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Sulfur-Mediated Decarboxylative Coupling of 2-Nitrobenzyl Alcohols and Arylacetic Acids

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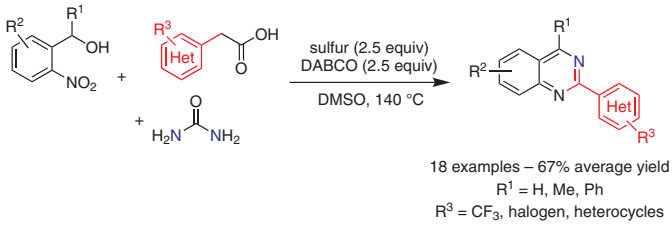
In memory of Assoc. Prof. Dr. Quan Thanh Pham



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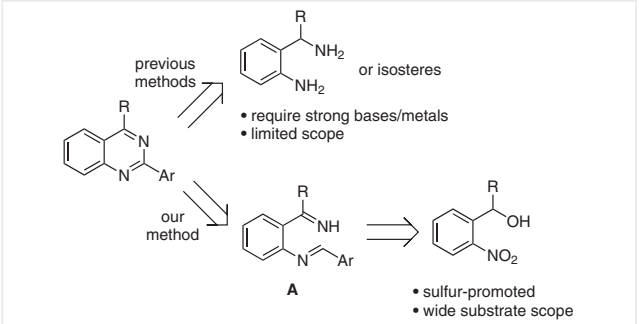
Abstract We report a new method for the synthesis of substituted quinazolines by the condensation of 2-nitrobenzyl alcohols with arylacetic acids. The transformation requires the use of urea as a nitrogen source, elemental sulfur as a promoter, DABCO as a base, and DMSO as a solvent. Functionalities such as chloro, fluoro, trifluoromethyl, thienyl, and indolyl groups were all compatible with the reaction conditions. Because our method uses stable simple substrates to obtain the N,N-heterocycles in the absence of transition metals, it offers a potential pathway for preparing complex structures under mild conditions.

Key words quinazolines, nitrobenzyl alcohols, arylacetic acids, cyclocondensation, decarboxylation

Quinazolines are quintessential N,N-heterocycles that, due to their biological activities, have attracted substantial attention from synthetic chemists.[1] The seminal method developed by Reddy and co-workers for coupling 2-aminobenzyl amines and aldehydes is perhaps the most reliable method for obtaining substituted quinazolines and their isosteres.[2a] Later attempts have been devoted to developing more-general substrate scopes. Prevalent successes have relied on the use of transition metals and/or strong bases.[2b–d] Notably, most of the examples began with prefunctionalized amine precursors such as *ortho*-substituted benzylamines or anilines (Scheme 1). Replacement of amines with more-stable nitro compounds in these transformations is arguably advantageous, because prefunctionalization of the starting materials by reduction is unnecessary. The use of nitroarenes as a nitrogen source is known.[3] Silane-mediated reductive coupling reactions for the synthesis of secondary anilines and indoles have been reported.[3a–c] A few examples that required strong reductants such as zinc have also been described.[3d,e]

It is possible to use elemental sulfur to synthesize anilines from nitroarenes. There are previous reports of sulfur-mediated chemoselective reductions of nitro groups in the presence of other competitive functionalities such as ester, nitrile, or amide groups.[4a–c] Coupling of *ortho*-halo nitroarenes with elemental sulfur and activated sp^3 C–H bonds is feasible.[4d,e] Simple nitroarenes might be competent substrates,[4f,g] but known methods are limited to syntheses of 2-arylbenzothiazoles.[5] Our goal was to expand the scope to include more complex structures, such as substituted quinazolines, by using a specifically designed sulfur-mediated transformation that employs commercially available simple substrates.

We recently reported a synthesis of arylthioamides through coupling of nitroarenes, phenylacetic acids, and elemental sulfur.[4f] The redox process may involve the formation of an imine intermediate before sulfurization. We speculated that if an imine is incorporated with another imine in a 6π-system such as intermediate **A** (Scheme 1), cyclization followed by oxidation should afford a substituted quinazoline. Such an arrangement is possible with 2-nitrobenzyl alcohols. Note that the redox condensation of *or-*



Scheme 1 Retrosynthesis of 2-arylquinazolines

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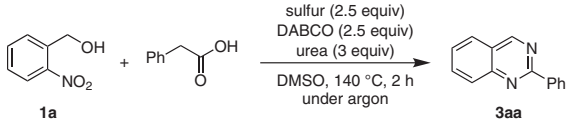
tho-nitrobenzyl alcohols with amines to give 2*H*-indazoles is possible under strongly basic or photochemical conditions.[6] Here, we report our attempts to obtain 2-arylquinazolines by a sulfur-mediated coupling of 2-nitrobenzyl alcohols and arylacetic acids, with urea as a nitrogen source. The reaction tolerates a broad range of functional groups, and could serve as a competent method for the synthesis of N,N-heterocycles. Note that our method is somewhat more atom-economical than those previously developed, in which α-amino acids served as the coupling partners.[7]

The condensation of 2-nitrobenzyl alcohol (**1a**), phenylacetic acid (**2a**), and urea to afford 2-phenylquinazoline (**3aa)** was first investigated. A summary of the results of our extensive screening of the reactions conditions is presented in Table 1. As in previous reports,[5d,e] our conditions required the use of an excess of elemental sulfur to obtain a reasonable yield of **3aa** (Table 1, entry 1). The use of more than 2.5 equivalents of sulfur did not dramatically change the yield (entry 2). A 38% yield of the quinazoline **3aa** was obtained when one equivalent of elemental sulfur was used (entry 3). Omission of elemental sulfur gave no product (entry 4). As a nitrogen source, urea was superior to ammonium salts such as NH_4OAc or NH_4HCO_3 (entries 5 and 6).[8] Common solvents such as DMF and 1,4-dioxane gave the product in lower yields than that obtained in DMSO (entries 7 and 8). This observation was consistent with that reported by Nguyen and co-workers.[9] If *N*-methylpiperidine was used as the base, a 40% yield of **3aa** was obtained (entry 9). The use of a catalytic mixture of iron and a group VI element such as sulfur or selenium[10] gave **3aa** in moderate yields (entries 10 and 11). Reactions at temperatures below 140 °C gave significantly lower yields of **3aa** (entries 12 and 13). When the reaction was performed under an oxygen atmosphere, the quinazoline **3aa** was obtained in 73% yield (entry 12). Notably, the reaction could be performed under air without a significant loss of yield (entry 13).

We next paid attention to the condensation of various benzylic synthons (Table 2). When esters of phenylacetic acids were used, the reaction proceeded much more slowly than that of phenylacetic acid (Table 2, entries 1 and 2). Because a relatively high yield of **3aa** was obtained by the reaction of phenylglyoxylic acid, this compound might be a key intermediate for the transformation (entry 3). Benzaldehyde coupled with 2-nitrobenzyl alcohol to afford **3aa** in 64% yield (entry 4). Other compounds with unsubstituted α C–H bonds gave **3aa** in low yields, presumably due to oxidation problem (entries 5–7). Notably, the activated sp^3 C–H bonds in 2-picolines or their isosteres were inert under our conditions.[5e,f]

Table 1 Reaction Conditions and Control Experiments[a]

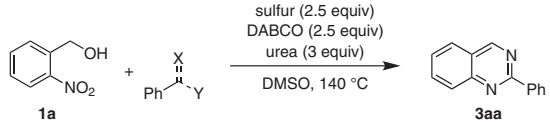


1a 3aa

Entry	Variation from standard conditions	Yield of **3aa** (%)
1	none	86
2	three equivalents of sulfur	83
3	one equivalent of sulfur	38
4	no sulfur	trace
5	NH_4OAc instead of urea	18
6	NH_4HCO_3 instead of urea	12
7	DMF instead of DMSO	28
8	1,4-dioxane instead of DMSO	5
9	*N*-methylpiperidine instead of DABCO	40
10	Fe (20 mol%) + S (80 mol%) instead of S (2.5 equiv)	50
11	Fe (20 mol%) + Se (20 mol%) instead of S (2.5 equiv)	13
12	120 °C instead of 140 °C	60
13	100 °C instead of 140 °C	18
14	oxygen instead of argon	73
15	air instead of argon	85

[a] Standard reaction conditions: 2-nitrobenzyl alcohol (**1a**, 0.1 mmol), phenylacetic acid (**2a**, 0.25 mmol), sulfur (0.25 mmol, 32 g/mol), DABCO (0.25 mmol), urea (0.3 mmol), DMSO (0.5 mL), 140 °C, 2 h, under argon. Yields by GC with diphenyl ether as internal standard.

Table 2 Study of Benzyl Coupling Partner[a]



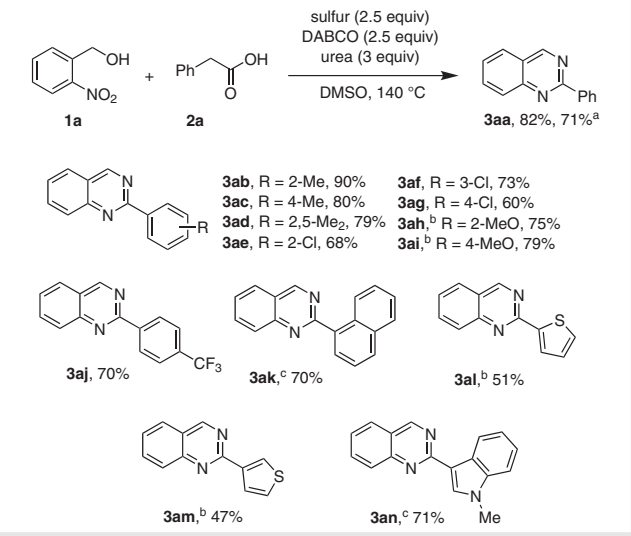
1a 3aa

Entry	Benzylic coupling partner	Yield of **3aa** (%)
1[b]	methyl phenylacetate	51
2[b]	ethyl phenylacetate	36
3	phenylglyoxylic acid	73
4	benzaldehyde	64
5	benzyl alcohol	25
6	benzylamine	32
7	mandelic acid	35

[a] **1a** (0.1 mmol), benzylic coupling partner (0.25 mmol), sulfur (0.25 mmol, 32 g/mol), DABCO (0.25 mmol), urea (0.3 mmol), DMSO (0.3 mL), 140 °C, 2 h. Isolated yields are given. See Supporting Information (SI) for details.
[b] 8 h.

The reaction scope with respect to the phenylacetic acid was then studied (Scheme 2). In general, common functionalities were tolerated under the reaction conditions. Good yields of the quinoxalines were obtained with either electron-rich (**3ac** and **3ai**) or electron-deficient arylacetic acids (**3aj**). Coupling of 2-nitrobenzyl alcohol with halogenat-

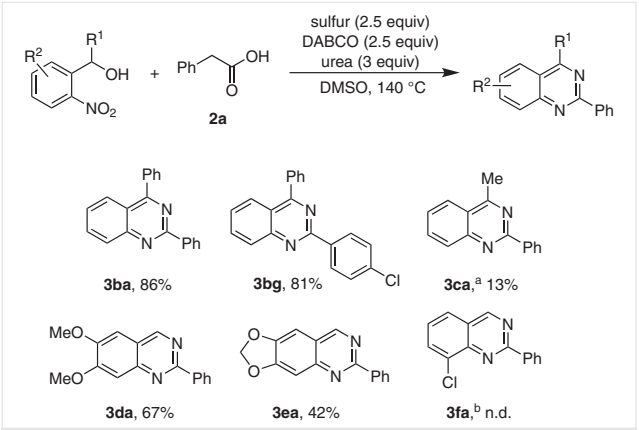
ed phenylacetic acids, which are often incompatible with elemental sulfur,[4f] proceeded successfully (**3ae–ag**). Sterically hindered 1-naphthylacetic acid reacted with 2-nitrobenzyl alcohol to afford the quinazoline **3ak** in 70% yield. Thiophene-derived quinazolines **3al** and **3am** and the indole-derived quinazoline **3an** were obtained without significantly changing the reaction conditions, demonstrating the compatibility of heterocycles with this reaction. Notably, the transformation was scalable, up to 4 mmol without a significant reduction in yield. Besides these successes, our method also showed a few limitation. No product was detected if the substrate contained a nitro, hydroxy, or unprotected indole functionality. Derivatives of cinnamic acids and other aliphatic carboxylic acids were also unsuitable as substrates.



Scheme 2 Reaction scope with respect to phenylacetic acids. *Reagents and conditions*: **1a** (0.1 mmol), phenylacetic acid (0.25 mmol), sulfur (0.25 mmol, 32 g/mol), DABCO (0.25 mmol), urea (0.3 mmol), DMSO (0.3 mL), 140 °C, 2 h. Isolated yields are reported: see SI for details. [a] 4 mmol scale. [b] 8 h. [c] 12 h.

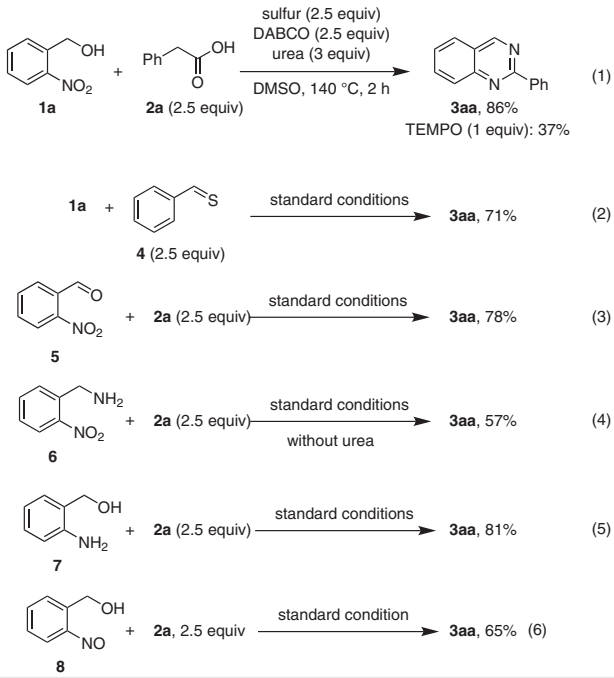
The scope of the 2-nitrobenzyl alcohol was next studied (Scheme 3). Coupling of aryl(2-nitrophenyl)methanols was successful, affording good yields of the highly condensed quinazolines **3ba** and **3bg**. 1-(2-Nitrophenyl)ethanol was much less active, yielding a small amount of the quinazoline **3ca**. Reactions of substituted 2-nitrobenzyl alcohols were also attempted. Dimethoxy and methylenedioxy derivatives showed no problems, giving moderate to good yields of the quinazolines **3da** and **3ea**, respectively.[11] Coupling of hindered 3-chloro-2-nitrobenzyl alcohol gave a complex mixture as a result of the steric effect. Attempts to expand the reaction scope with respect to the 2-nitrobenzyl alcohol are ongoing.

To understand the mechanism, we carried out some test experiments (Scheme 4). It is likely that the transformation

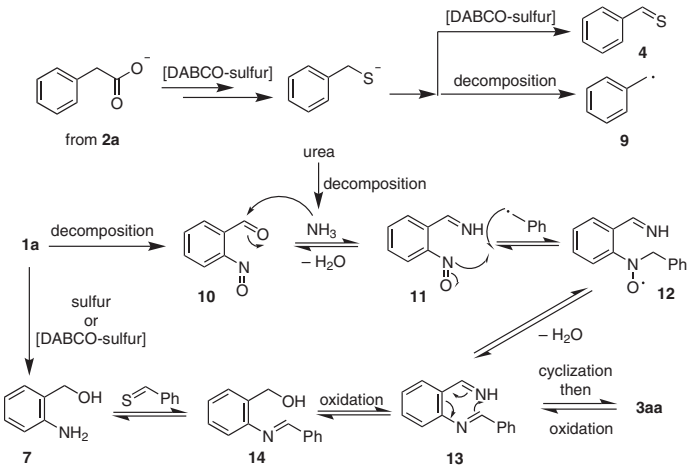


Scheme 3 Synthesis of 2-phenylquinazolines from 2-nitrobenzylic alcohols. *Reagents and conditions*: 2-nitrobenzylic alcohol (0.1 mmol), phenylacetic acid (**2a**; 0.25 mmol), sulfur (0.25 mmol, 32 g/mol), DABCO (0.25 mmol), urea (0.3 mmol), DMSO (0.3 mL), 140 °C, 2 h. [a] 8 h. [b] 12 h.

involves formation of a radical species, because the addition of the radical quencher TEMPO dramatically decreased the yield of the quinazoline **3aa** (Scheme 4, eq. 1). The use of thiobenzaldehyde **4** afforded **3aa** in 71% yield (Scheme 4, eq. 2). The formation of such adduct in the presence of phenylacetic acid and elemental sulfur has been proposed.[5g] We surmised that **4** probably furnishes an active benzyl synthon under the standard conditions. Given that the redox decomposition of **1a** in the presence of a strong base might afford a nitrosobenzaldehyde,[6] reactions of some sur-



Scheme 4 Mechanistic studies. Yields were determined by GC analysis with diphenyl ether as internal standard.



Scheme 5 Plausible mechanism

rogates of **1a** were attempted. 2-Nitrobenzaldehyde (**5**) reacted with **2a** to give quinazoline **3aa** in 78% yield (Scheme 4, eq. 3), confirming the presence of this intermediate during the course of the reaction. When 2-nitrobenzylamine (**6**) was used as a substrate, **3aa** was obtained in 57% yield without an addition of urea (Scheme 4, eq. 4), presumably due to slower oxidation of the C–N bond. Precursors of **1a** derived by reduction of the nitro group also reacted with phenylacetic acid (**2a**). The reaction of 2-aminobenzyl alcohol (**7**) gave **3aa** in 81% yield (Scheme 4, eq. 5), whereas the use of the nitroso intermediate **8** afforded quinazoline **3aa** in 65% yield (Scheme 4, eq. 6).[12]

Based on the above results and previous studies,[5g,6b] a possible mechanism is proposed (Scheme 5). Initially, complexation of DABCO base with elemental sulfur forms an active sulfur species[5g] that then reacts with a phenylacetate anion to afford a benzyl polysulfide. This adduct either decomposes in the presence of the DABCO–sulfur complex to form thiobenzaldehyde (**4**) or undergoes single-electron-based fragmentation to afford benzylic radical **9**. Meanwhile, 2-nitrobenzyl alcohol (**1a**) decomposes to provide 2-nitrosobenzaldehyde (**10**).[6b] Condensation of **10** with NH_3 followed by sequential addition to the benzyl radical **9** and dehydration gives the bisimine **13**. A nonradical pathway cannot be completely ruled out, since addition of a radical quencher such as TEMPO still gave a small amount of **3aa**. Reduction of **1a** might afford **7** which could undergo an imine condensation and oxidation to furnish intermediate **13**. Electrocyclization of **13** followed by oxidation gives the desired quinazoline **3aa**. The optimization results suggest that the combination of elemental sulfur and DMSO solvent accounts for the successful oxidation.

In conclusion, we have developed a method for sulfur-promoted synthesis of 2-arylquinazolines from 2-nitrobenzyl alcohols and phenylacetic acids, with urea as a nitrogen source. The reaction proceeds in the presence of DABCO as base and DMSO as solvent. Excellent tolerance of functionalities such as halo, methoxy, or trifluoromethyl groups was observed. Heterocycles such as thiophenes and indole were also compatible with the reaction conditions. Initial mechanistic studies suggested the formation of a bisimine intermediate either through trapping of 2-nitrosobenzaldehyde with a benzylic radical or condensation of a thioaldehyde with 2-aminobenzyl alcohol.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707113.

References and Notes

(1) For selected examples, see: (a) Wu, Y.; Yi, H.; Lei, A. *ACS Catal.* **2018**, *8*, 1192. (b) Sikari, R.; Sinha, S.; Chakraborty, G.; Das, S.; van Leest, N. P.; Paul, N. D. *Adv. Synth. Catal.* **2019**, *361*, 4342. (c) Wendlandt, A. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 506. (d) Zhang, J.; Chen, S.; Chen, F.; Xu, W.; Deng, G.-J.; Gong, H. *Adv. Synth. Catal.* **2017**, *359*, 2358. (e) Malakar, C. C.; Baskakova, A.; Conrad, J.; Beifuss, U. *Chem. Eur. J.* **2012**, *18*, 8882. (f) Han, B.; Yang, X.-L.; Wang, C.; Bai, Y.-W.; Pan, T.-C.; Chen, X.; Yu, W. *J. Org. Chem.* **2012**, *77*, 1136. (g) Wang, X.; Jiao, N. *Org. Lett.* **2016**, *18*, 2150. (h) Chen, J.; Chang, D.; Xiao, F.; Deng, G.-J. *Green Chem.* **2018**, *20*, 5459. (i) Arachchige, P. T. K.; Yi, C. S. *Org. Lett.* **2019**, *21*, 3337.

(2) (a) Maheswari, C. U.; Kumar, G. S.; Venkateshwar, M.; Kumar, R. A.; Kantam, M. L.; Reddy, K. R. *Adv. Synth. Catal.* **2010**, *352*, 341. (b) Das, K.; Mondal, A.; Pal, D.; Srimani, D. *Org. Lett.* **2019**, *21*, 3223. (c) Chen, Z.; Chen, J.; Liu, M.; Ding, J.; Gao, W.; Huang, X.; Wu, H. *J. Org. Chem.* **2013**, *78*, 11342. (d) Yao, S.; Zhou, K.; Wang, J.; Cao, H.; Yu, L.; Wu, J.; Qiu, P.; Xu, Q. *Green Chem.* **2017**, *19*, 2945.

(3) (a) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. *Science* **2015**, *348*, 886. (b) Shevlin, M.; Guan, X.; Driver, T. G. *ACS Catal.* **2017**, *7*, 5518. (c) Nykaza, T. V.; Cooper, J. C.; Li, G.; Mahieu, N.; Ramirez, A.; Luzung, M. R.; Radosevich, A. T. *J. Am. Chem. Soc.* **2018**, *140*, 15200. (d) Rauser, M.; Eckert, R.; Gerbershagen, M.; Niggemann, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 6713. (e) Cheung, C. W.; Hu, X. *Nat. Commun.* **2016**, *7*, 12494.

(4) (a) Sato, R.; Takizawa, S.; Oae, S. *Phosphorus Sulfur Relat. Elem.* **1979**, *7*, 229. (b) Kas'yan, O. A.; Tarabara, I. N.; Zlenko, E. T.; Kas'yan, L. I. *Russ. J. Org. Chem.* **2002**, *38*, 165. (c) McLaughlin, M. A.; Barnes, D. M. *Tetrahedron Lett.* **2006**, *47*, 9095. (d) Nguyen, T. B.; Ermolenko, L.; Retailleau, P.; Al-Mourabit, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 13808. (e) Guntreddi, T.; Vanjari, R.; Singh, K. N. *Org. Lett.* **2015**, *17*, 976. (f) Do, N. T.; Tran, K. M.; Phan, H. T.; To, T. A.; Nguyen, T. T.; Phan, N. T. S. *Org. Biomol. Chem.* **2019**, *17*, 8987. (g) Xing, Q.; Ma, Y.; Xie, H.; Xiao, F.; Zhang, F.; Deng, G.-J. *J. Org. Chem.* **2019**, *84*, 1238.

(5) For selected examples of elemental sulfur-promoted synthesis of heterocycles other than 2-arylbenzothiazoles, see: (a) Deng, S.; Chen, H.; Ma, X.; Zhou, Y.; Yang, K.; Lan, Y.; Song, Q. *Chem. Sci.* **2019**, *10*, 6828. (b) Liu, J.; Yan, X.; Liu, N.; Zhang, Y.; Zhao, S.; Wang, X.; Zhuo, K.; Yue, Y. *Org. Chem. Front.* **2018**, *5*, 1034. (c) Vanjari, R.; Guntreddi, T.; Kumar, S.; Singh, K. N. *Chem. Commun.* **2015**, *51*, 366. (d) Nguyen, T. B.; Nguyen, L. A.; Retailleau, P. *Org. Lett.* **2019**, *21*, 6570. (e) Huang, H.; Wang, Q.; Xu, Z.; Deng, G.-J. *Adv. Synth. Catal.* **2019**, *361*, 591. (f) Pham, P. H.; Nguyen, K. X.; Pham, H. T. B.; Nguyen, T. T.; Phan, N. T. S. *Org. Lett.* **2019**, *21*, 8795. (g) Nguyen, T. B.; Retailleau, P. *Org. Lett.* **2019**, *21*, 279.

(6) For a review, see: (a) Zhu, J. S.; Haddadin, M. J.; Kurth, M. J. *Acc. Chem. Res.* **2019**, *52*, 2256. For selected examples, see: (b) Zhu, J. S.; Kraemer, N.; Shatskikh, M. E.; Li, C. J.; Son, J.-H.; Haddadin, M. J.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2018**, *20*, 4736. (c) Yang, T.; Lu, H.; Qiu, R.; Hong, L.; Yin, S.-F.; Kambe, N. *Chem. Asian J.* **2019**, *14*, 1436.

(7) For selected examples, see: (a) Yan, Y.; Wang, Z. *Chem. Commun.* **2011**, *47*, 9513. (b) Kumar, M.; Richa; Sharma, S.; Bhatt, V.; Kumar, N. *Adv. Synth. Catal.* **2015**, *357*, 2862.

(8) For selected examples of ammonium salts as nitrogen sources for the synthesis of heterocycles, see: (a) Chen, J.; Meng, H.; Zhang, F.; Xiao, F.; Deng, G.-J. *Green Chem.* **2019**, *21*, 5201. (b) Jiang, J.; Huang, H.; Deng, G.-J. *Green Chem.* **2019**, *21*, 986.

(9) Nguyen, T. B.; Retailleau, P. *Adv. Synth. Catal.* **2018**, *360*, 2389; See also ref. 5d.

(10) (a) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *J. Am. Chem. Soc.* **2013**, *135*, 118. (b) To, T. A.; Nguyen, C. T.; Tran, M. H. P.; Huynh, T. Q.; Nguyen, T. T.; Le, N. T. H.; Nguyen, A. D.; Tran, P. D.; Phan, N. T. S. *J. Catal.* **2019**, *377*, 163.

(11) **6,7-Dimethoxy-2-phenylquinazoline (3da); Typical Procedure**

A 4-mL screw-cap vial was charged with 4,5-dimethoxy-2-nitrobenzyl alcohol (21 mg, 0.1 mmol), phenylacetic acid (**2a**; 34 mg, 0.25 mmol), DABCO (28 mg, 0.25 mmol), elemental sulfur (8 mg, 0.25 mmol, 32 g/mol), urea (18 mg, 0.3 mmol), and DMSO (0.3 mL). The tube was tightly capped and the mixture was stirred at 140 °C for 2 h until the reaction was complete. The mixture was then cooled to r.t. and diluted with EtOAc (5 mL) and 10% aq $NaHCO_3$ (5 mL). The mixture was extracted with 10% aq $NaHCO_3$ (2 × 3 mL), and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude product was purified by column chromatography [silica gel, hexanes–EtOAc (10:1)] to give a light-yellow solid; yield: 17.8 mg (67%); mp 125–126 °C; R_f = 0.45 (hexanes–EtOAc, 5:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.16 (s, 1 H), 8.48 (d, *J* = 7.1 Hz, 2 H), 7.46–7.41 (m, 3 H), 7.33 (s, 1 H), 7.05 (s, 1 H), 4.02 (s, 3 H), 3.97 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.8, 157.0, 156.4, 150.5, 148.6, 138.2, 130.2, 128.6, 128.2, 119.4, 106.8, 104.0, 56.5, 56.3. HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_2O_2$: 267.1128; found: 267.1131.

(12) Tanaka, K.; Yamamoto, Y.; Kuyuza, A.; Komiyama, M. *Nucleosides, Nucleotides Nucleic Acids* **2008**, *27*, 1175.