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# Palladium-catalyzed one-pot synthesis of 2-substituted quinazolin-4(3*H*)-ones from *o*-nitrobenzamide and alcohols†

 Ke Wang,<sup>1</sup> Hao Chen,<sup>1</sup> Xinyan Dai,<sup>1</sup> Xupeng Huang and Zhiqiang Feng\*<sup>1</sup>

Palladium-catalyzed 2-substituted quinazolin-4(3*H*)-one formation from readily available *o*-nitrobenzamides and alcohols using hydrogen transfer is described. Various quinazolin-4(3*H*)-ones were obtained in good to high yields. The cascade reaction including alcohol oxidation, nitro reduction, condensation, and dehydrogenation occurs without any added reducing or oxidizing agent.

The quinazolinones and their derivatives are a family of privileged heterocyclic structures commonly found in a wide variety of natural products, biologically active molecules, and functional organic materials.<sup>1</sup> Due to quinazolinone's important value, various conventional methods have been developed for the synthesis of these molecules in both academic and industrial settings.<sup>2</sup> The most common approaches utilize 2-aminobenzoic acid and its derivatives as the starting materials along with aldehydes,<sup>3</sup> acyl chlorides or their analogues<sup>4</sup> to obtain the corresponding structural motifs. These methods usually have the disadvantages of multistep reactions,<sup>5</sup> low yields,<sup>6</sup> long reaction times,<sup>7</sup> and the use of stoichiometric amounts of strong or toxic oxidants.<sup>8</sup>

In the past decade, direct coupling methods of C–N bonds<sup>9</sup> through which *o*-aminobenzamides react with benzylic alcohols by metal-catalyzed cascade reactions have been recognized as an attractive methods for the synthesis of 2-substituted quinazolinone derivatives. For example, Yokoyama and coworkers reported the synthesis of quinazolin-4(3*H*)-ones *via* a palladium-catalyzed domino reaction of *o*-aminobenzamides with benzylic alcohols.<sup>10</sup> Wang *et al.* also reported the one-pot oxidative cyclization of *o*-aminobenzamide with alcohols to quinazolin-4(3*H*)-ones catalyzed by MnO<sub>2</sub> under hydrogen transfer conditions.<sup>11</sup> The groups of Watson,<sup>12</sup> Paul,<sup>13</sup> and some others<sup>14</sup> also independently reported the Ru-, Ni-, and Cu-catalyzed synthesis of quinazolin-4(3*H*)-ones *via* the acceptorless dehydrogenative coupling of *o*-aminobenzamides with alcohols. Considering that aniline is prepared from the corresponding nitroarenes,<sup>15</sup> and that nitroarenes are cheaper and commercially available, the direct use of nitroarenes as amino

sources for quinazolinone synthesis features their atom-economic advantage over anilines. However, methodologies for the synthesis quinazolinone derivatives *via* the acceptorless

**Table 1** Optimization of the reaction conditions<sup>a</sup>

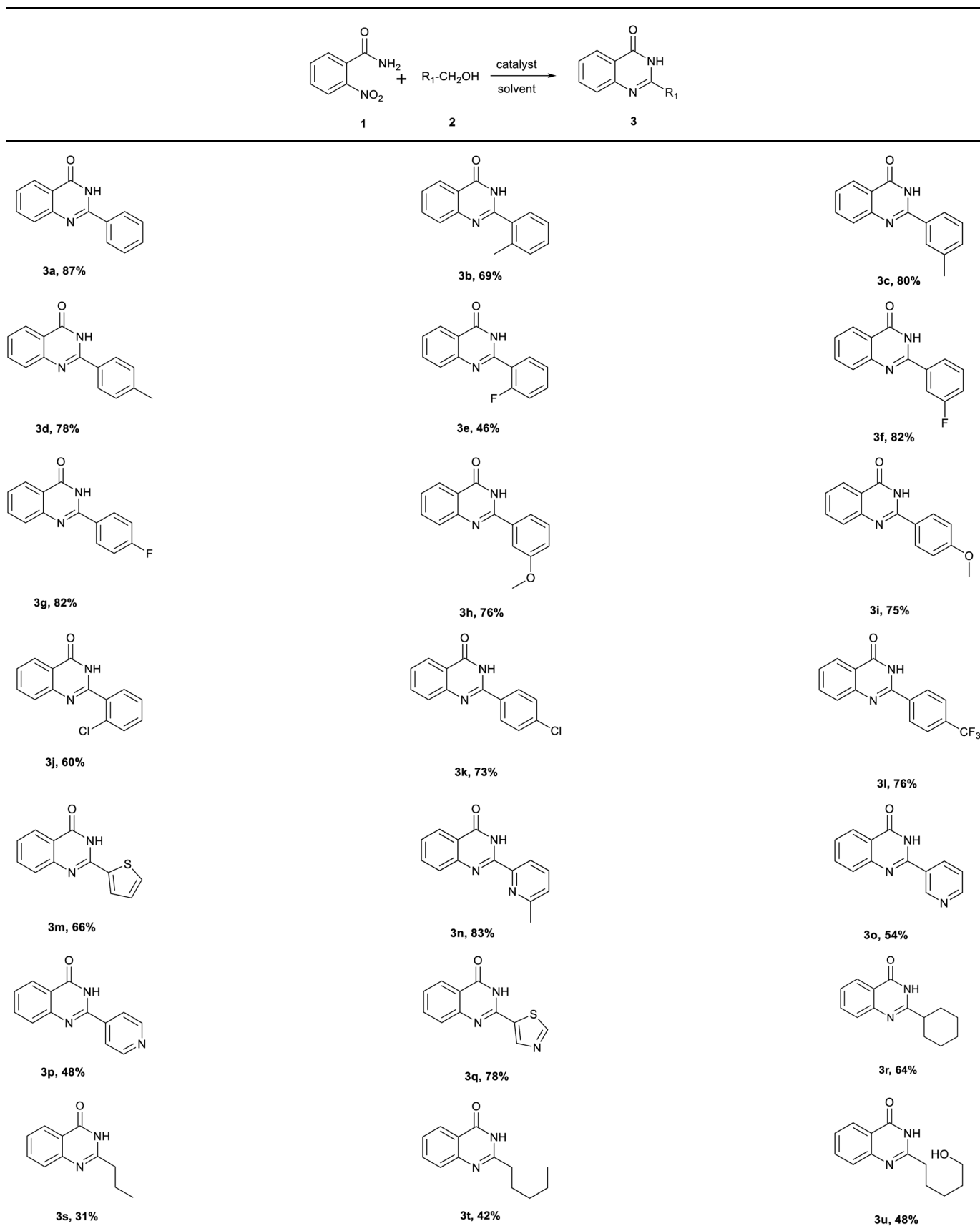
Entry	Catalyst	Solvent	<i>t</i> (h)	Yield (%)
1	CuCl	Toluene	8	0
2	CuCl <sub>2</sub>	Toluene	8	0
3	dppf	Toluene	8	28
4	FeCl <sub>3</sub>	Toluene	8	22
5	Cu(OAc) <sub>2</sub>	Toluene	8	0
6	CuBr <sub>2</sub>	Toluene	8	Trace
7	CuBr	Toluene	8	Trace
8	PdCl <sub>2</sub>	Toluene	8	14
9	Pd(OAc) <sub>2</sub>	Toluene	8	42
10	Pd(dppf)Cl <sub>2</sub>	Toluene	8	59
11	Pd(dppf)Cl <sub>2</sub>	DMF	8	77
12	Pd(dppf)Cl <sub>2</sub>	DMSO	8	56
13	Pd(dppf)Cl <sub>2</sub>	PhCl	8	80
14	Pd(dppf)Cl <sub>2</sub> <sup>b</sup>	PhCl	8	87
15	Pd(dppf)Cl <sub>2</sub> <sup>c</sup>	PhCl	8	80
16	Pd(dppf)Cl <sub>2</sub> <sup>d</sup>	PhCl	5	79
17	Pd(dppf)Cl <sub>2</sub> <sup>e</sup>	PhCl	8	78
18	Pd(dppf)Cl <sub>2</sub> <sup>f</sup>	PhCl	8	87
19	Pd(dppf)Cl <sub>2</sub> <sup>g</sup>	PhCl	8	80

<sup>a</sup> Reaction conditions: 1 mmol of **1a**, 2.5 equiv. of **2a**, catalyst and 1 mL of solvent in a 10 mL sealed tube at 150 °C under Ar for 8 h. Yield of the isolated product based on **1a**. <sup>b</sup> At 140 °C under Ar for 8 h. <sup>c</sup> At 130 °C under Ar for 8 h. <sup>d</sup> At 140 °C under Ar for 5 h. <sup>e</sup> Pd(dppf)Cl<sub>2</sub>, 5%. <sup>f</sup> Pd(dppf)Cl<sub>2</sub>, 15%. <sup>g</sup> At 140 °C under air for 8 h.

Beijing Key Laboratory of Active Substance Discovery and Drugability Evaluation, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1 Xiannongtan Street, Beijing 100050, P R China. E-mail: fengzhiq@imm.ac.cn

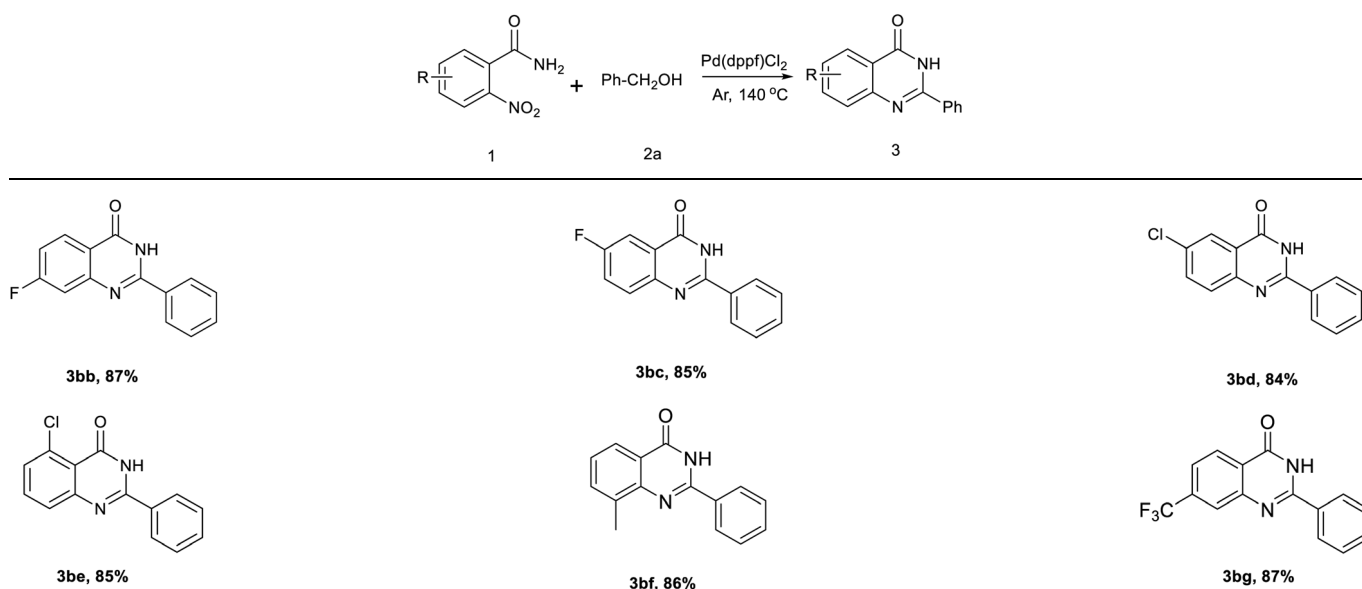
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra01755a



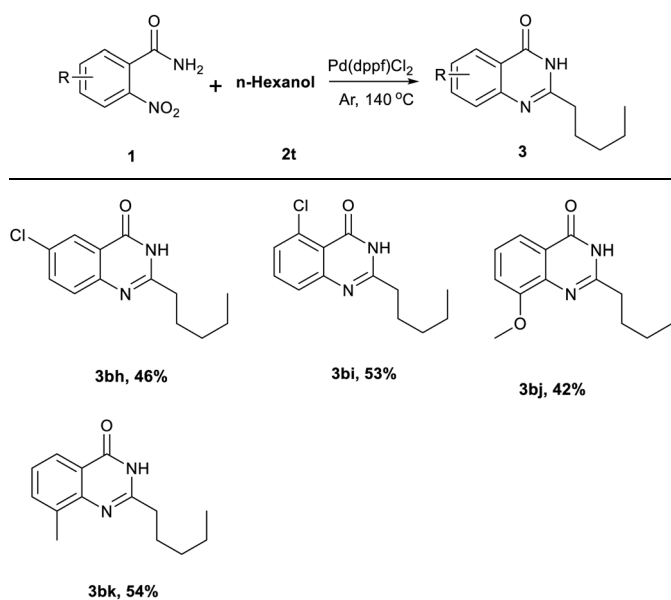
Table 2 Reaction of **1a** with various alcohols<sup>a,b</sup>

<sup>a</sup> Reaction conditions: 1 mmol of **1a**, 2.5 equiv. of **2a**, catalyst and 1 mL of solvent in a 10 mL sealed tube at 140 °C under Ar for 8 h. <sup>b</sup> Isolated yield.



Table 3 Reaction of 2a with substituted amides<sup>a,b</sup>

<sup>a</sup> Reaction conditions: 1 mmol of **1**, 2.5 equiv. of **2a**, catalyst and 1 mL of solvent in a 10 mL sealed tube at 140 °C under Ar for 8 h. <sup>b</sup> Isolated yield.

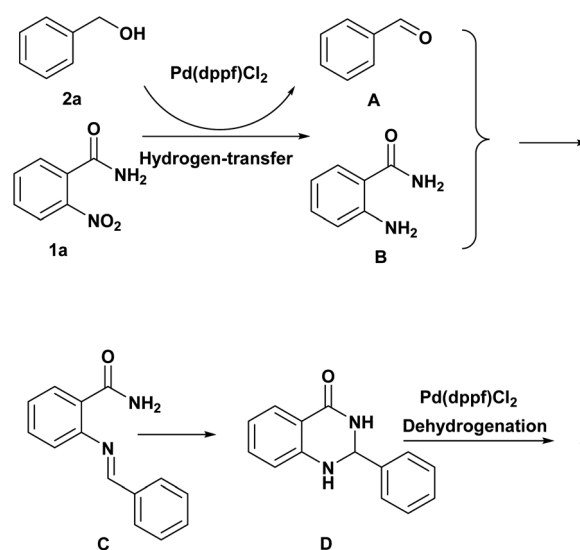
Table 4 Reaction of 2t with substituted amides<sup>a,b</sup>

<sup>a</sup> Reaction conditions: 1 mmol of **1**, 2.5 equiv. of **2t**, catalyst and 1 mL of solvent in a 10 mL sealed tube at 140 °C under Ar for 8 h. <sup>b</sup> Isolated yield.

dehydrogenative coupling of nitroarenes with alcohols are relatively scarce.<sup>16</sup>

Herein, we report a new approach for directly synthesizing 2-substituted quinazolin-4(3H)-ones from *o*-nitrobenzamides with alcohols *via* a hydrogen transfer methodology.<sup>17</sup>

Initially, a model reaction of *o*-nitrobenzamide (**1a**) and benzyl alcohol (**2a**) was chosen to optimize the reaction conditions (Table 1). We carried out the reaction of *o*-nitrobenzamide with 2.5 equivalents alcohol in toluene at 150 °C and an argon atmosphere for 8 h. As shown in Table 1, various catalysts were screened for the reaction. No or poor yield was observed in the presence of either a copper or an iron catalyst (Table 1, entries 1–7). With regard to the palladium catalyst (Table 1, entries 8–10), Pd(dppf)Cl<sub>2</sub> showed the best activity, and **3a** was obtained in 59% yield (Table 1, entry 10). Several solvents such as DMF, DMSO, and chlorobenzene were screened, and chlorobenzene



Scheme 1 Postulated reaction pathway.



was found to be the optimal solvent (Table 1, compared entries 11–13), the yield of **3a** increased to 80% (Table 1, entry 13). The impact of reaction temperatures was also investigated. The reaction conducted at 140 °C resulted in a higher yield (87%) than that conducted at 150 °C (Table 1, entry 14). But the reaction performed at 130 °C resulted in a lower **3a** yield of 80% (Table 1, entry 15). When the reaction time was reduced to 5 h, the yield of **3a** was slightly reduced to 79% (Table 1, entry 17), but the yield did not increase with increasing of reaction time to 10 h. When the amount of catalyst was decreased from 0.1 to 0.05 equiv., the yield of **3a** decreased to 78% (Table 1, entry 17). However, 0.15 equiv. of catalyst did not change the yield of the product (Table 1, entry 18). A slightly lower yield was obtained when the reaction was carried out in air (80%) (Table 1, entry 19).

After optimized reaction conditions (Pd(dppf)Cl<sub>2</sub>, chlorobenzene, 140 °C, argon) were established, the reaction scope and generality of various primary alcohols were tested, as shown in Table 2. The position and electronic effect of substituents on the phenyl ring of benzyl alcohols was examined. A series of benzyl alcohols with electron-donating groups (Me and MeO) could be converted to the desired products in good yields. Benzyl alcohols with methyl substituents at ortho-, meta-, or para-positions (Table 2, **3b–d**) produced the corresponding quinazolin-4(3*H*)-ones in 69%, 80% and 78% isolated yields. The lower yield of the *o*-methylbenzyl alcohol may be due to the steric effect of ortho groups on the substrate. Benzyl alcohols having methoxyl substituents at meta- or para-positions also produced the corresponding quinazolin-4(3*H*)-ones in 76% and 75% isolated yields. Halogen substituents on the benzylic alcohols were also well tolerated in the reaction. Fluorine and chlorine substituted at the meta- and para-positions of substrates were applied to the synthesis of the corresponding quinazolin-4(3*H*)-ones in good yields (Table 2, **3f**, **3g** and **3k**). Similarly, lower yields were observed using *o*-fluorobenzyl alcohol and *o*-chlorobenzyl alcohol as coupling partners (46% and 60%) (Table 2, **3e** and **3j**). A strong electron-withdrawing group such as CF<sub>3</sub> was also found to be compatible affording quinazolin-4(3*H*)-ones in good yield (76%) (Table 2, **3l**). Starting from 6-methyl-2-pyridinemethanol, 2-thiophenemethanol and thiazole-5-methanol, the corresponding quinazolin-4(3*H*)-ones were obtained in 83%, 66% and 78% isolated yields. However, lower yields (54% and 48%) (Table 2, **3o** and **3p**) were observed using 3-pyridinemethanol and 4-pyridinemethanol as coupling partners. Aliphatic alcohols were also tested, providing the corresponding products in moderate to good yields. The reaction of cyclohexyl methanol with 2-nitrobenzamide afforded the corresponding quinazolin-4(3*H*)-ones in 64% isolated yield (Table 2, **3r**). 1-Butanol and 1-hexanol afforded the corresponding quinazolin-4(3*H*)-ones (**3s** and **3t**) in moderate yields of 31% and 42%. Notably, 1,6-hexanediol was also smoothly coupled with *o*-nitrobenzamide **1a** and afforded **3u** in 48% yield.

Next, substituent effects on the *o*-nitrobenzamide were also evaluated. Not surprisingly, *o*-nitrobenzamide with either electron-donating or electron-withdrawing groups could be successfully coupled with benzyl alcohol **2a** to provide the corresponding products in high yields (84–87%) (Table 3, **3bb–**

**3bg**). The yield of the product was not affected by the *o*-nitrobenzamide with substituents at the 3 or 6 positions (Table 3, **3be–3bf**). In addition to benzylic alcohols, long-chain aliphatic alcohols such as 1-hexanol also yielded the corresponding quinazolin-4(3*H*)-one in moderate to good yields (42–54%) (Table 4, **3bh–3bk**).

Based on the above experimental results along with the literature,<sup>17</sup> we proposed possible mechanisms of the reaction (Scheme 1). The reaction involved the oxidation of the alcohol to aldehyde (**A**) and the generation of hydrogen in the presence of Pd(dppf)Cl<sub>2</sub>, and the hydrogen will reduce 2-nitrobenzamide to 2-aminobenzamide (**B**) *via* a hydrogen-transfer process. One equivalent of 2-aminobenzamide (**B**) condenses with the aldehyde (**A**) and an intermediate that easily dehydrates to yield the imine (**C**). Then, the nitrogen atom of the amine attacked the imine to generate dehydrogenated quinazolinone (**D**). Finally, dehydrogenation of **D** can achieve the desired product **3a** *via* a hydrogen-transfer process.

## Conclusions

We have developed a strategy for Pd(dppf)Cl<sub>2</sub>-catalyzed quinazolin-4(3*H*)-one formation from *o*-nitrobenzamides and alcohols *via* the hydrogen-transfer. Functional groups such as halogen, methoxy, methyl and hydroxyl groups were all well tolerated under the optimized reaction conditions. A wide variety of desired quinazolin-4(3*H*)-ones were obtained in moderate to high yields starting from inexpensive and easily available nitrobenzamides and alcohols. Further studies on the synthetic applications of this reaction are under investigation in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- (a) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787; (b) I. Khan, A. Ibrar, N. Abbas and A. Saeed, *Eur. J. Med. Chem.*, 2014, **76**, 193–244; (c) T. Gupta, A. Rohilla, A. Pathak, M. J. Akhtar, M. R. Haider and M. S. Yar, *Synth. Commun.*, 2018, **48**, 1099; (d) U. A. Kshirsagar, *Org. Biomol. Chem.*, 2015, **13**, 9336.
- (a) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153; (b) A. Witt and J. Bergman, *Curr. Org. Chem.*, 2003, **7**, 659; (c) Z. Ma, T. Song, Y. Yuan and Y. Yang, *Chem. Sci.*, 2019, **10**, 10283; (d) T. B. Nguyen, J. L. Bescont, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*,



- 2013, **15**, 6218; (e) M. Kumar, Richa, S. Sharma, V. Bhatt and N. Kumar, *Adv. Synth. Catal.*, 2015, **357**, 2862; (f) F. Hu, X. Cui, Z. Ban, G. Lu, N. Luo and G. Huang, *Org. Biomol. Chem.*, 2019, **17**, 2356.
- 3 (a) X. Chen, T. Chen, Y. Zhou, D. Han, L. B. Han and S. F. Yin, *Org. Biomol. Chem.*, 2014, **23**, 3802; (b) I. Yoshio, S. Sadayuki, T. Ryuichi and U. Mitsuru, *Synthesis*, 1981, **1**, 35; (c) J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730; (d) W. Ge, X. Zhu and Y. Wei, *RSC Adv.*, 2013, **3**, 10817; (e) Z. Ma, T. Song, Y. Yuan and Y. Yang, *Chem. Sci.*, 2019, **10**, 10283; (f) J. K. Laha, K. V. Patel, T. Satanarayana and N. Dayal, *Chem. Commun.*, 2016, **52**, 10245.
- 4 (a) T. M. Potewar, R. N. Nadaf, T. Daniel, R. J. Lahoti and K. V. Srinivasan, *Synth. Commun.*, 2005, **35**, 231; (b) J. Li, W. Wang, X. Su, X. Zhang, Y. Zhang, X. Zhang, M. Cai, Y. Cao, J. Jin and Y. Xu, *Heterocycles*, 2018, **96**, 2107.
- 5 (a) B. Q. Hu, L. X. Wang, Y. Luo, J. F. Xiang and Y. L. Yang, *Eur. J. Org. Chem.*, 2015, **2015**, 4504; (b) W. Zhao, P. Liu and F. Li, *ChemCatChem*, 2016, **8**, 1523; (c) L. Long, Y. H. Wang, J. X. Zhuo, Z. C. Tu, R. Wu, M. Yan, Q. Liu and G. Liu, *Eur. J. Med. Chem.*, 2018, **157**, 1361.
- 6 S. M. Patel, H. Chada, S. Biswal, S. Sharma and D. S. Sharada, *Synthesis*, 2019, **51**, 3160.
- 7 Y. Jang, S. B. Lee, J. Hong, S. Chun, J. Lee and S. Hong, *Org. Biomol. Chem.*, 2020, **18**, 5435.
- 8 (a) J. Li, W. Wang, X. Su, X. Zhang, Y. Zhang, X. Zhang, M. Cai, Y. Cao, J. Jin and Y. Xu, *Heterocycles*, 2018, **96**, 2107; (b) D. Zhan, T. Li, X. Zhang, C. Dai, H. Wei, Y. Zhang and Q. Zeng, *Synth. Commun.*, 2013, **43**, 2493.
- 9 (a) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450; (b) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400.
- 10 H. Hikawa, Y. Ino, H. Suzuki and Y. Yokoyama, *J. Org. Chem.*, 2012, **77**, 7046.
- 11 Z. Zhang, M. Wang, C. Zhang, Z. Zhang, J. Lu and F. Wang, *Chem. Commun.*, 2015, **51**, 9205.
- 12 A. A. Watson, A. C. Maxwell and J. M. Williams, *Org. Biomol. Chem.*, 2012, **10**, 240.
- 13 (a) S. Parua, S. Das, R. Sikari, S. Sinha and N. D. Paul, *J. Org. Chem.*, 2017, **82**, 7165; (b) S. Das, S. Sinha, D. Samanta, R. Mondal, G. Chakraborty, P. Brandao and N. D. Paul, *J. Org. Chem.*, 2019, **84**, 10160.
- 14 (a) R. J. Abdel-Jalil, W. Voelter and M. Saeed, *Tetrahedron Lett.*, 2004, **45**, 3475; (b) N. Montazeri, K. Pourshamsian, S. Yosefiyan and S. S. Momeni, *J. Chem. Sci.*, 2012, **124**, 883; (c) A. Davoodnia, S. Allameh, A. R. Fakhari and N. Tavakoli-Hoseini, *Chin. Chem. Lett.*, 2010, **21**, 550.
- 15 (a) H. P. Hemantha and V. V. Sureshbabu, *Org. Biomol. Chem.*, 2011, **9**, 2597; (b) C. Yu, B. Liu and L. Hu, *J. Org. Chem.*, 2001, **66**, 919; (c) Y. Zhou, H. Zhou, S. Liu, D. Pi and G. Shen, *Tetrahedron*, 2017, **73**, 27.
- 16 (a) A. H. Romero, J. Salazar and S. E. Lopez, *Synthesis*, 2013, **45**, 2043; (b) H. Wang, X. Cao, F. Xiao, S. Liu and G. J. Deng, *Org. Lett.*, 2013, **15**, 4900.
- 17 (a) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825; (b) G. Guillena, D. J. Ramon and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (c) Y. Obora, *Top. Curr. Chem.*, 2016, **374**, 11.

