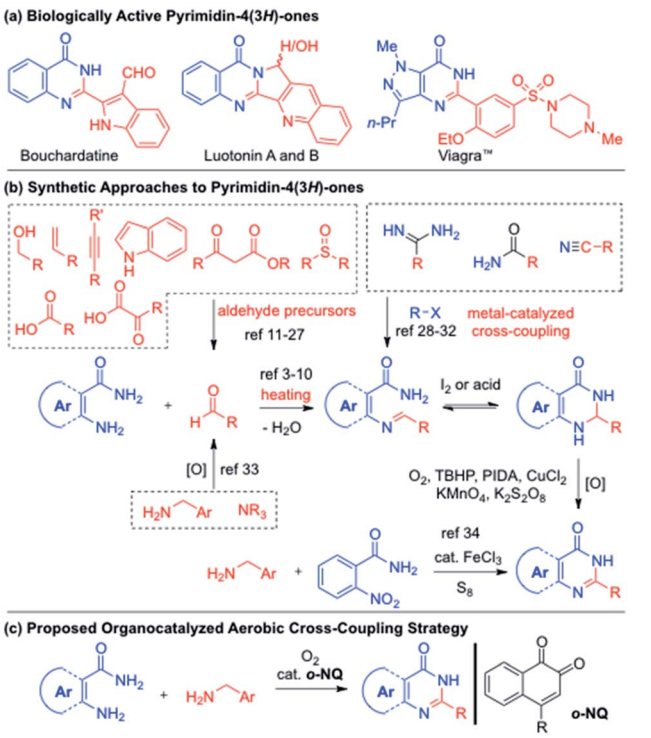
Received 7th August 2020
Accepted 14th August 2020

DOI: 10.1039/d0ra06820a

rsc.li/rsc-advances

A facile access to fused pyrimidin-4(3*H*)-one derivatives has been established by using the metal-free *ortho*-naphthoquinone-catalyzed aerobic cross-coupling reactions of amines. The utilization of two readily available amines allowed a direct coupling strategy to quinazolinone natural product, bouchardatine, as well as sildenafil (Viagra™) in a highly convergent manner.

N-Heterocyclic compounds with a pyrimidin-4(3*H*)-one core constitute a large number of natural products and biologically active molecules. For example, quinazolinone alkaloids possess a phenyl-fused pyrimidin-4(3*H*)-one structure and display a wide spectrum of pharmacological activities (Scheme 1a).[1] Sildenafil (Viagra™), a potent and selective inhibitor of type 5 phosphodiesterases on smooth muscle cell, is based on the pyrazole-fused pyrimidin-4(3*H*)-one structure and marketed for erectile dysfunction.[2] The synthetic approaches to the phenyl-fused pyrimidin-4(3*H*)-ones, quinazolinones, typically involve the condensation between anthranilamides and aldehydes to give aminal intermediates that in turn oxidized to quinazolinones under oxidation conditions (Scheme 1b). The oxidation catalysts include Cu,[3] Fe,[4] Ga,[5] Ir,[6] Mn,[7] iodine,[8] peroxide,[9] however the aerobic oxidation of aminal intermediates is also known at 150 °C.[10] The utilization of alcohols also effects the one-pot synthesis of quinazolinones through *in situ* oxidation to aldehydes in the presence of Fe,[11] Ir,[12] Mn,[13] Ni,[14] Pd,[15] Ru,[16] V,[17] Zn,[18] and iodine catalysts.[19] Other precursors to aldehydes have been also identified using alkynes,[20] benzoic acids,[21] indoles,[22] α-keto acid salts,[23] β-keto esters,[24] styrenes,[25] sulfoxides,[26] and toluenes.[27] Non-aldehyde approaches to quinazolinones have been also demonstrated in the cross coupling of amidines,[28] amines,[29] benzamides,[30] isocyanides,[31] and nitriles.[32] In 2013, the Nguyen group disclosed the synthesis of four quinazolinones, utilizing the autooxidation of benzylamines to imines that subsequently condensed with anthranilamides.[33] While a closed system at 150 °C was necessary, the use of 40 mol% AcOH without solvent provided the quinazolinones in 46–75% yields. The Nguyen group also developed the $FeCl_3 \cdot 6H_2O$-catalyzed condensation of 2-nitroanilines and benzylamines in the presence of 20 mol% of S_8, where six quinazolinones were obtained in 68–75% yields.[34] While the cross condensation of anthranilamides and benzylamines was accomplished, there exists a significant knowledge gap due to the limited substrate scope combined with less optimal reaction conditions (*i.e.* high



Scheme 1 Biologically active fused pyrimidin-4(3*H*)-one derivatives and their synthetic methods.

Center for Metareceptome Research, Graduate School of Pharmaceutical Sciences, Chung-Ang University, 84 Heukseok-ro, Dongjak, Seoul 06974, Republic of Korea. E-mail: kyungsoooh@cau.ac.kr

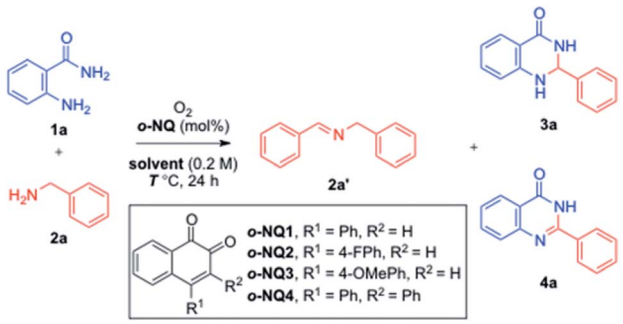
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra06820a

reaction temperature, closed system in neat conditions and excess use of amines). In addition, it is not entirely clear if the cross condensation of amide-containing amines and benzylamines would work for other fused pyrimidin-4(3*H*)-one derivatives.[35] To address such shortcomings in the cross condensation of amines, the *ortho*-naphthoquinone (***o*-NQ**)-catalyzed aerobic cross amination strategy was investigated (Scheme 1c).[36] Herein, we report a highly general approach to fused pyrimidin-4(3*H*)-one derivatives in the presence of ***o*-NQ** catalyst, culminating to the direct aerobic coupling of two amines to bouchardatine and sildenafil.

Given that the ***o*-NQ**-catalyzed aerobic cross coupling of benzylamines and aniline derivatives such as *o*-phenylenediamines provided a facile approach to heterocyclic compounds including benzoimidazoles,[37] the use of anthranilamide **1a** and benzylamine **2a** was examined as a model study (Table 1). The catalytic use of ***o*-NQ1** smoothly converted benzylamine **2a** to the corresponding homocoupled imine **2a′** under aerobic conditions. However, the subsequent *in situ* condensation reaction of **2a′** with anthranilamide **1a** only provided the aminal product **3a** in 11% yield (entry 1). To facilitate the cross coupling between the amine **2a** and anthranilamide **1a**, a catalytic amount of TFA was utilized where a significant improvement in yield was observed for **3a** (entry 2). Faced with the inability to oxidize the aminal **3a** to the corresponding product, quinazolinone **4a**, other *ortho*-naphthoquinone catalysts were screened without much success (entries 3–5). To our delight, the examination of solvents revealed that the reaction temperature of 100 °C was needed for the formation of **4a** (entries 6–11).[38] The reaction in DMSO lowered down the ratio of **1a** and **2a** from 1.0 : 1.5 to 1.0 : 1.2 (entry 12) and the catalyst loading to 5 mol% without affecting the overall reaction efficiency (entry 13). The control experiments confirmed the critical roles of both ***o*-NQ1** and TFA (entries 15–18), and the reaction utilized molecular oxygen as a terminal oxidant (entries 19 and 20). Piecing together the experimental data, the employment of 5 mol% ***o*-NQ1** and 20 mol% TFA in DMSO at 100 °C was selected for further studies.

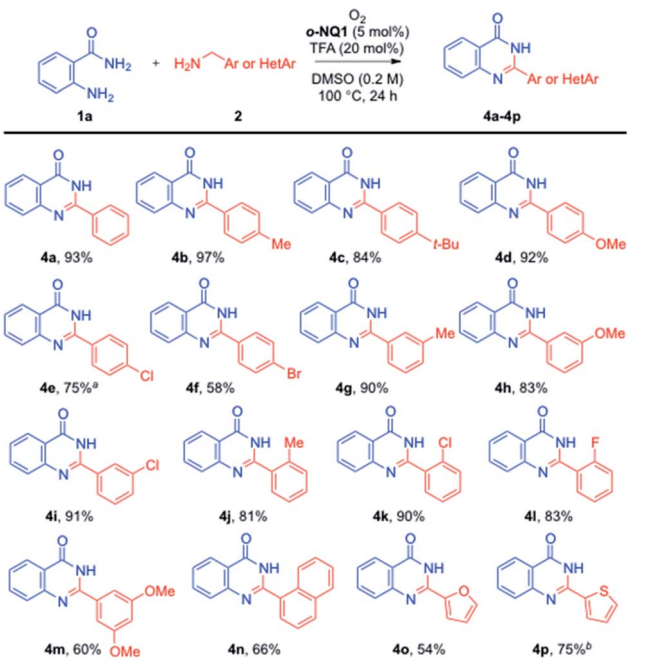
The optimized aerobic cross-coupling condition was applied to a variety of benzylamine derivatives (Scheme 2). In general, the electronic and steric characters of benzylamines did not significantly affect the formation of quinazolinones (**4a–4m**). However, the use of halogen-substituted and dimethoxy-substituted benzylamines led to the slightly lower yields of quinazolinones (**4e**, **4f** and **4m**) in 58–75% yields. In addition, the current aerobic cross-coupling reaction tolerated the furanyl and thiophenyl moieties, where the corresponding quinazolinones (**4o** and **4p**) were obtained in 54% and 75% yields, respectively.

Table 1 Optimization of *o*-NQ-catalyzed aerobic cross-coupling of amines to quinazolinone[a]



Entry	Cat. (mol%)	Solvent	T (°C)	Yield[b] (%)
1	***o*-NQ1** (10)	CH_3CN	80	**3a**, 11
2	***o*-NQ1** (10)/TFA (20)	CH_3CN	80	**3a**, 83
3	***o*-NQ2** (10)/TFA (20)	CH_3CN	80	**3a**, 13
4	***o*-NQ3** (10)/TFA (20)	CH_3CN	80	**3a**, 66
5	***o*-NQ4** (10)/TFA (20)	CH_3CN	80	**3a**, 32
6	***o*-NQ1** (10)/TFA (20)	MeOH	65	**3a**, 5
7	***o*-NQ1** (10)/TFA (20)	EtOH	78	**3a**, 31
8	***o*-NQ1** (10)/TFA (20)	DMF	150	**4a**, >95
9[c]	***o*-NQ1** (10)/TFA (20)	DMSO	150	**4a**, >95
10	***o*-NQ1** (10)/TFA (20)	DMSO	100	**4a**, >95
11	***o*-NQ1** (10)/TFA (20)	DMSO	80	**3a**, 30
12[d]	***o*-NQ1** (10)/TFA (20)	DMSO	100	**4a**, >95
13[d]	***o*-NQ1** (5)/TFA (20)	DMSO	100	**4a**, >95 (93)
14	***o*-NQ1** (5)/TFA (10)	DMSO	100	**3a**/**4a**, 45/50
15	—	DMSO	100	**3a**, 10
16	***o*-NQ1** (10)	DMSO	100	**3a**/**4a**, 34/51
17	TFA (20)	DMSO	100	NR
18	***o*-NQ1** (5)/AcOH (20)	DMSO	100	**3a**, 25
19[e]	***o*-NQ1** (5)/TFA (20)	DMSO	100	**3a**, 33
20[f]	***o*-NQ1** (5)/TFA (20)	DMSO	100	NR

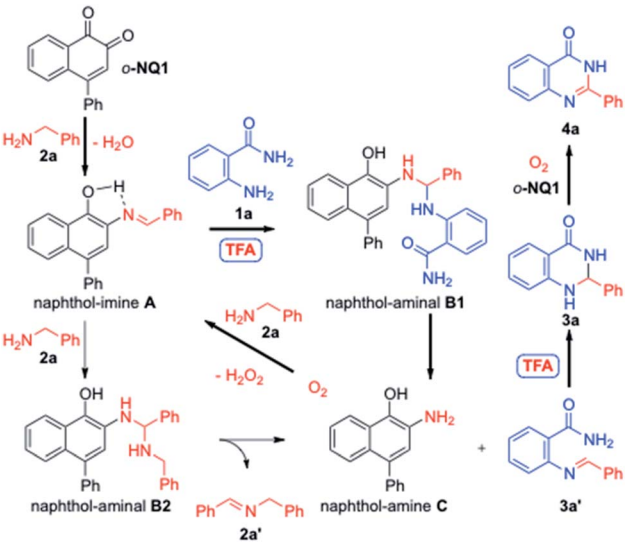
[a] Reaction using **1a** (0.20 mmol), **2a** (0.30 mmol), and ***o*-NQ** in solvent (0.2 M) under O_2 balloon for 24 h. [b] Yields based on internal standard and isolated yield in parentheses. [c] Reaction for 6 h. [d] Use of **2a** (0.24 mmol, 1.2 equiv.). [e] Reaction under air. [f] Reaction under argon. NR = no reaction.



Scheme 2 Substrate scope of aerobic oxidation to quinazolinones ([a]reaction for 36 h, [b]reaction for 12 h).

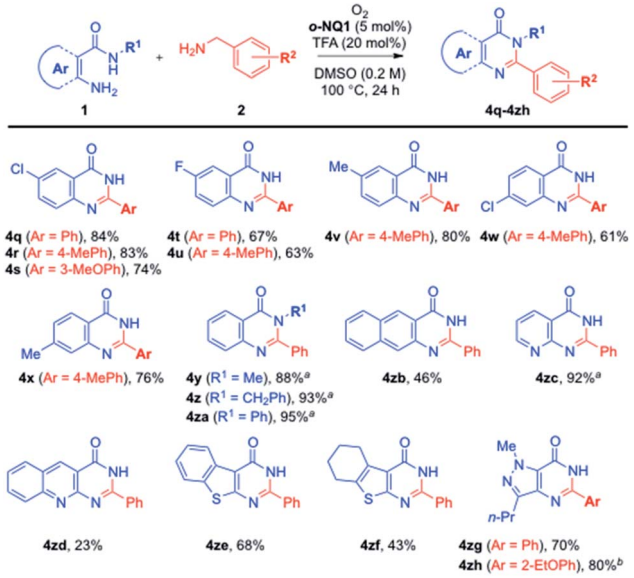
Further extension of the current aerobic cross-coupling reactions of amines is illustrated in Scheme 3. Thus, an array of substituted anthranilamides was readily employed to give the fused pyrimidin-4(3*H*)-one derivatives (**4q–4x**) in 61–84% yields. In particular, the *N*-substituted anthranilamides also participated in the current aerobic cross-coupling reaction in excellent yields (**4y–4za**). While the use of 3-amino-2-naphthamide led to the corresponding quinazolinone **4zb** in 46% yield, the synthetic advantage of the current method was well demonstrated in the preparation of heteroaryl fused pyrimidin-4(3*H*)-one derivatives (**4zc–4zh**), where a variety of heterocyclic amines were successfully utilized in a tandem sequence of aerobic oxidation processes.

The mechanistic rationale of the aerobic cross-coupling reactions of amines is depicted in Scheme 4. Thus, the benzylamine **2a** is condensed with the ***o*-NQ1** catalyst to give the naphthol-imine species **A**.[37a] While the nucleophilic attack of **2a** to the naphthol-imine **A** is favored due to the low nucleophilicity of the anthranilamide **1a**, the presence of TFA promotes the cross-coupling between naphthol-imine **A** and anthranilamide **1a** to give the naphthol-aminal **B1**. This process releases the hetero-coupled imine **3a′** and naphthol-amine **C**. The use of TFA promotes the intramolecular Mannich cyclization of imine **3a′**, leading to the aminal **3a** that in turn converts to the desired fused pyrimidin-4(3*H*)-one **4a** with the help of ***o*-NQ1** catalyst and molecular oxygen. Alternatively, the naphthol-imine **A** can produce the homocoupled imine **2a′** and the naphthol-amine **C** *via* the naphthol-aminal **B2** through the nucleophilic attack of benzylamine **2a**. The conversion of the naphthol-amine **C** to ***o*-NQ1** catalyst is effected upon exposure to oxygen atmosphere.[38] The homocoupled imine **2a′** undergoes hydrolysis at >80 °C to the benzaldehyde and benzylamine **2a** that in turn re-enters the catalytic cycle.[37b] Our experimental observation of the homocoupled imine **2a′** by the ^{1}H NMR and TLC analysis during the reaction supports the involvement of **2a′**. However, the major pathway to the fused pyrimidin-4(3*H*)-one **4a** appears to involve the naphthol-aminal **B1** since the use of benzaldehyde instead of benzylamine **2a** under the optimized conditions only led to the 80% conversion. The ***o*-NQ1** catalyst without added TFA provided a mixture of aminal **3a** and quinazolinone **4a** in 34% and 51% yields, respectively (Table 1, entry 16). Thus, it is likely that the role of TFA is the catalyst for the cross-coupling of two amines to give the naphthol-aminal **B1** and the cyclization of the imine **3a′** to aminal **3a**. Our control experiments also revealed that TFA alone slowly oxidize **3a** to **4a**, but rapidly oxidized by the action of ***o*-NQ1** within 10 h.[39]

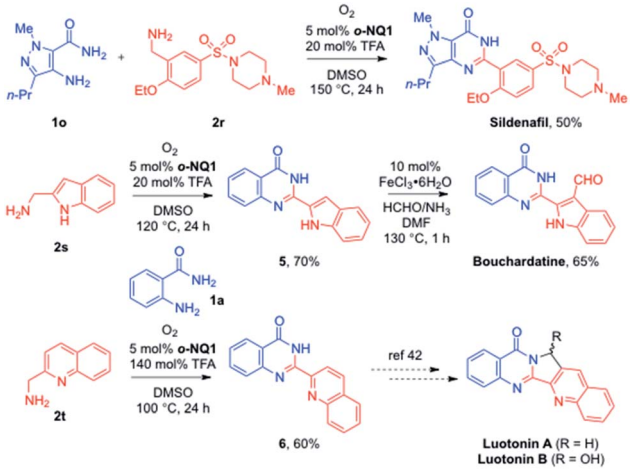


Scheme 4 Mechanistic rationale for aerobic cross coupling reaction of amines.

The synthetic utility of the aerobic cross-coupling strategy is demonstrated in the synthesis of quinazolinone alkaloids and sildenafil (Scheme 5). The direct cross coupling of a commercially available pyrazole amine **1o** and benzylamine **2r** afforded



Scheme 3 Further substrate scope for fused pyrimidin-4(3*H*)-one derivatives ([a]reaction at 120 °C, [b]reaction at 140 °C).



Scheme 5 Synthetic utilization to quinazolinone alkaloids and sildenafil.

a highly convergent synthetic approach to sildenafil.[40] Likewise, the employment of anthranilamide **1a** and 2-(aminomethyl) indole **2s** provided the desired quinazolinone **5** in 70% yield, and the subsequent formylation under the Zeng's conditions[41] paved a way to the total synthesis of bouchardatine. In addition, while the basicity of quinolin-2-ylmethanamine **2t** required an excess of TFA, the corresponding quinazolinone **6** was obtained in 60% yield under the optimized conditions. The conversion of **6** to the luotonin natural products has been reported by the Argade group and others.[42]

Conclusions

In summary, we have developed the aerobic cross-coupling reactions of amines to fused pyrimidin-4(3*H*)-one derivatives. This metal-free tandem aerobic oxidation sequence utilizes 5 mol% of ***o*-NQ** catalyst and 20 mol% of TFA as co-catalyst. The developed aerobic oxidation protocol allows a highly convergent approach to quinazolinone alkaloids and sildenafil. Given that the fused pyrimidin-4(3*H*)-one derivatives possess a diverse array of biological activities, the ***o*-NQ**-catalyzed tandem aerobic cross-coupling reactions should find their synthetic utility in the medicinal chemistry projects. We are current extending the ***o*-NQ**-catalyzed aerobic oxidation protocols to other heterocycles of medicinal interest, and our results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by the Chung-Ang University Research Scholarship Grants in 2019 and the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSICT) (NRF-2015R1A5A1008958 and NRF-2019R1A2C2089953).

Notes and references

1 For reviews, see: (*a*) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787; (*b*) U. A. Kshirsagar, *Org. Biomol. Chem.*, 2015, **13**, 9336.
2 (*a*) M. Boolell, M. J. Allen, S. A. Ballard, S. Gepi-Attee, G. J. Muirhead, A. M. Naylor, I. H. Osterloh and C. Gingell, *Int. J. Impotence Res.*, 1996, **8**, 47; (*b*) P. J. Dunn, *Org. Process Res. Dev.*, 2005, **9**, 88; (*c*) M. A. Gouda and W. S. Hamama, *Synth. Commun.*, 2017, **47**, 1269.
3 (*a*) R. J. Abdel-Jalil, W. Voelter and M. Saeed, *Tetrahedron Lett.*, 2004, **45**, 3475; (*b*) D. Zhan, T. Li, H. Wei, W. Weng, K. Ghandi and Q. Zeng, *RSC Adv.*, 2013, **3**, 9325; (*c*) S. Guo, Y. Li, L. Tao, W. Zhang and X. Fan, *RSC Adv.*, 2014, **4**, 59289; (*d*) K. Upadhyaya, R. K. Thakur, S. K. Shukla and R. P. Tripathi, *J. Org. Chem.*, 2016, **81**, 5046.
4 G.-W. Wang, C.-B. Miao and H. Kang, *Bull. Chem. Soc. Jpn.*, 2006, **9**, 1426.
5 J. Chen, D. Wu, F. He, M. Liu, H. Wu, J. Ding and W. Su, *Tetrahedron Lett.*, 2008, **49**, 3814.
6 F. Li, L. Lu and J. Ma, *Org. Chem. Front.*, 2015, **2**, 1589.
7 M. Bakavoli, O. Sabzevari and M. Rahimizadeh, *Chin. Chem. Lett.*, 2007, **18**, 1466.
8 (*a*) X.-S. Wang, K. Yang, M.-M. Zhang and C.-S. Yao, *Synth. Commun.*, 2010, **40**, 2633; (*b*) Y. Nagasawa, Y. Matsusaki, T. Nobuta, N. Tada, T. Miura and A. Itoh, *RSC Adv.*, 2015, **5**, 63952; (*c*) R. Cheng, T. Guo, D. Zhang-Negrerie, Y. Du and K. Zhao, *Synthesis*, 2013, **45**, 2998.
9 X.-F. Wu, S. Oschatz, A. Block, A. Spannenbergb and P. Langer, *Org. Biomol. Chem.*, 2014, **12**, 1865.
10 (*a*) Y.-F. Wang, F.-L. Zhang and S. Chiba, *Org. Lett.*, 2013, **15**, 2842; (*b*) N. Y. Kim and C.-H. Cheon, *Tetrahedron Lett.*, 2014, **55**, 2340; (*c*) B.-Q. Hu, J. Cui, L.-X. Wang, Y.-L. Tang and L. Yang, *RSC Adv.*, 2016, **6**, 43950; (*d*) Z.-z. Wang and Y. Tang, *Tetrahedron*, 2016, **72**, 1330.
11 (*a*) D. Zhao, Y.-R. Zhou, Q. Shen and J.-X. Li, *RSC Adv.*, 2014, **4**, 6486; (*b*) Y. Hu, L. Chen and B. Li, *RSC Adv.*, 2016, **6**, 65196.
12 (*a*) J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730; (*b*) F. Li, L. Lu and P. Liu, *Org. Lett.*, 2016, **18**, 2580.
13 Z. Zhang, M. Wang, C. Zhang, Z. Zhang, J. Lu and F. Wang, *Chem. Commun.*, 2015, **51**, 9205.
14 S. Parua, S. Das, R. Sikari, S. Sinha and N. D. Paul, *J. Org. Chem.*, 2017, **82**, 7165.
15 H. Hikawa, Y. Ino, H. Suzuki and Y. Yokoyama, *J. Org. Chem.*, 2012, **77**, 7046.
16 A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Biomol. Chem.*, 2012, **10**, 240.
17 Z. Bie, G. Li, L. Wang, Y. Lv, J. Niu and S. Gao, *Tetrahedron Lett.*, 2016, **57**, 4935.
18 M. Sharif, J. Opalach, P. Langer, M. Beller and X.-F. Wu, *RSC Adv.*, 2014, **4**, 8.
19 W. Ge, X. Zhu and Y. Wei, *RSC Adv.*, 2013, **3**, 10817.
20 (*a*) X. Yang, G. Cheong, J. Shen, C. Kuai and X. Cui, *Org. Chem. Front.*, 2015, **2**, 366; (*b*) M. Abdullaha, S. Mohammed, M. Ali, A. Kumar, R. A. Vishwakarma and S. B. Bharate, *J. Org. Chem.*, 2019, **84**, 5129.
21 X. Chen, T. Chen, F. Ji, Y. Zhou and S.-F. Yin, *Catal. Sci. Technol.*, 2015, **5**, 2197.
22 (*a*) Y. Feng, Y. Li, G. Cheng, L. Wang and X. Cui, *J. Org. Chem.*, 2015, **80**, 7099; (*b*) F.-C. Jia, Z.-W. Zhou, C. Xu, Y.-D. Wu and A.-X. Wu, *Org. Lett.*, 2016, **18**, 2942.
23 J. K. Laha, K. V. Patel, K. S. S. Tummalapalli and N. Dayal, *Chem. Commun.*, 2016, **52**, 10245.
24 Z. Li, J. Dong, X. Chen, Q. Li, Y. Zhou and S.-F. Yin, *J. Org. Chem.*, 2015, **80**, 9392.
25 W. Liu, W. Gao, J. Ding, X. Huang, M. Liu and H. Wu, *Org. Chem. Front.*, 2018, **5**, 2734.
26 S. Lee, J. Sim, H. Jo, M. Viji, L. Srinu, K. Lee, H. Lee, V. Manjunatha and J. Jung, *Org. Biomol. Chem.*, 2019, **17**, 8067.
27 (*a*) D. Zhao, T. Wang and J.-X. Li, *Chem. Commun.*, 2014, **50**, 6471; (*b*) S. Mohammed, R. A. Vishwakarma and S. B. Bharate, *J. Org. Chem.*, 2015, **80**, 6915; (*c*) Y. Jang, S. B. Lee, J. Hong, S. Chun, J. Lee and S. Hong, *Org. Biomol. Chem.*, 2020, **18**, 5435.

28 (*a*) C. Huang, Y. Fu, H. Fu, Y. Jiang and Y. Zhao, *Chem. Commun.*, 2008, 6333; (*b*) X. Liu, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 348; (*c*) D. Yang, H. Fu, L. Hu, Y. Jiang and Y. Zhao, *J. Comb. Chem.*, 2009, **11**, 653; (*d*) X. Zhang, D. Ye, H. Sun, D. Guo, J. Wang, H. Huang, X. Zhang, H. Jiang and H. Liu, *Green Chem.*, 2009, **11**, 1881; (*e*) B. Ma, Y. Wang, J. Peng and Q. Zhu, *J. Org. Chem.*, 2011, **76**, 6362.

29 (*a*) W. Xu, Y. Jin, H. Liu, Y. Jiang and H. Fu, *Org. Lett.*, 2011, **13**, 1274; (*b*) W. Xu and H. Fu, *J. Org. Chem.*, 2011, **76**, 3846; (*c*) H. Wei, T. Li, Y. Zhou, L. Zhou and Q. Zeng, *Synthesis*, 2013, **45**, 3349; (*d*) H. Li, L. He, H. Neumann, M. Beller and X.-F. Wu, *Green Chem.*, 2014, **16**, 1336; (*e*) X.-F. Wu, S. Oschatz, M. Sharif, M. Beller and P. Langer, *Tetrahedron*, 2014, **70**, 23; (*f*) M. Kumar, Richa, S. Sharma, V. Bhatt and N. Kumar, *Adv. Synth. Catal.*, 2015, **357**, 2862.

30 H. Chai, J. Li, L. Yang, H. Lu, Z. Qi and D. Shi, *RSC Adv.*, 2014, **4**, 44811.

31 X. Jiang, T. Tang, J.-M. Wang, Z. Chen, Y.-M. Zhu and S.-J. Ji, *J. Org. Chem.*, 2014, **79**, 5082.

32 X. Yu, L. Gao, L. Jia, Y. Yamamoto and M. Bao, *J. Org. Chem.*, 2018, **83**, 10352.

33 (*a*) T. B. Nguyen, L. Ermolenko and A. Al-Mourabit, *Green Chem.*, 2013, **15**, 2713. For the use of tertiary amines as aldehyde precursors, see: (*b*) X. Chen, T. Chen, Y. Zhou, D. Han, L.-B. Han and S.-F. Yin, *Org. Biomol. Chem.*, 2014, **12**, 3802.

34 T. B. Nguyen, J. L. Bescont, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2013, **15**, 6218.

35 For the use of 2 equiv. of $K_2S_2O_8$, see: A. D. Hudwekar, G. L. Reddy, P. K. Verma, S. Gupta, R. A. Vishwakarma and S. D. Sawant, *ChemistrySelect*, 2017, **2**, 4963.

36 For recent reviews on the biomimetic aerobic oxidation of amines by *ortho*-quinone catalyst-based oxidation protocols, see: (*a*) B. Chen, L. Wang and S. Gao, *ACS Catal.*, 2015, **5**, 5851; (*b*) A. E. Wendlandt and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2015, **54**, 14638; (*c*) M. Largeron, *Org. Biomol. Chem.*, 2017, **15**, 4722; (*d*) R. Zhang and S. Luo, *Chin. Chem. Lett.*, 2018, **29**, 1193; (*e*) M. Largeron, *Pure Appl. Chem.*, 2020, **92**, 233. For the aerobic oxidation of benzylamines to pyrimidin-4(3*H*)-ones see: (*f*) S. A. Pawar, A. N. Chand and A. V. Kumar, *ACS Sustainable Chem. Eng.*, 2019, **7**, 8274 (using non-catalytic *ortho*-quinone promoters); (*g*) R. Sharma, M. Abdullaha and S. B. Bhatate, *Asian J. Org. Chem.*, 2017, **6**, 1370 (using ionic liquid).

37 ***o*-NQ** catalysts are stable up to 150 °C, see: (*a*) G. Golime, H. Y. Kim and K. Oh, *Org. Lett.*, 2018, **20**, 942; (*b*) Y. Goriya, H. Y. Kim and K. Oh, *Org. Lett.*, 2016, **18**, 5174; (*c*) G. Golime, G. Bogonda, H. Y. Kim and K. Oh, *ACS Catal.*, 2018, **8**, 4986; (*d*) K. Kim, H. Y. Kim and K. Oh, *Org. Lett.*, 2019, **21**, 6731; (*e*) T. Si, H. Y. Kim and K. Oh, *ACS Catal.*, 2019, **9**, 9216.

38 H. Y. Kim, S. Takizawa and K. Oh, *Org. Biomol. Chem.*, 2016, **14**, 7191.

39 The conversion of aminal **3a** to quinazolinone **4a** was investigated by using 20 mol% TFA/O_2 (86% conv. at 24 h), 5 mol% ***o*-NQ1**/O_2 (92% conv. at 10 h), and O_2 (81% conv. at 24 h) at 100 °C in DMSO (0.2 M).

40 The commercial synthesis of sildenafil involves the amide coupling strategy, rather than the condensation of aldehyde and aminopyrazole route, possibly due to the two-step procedure (the formation of dihydrosildenafil by condensation and the following oxidation step to sildenafil), see: ref. 2*b*.

41 Q.-D. Wang, B. Zhou, J.-M. Yang, D. Fang, J. Ren and B.-B. Zeng, *Synlett*, 2017, **28**, 2670.

42 (*a*) S. B. Mhaske and N. P. Argade, *J. Org. Chem.*, 2004, **69**, 4563; (*b*) K. R. Rao, R. Mekala, A. Raghunadh, S. B. Meruva, S. P. Kumar, D. Kalita, E. Laxminarayana, B. Prasad and M. Pal, *RSC Adv.*, 2015, **5**, 61575; (*c*) R. Mekala, R. Kamaraju, S. Regati, N. Gudimalla, C. K. Bannoath and J. Sarva, *Tetrahedron Lett.*, 2016, **57**, 1418.