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# Copper-promoted dehydrosulfurative carbon–nitrogen cross-coupling with concomitant aromatization for synthesis of 2-aminopyrimidines†

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Copper-promoted dehydrosulfurative C–N cross-coupling of 3,4-dihydropyrimidin-1*H*-2-thione with amine accompanied by concomitant aromatization to generate 2-aryl(alkyl)aminopyrimidine derivatives is described. The reaction proceeded well with a wide range of thiono substrates and aryl/aliphatic amines as the coupling partners, offering efficient access to biologically and pharmacologically valuable 2-aryl(alkyl)aminopyrimidines with rapid diversification.

Owing to their roles as a critical binding fragment toward biological targets in many drugs and natural products, pyrimidine motifs have been of great interest in the field of drug discovery and development.<sup>1</sup> In particular, 2-aminopyrimidine structures have been incorporated into various commercialized drugs, such as the hypocholesterolemic agent rosuvastatin, antileukemic agents imatinib and nilotinib, the antiangiogenetic agent pazopanib, anti-HIV agents rilpivirine and etravirine, and the anxiolytic agent buspirone (Fig. 1).<sup>2</sup> In addition, 2-aminopyrimidine derivatives are known to be useful molecular probes in the research on chemical/biological interfaces.<sup>3</sup> The biological significance of this privileged scaffold has naturally generated much interest from organic and medicinal chemists for the efficient synthesis of 2-aminopyrimidine derivatives. In general, syntheses of 2-aryl(alkyl)aminopyrimidines have been performed by nucleophilic aromatic substitution or metal-catalyzed C–N cross-coupling of 2-(pseudo)halopyrimidine with amine.<sup>4–6</sup> However, the synthesis of many 2-(pseudo)halopyrimidine partners, especially for densely substituted partners, requires tedious multi-steps, which limits the rapid diversification of 2-aminopyrimidine derivatives by these reaction protocols. In this regard, we previously developed Liebeskind–Srogl-type Pd-catalyzed/Cu-mediated oxidative dehydrosulfurative C–N cross-coupling to offer 2-aminopyrimidines.<sup>7</sup> The reaction conditions of this method, however, required large amounts of metals (3 equivalents of Cu and 0.2 equivalents of Pd) for acceptable yields of the desired products. The requirement of the large amounts of metals directed us to

envision an alternative method using a stoichiometric amount of Cu with no Pd.

Copper-promoted carbon–carbon and carbon-heteroatom cross-coupling reactions have been extensively investigated<sup>8</sup> and are increasingly used in synthetic chemistry with advantages over other common transition-metals, such as palladium or nickel, which are costly, toxic, or air- and moisture-sensitive, and often require a specially tailored and expensive ligand.<sup>9</sup> To form carbon-heteroatom bonds, such as C–N, C–O, and C–S bonds, in the Cu-promoted couplings, organo(pseudo)halide substrates have been commonly used as the electrophilic partner (aryllating agent) to react with the nucleophilic partner (Scheme 1a).<sup>10</sup> Since independent reports by Chan,<sup>11</sup> Evans,<sup>12</sup> and Lam<sup>13</sup> regarding Cu-mediated arylation of amines or alcohols in 1998, arylboronic acids and derivatives have become another standard aryllating agent of nucleophiles (Scheme 1b).<sup>14</sup> Other organometallics, such as organobismuth, –lead, –tin, and

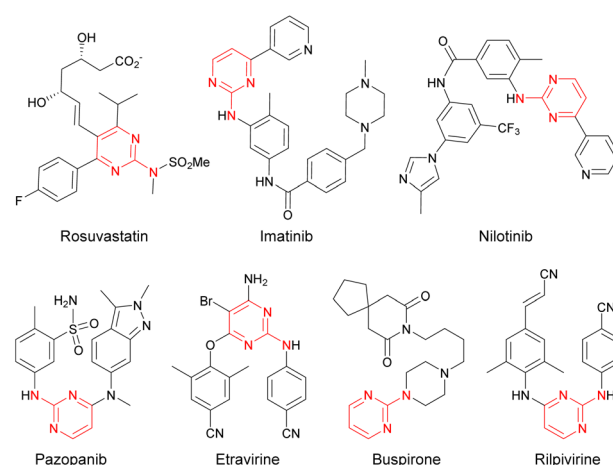
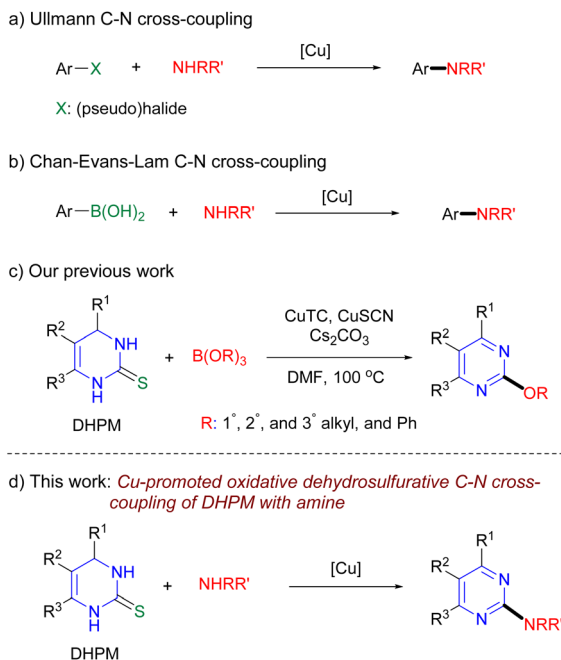


Fig. 1 Drugs containing 2-aminopyrimidine motif on the market.

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Scheme 1 Cu-promoted carbon-heteroatom cross-couplings.

-siloxane, or hypervalent iodonium salt, were also studied as the arylating agents, but their preparations are generally nontrivial.<sup>15</sup> Recently, we developed Cu-promoted C–O cross-coupling of DHPM with boric ester (borate) or alcohol accompanying concomitant oxidative dehydrogenation (aromatization) to produce 2-alkoxy pyrimidines (Scheme 1c).<sup>16</sup> Albeit large amounts of Cu (4.5 equivalents) as in the case of the Liebeskind–Srogl-type oxidative dehydrosulfurative C–N cross-coupling, the results demonstrated that the thiono substrate is a suitable electrophilic partner for Cu-promoted C–O cross-coupling, which inspired us to explore Cu-promoted oxidative dehydrosulfurative C–N cross-coupling of DHPM with amine to provide 2-aminopyrimidine compounds (Scheme 1d). As a surrogate for the 2-(pseudo)halopyrimidines, DHPMs bearing various C4–C6 substituents can be readily produced by the Biginelli three component reaction with versatile aldehyde,  $\beta$ -ketoester, and thiourea.<sup>17</sup> Thus, Cu-promoted oxidative dehydrosulfurative C–N cross-coupling of DHPM with amine could offer a shortcut and general access to a wide range of 2-aryl(alkyl)aminopyrimidine derivatives. To our knowledge, no reports describing Cu-promoted direct C–N cross-coupling of thiono substrate with amine have been published.<sup>18–20</sup>

Initial studies of the reaction were carried out under conditions similar to the previous C–O coupling of DHPM with borate.<sup>16a</sup> When DHPM **1a** (ref. 21) (0.25 mmol) was reacted with aniline **2a** (1.5 equiv.) in the presence of a mixture of Cu(i)-thiophene-2-carboxylate (CuTC, 3 equiv.) and CuSCN (1.5 equiv.), and Cs<sub>2</sub>CO<sub>3</sub> (3 equiv.) in *N,N*-dimethylformamide (DMF) at 100 °C for 18 h under Ar atmosphere, the desired aminated pyrimidine **3a** (ref. 4b) was produced in 22% yield (entry 1, Table 1). We found that the replacement of base Cs<sub>2</sub>CO<sub>3</sub> with K<sub>2</sub>CO<sub>3</sub> slightly increased the reaction yield (entry 2)

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

Entry	Cu (equiv.)	Base	Solvent	Yield (%)
1	CuTC (3.0)/CuSCN (1.5)	Cs <sub>2</sub> CO <sub>3</sub>	DMF	22
2	CuTC (3.0)/CuSCN (1.5)	K <sub>2</sub> CO <sub>3</sub>	DMF	25
3	CuSCN (3.0)	K <sub>2</sub> CO <sub>3</sub>	DMF	68
4	CuSCN (3.0)	K <sub>2</sub> CO <sub>3</sub>	PhMe	Trace
5	CuSCN (3.0)	K <sub>2</sub> CO <sub>3</sub>	Dioxane	Trace
6	CuSCN (3.0)	<sup>t</sup> BuOK	DMF	75
7	CuSCN (3.0)	K <sub>3</sub> PO <sub>4</sub>	DMF	57
8	CuSCN (3.0)	LDA	DMF	63
9	<b>CuSCN (3.0)</b>	<b>LiHMDS</b>	<b>DMF</b>	<b>90</b>
10	<b>CuSCN (2.0)</b>	<b>LiHMDS</b>	<b>DMF</b>	<b>86</b>
11	CuSCN (1.5)	LiHMDS	DMF	61
12	CuSCN (1.0)	LiHMDS	DMF	41
13	CuI (2.0)	LiHMDS	DMF	80
14	CuCl (2.0)	LiHMDS	DMF	23
15	CuBr (2.0)	LiHMDS	DMF	21
16	Cu <sub>2</sub> O (2.0)	LiHMDS	DMF	0
17	<b>Cu(OAc)<sub>2</sub> (2.0)</b>	<b>LiHMDS</b>	<b>DMF</b>	<b>88</b>
18	—	LiHMDS	DMF	0
19	Cu(OAc) <sub>2</sub> (2.0)	—	DMF	0
20 <sup>b</sup>	Cu(OAc) <sub>2</sub> (2.0)	LiHMDS	DMF	65
21 <sup>c</sup>	Cu(OAc) <sub>2</sub> (2.0)	LiHMDS	DMF	38
22 <sup>d</sup>	Cu(OAc) <sub>2</sub> (2.0)	LiHMDS	DMF	0

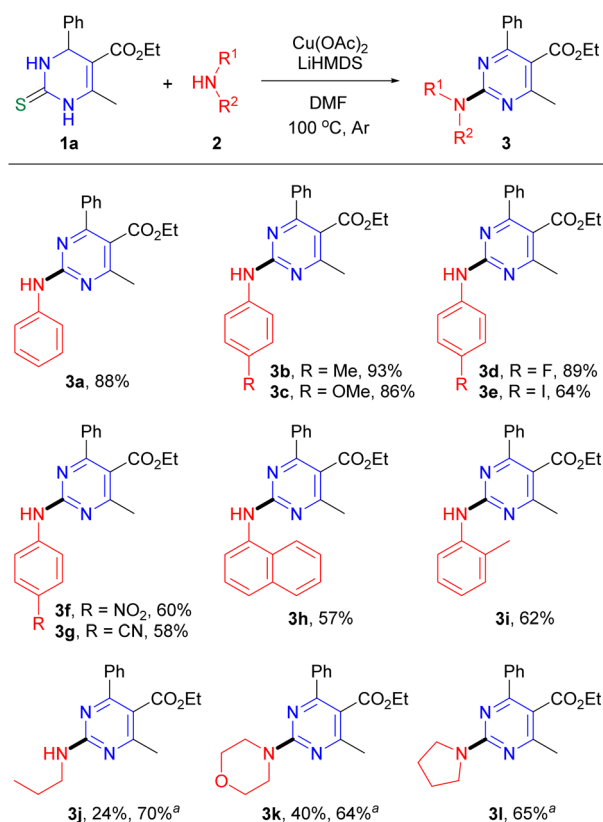
<sup>a</sup> Reaction conditions: DHPM **1a** (0.25 mmol), aniline (0.38 mmol), base (1.5–2.0 equiv.), and solvent (1.5 mL) at 100 °C for 18 h under Ar. <sup>b</sup> The reaction at 120 °C. <sup>c</sup> The reaction at 80 °C. <sup>d</sup> The reaction under air.

and the use of CuSCN alone (3 equiv.), instead of the mixture of the two Cu salts, gave the desired product in 68% yield (entry 3). These results encouraged us to perform further optimization studies by varying the reaction parameters. Solvents such as toluene (PhMe) and 1,4-dioxane were less effective than DMF (entries 4 and 5). With respect to base, we observed that lithium hexamethyldisilazide (LiHMDS), which provided the desired product in 90% yield, was superior to other bases examined in the studies, such as Cs<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, potassium *t*-butoxide (*t*-BuOK), K<sub>3</sub>PO<sub>4</sub>, and lithium diisopropylamide (LDA) (entries 6–9). Since the amount of Cu salt used in the reaction was 1.5 equivalents less than in the previous C–O coupling with borate, we expected that further reduction of the amount of Cu salt could be achieved. We found that 2 equivalents of CuSCN exhibited no significant decrease in the reaction yield (entry 10), while less than 2 equivalents of CuSCN significantly reduced the yield (entries 11 and 12). Next, we investigated the reaction with respect to the Cu source; we found that copper(II) acetate (Cu(OAc)<sub>2</sub>) provided the desired product in slightly higher yield (88%), compared with CuSCN (entry 17). No desired product was produced in the absence of either Cu salt or base (entries 18 and 19) and lower yields of the desired product were observed at other temperatures (entries 20 and 21). Instead of Ar atmosphere, the reaction under air did not give the desired product



(entry 22). Because of the higher stability, lower cost, and easier isolation of the desired product, we decided to use  $\text{Cu}(\text{OAc})_2$  rather than  $\text{CuSCN}$  to investigate the reaction scope.<sup>22</sup>

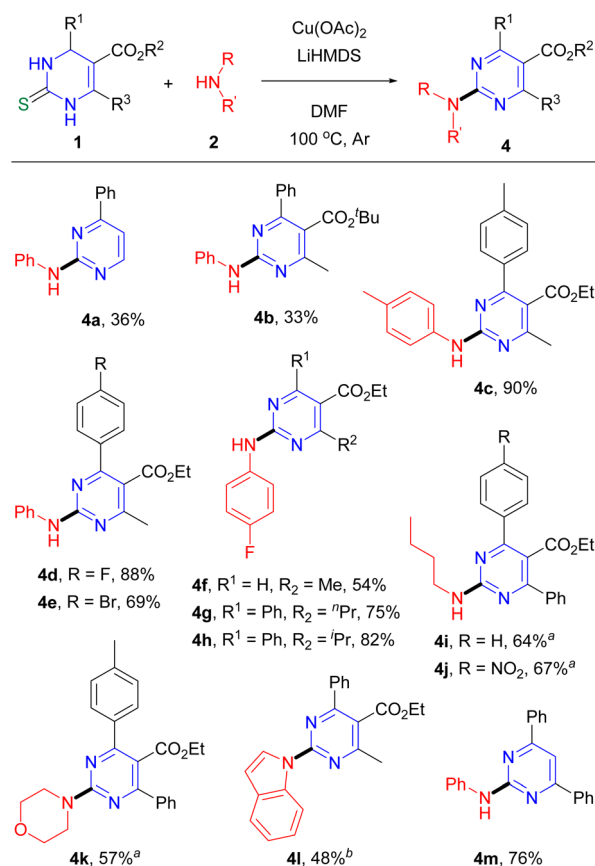
Under optimal reaction conditions, the scope of the reaction with various DHPMs and amines was assessed. With respect to aryl amines, we observed that various functional groups on the phenyl were compatible with the reaction method (Scheme 2). Electron-donating methyl and methoxy groups present at the *para* position on aniline provided the desired products **3b** (ref. 23) and **3c**,<sup>4b</sup> respectively, in high yields. Halide groups F and I at the *para* position gave **3d** (ref. 7) (89%) and **3e** (ref. 7) (64%), respectively, and other electron-withdrawing groups, such as nitro and cyano groups, yielded **3f** (ref. 7) and **3g**,<sup>7</sup> respectively, in 58–60% yields. Bicyclic 1-naphthylamine and sterically hindered *o*-methylaniline were also suitable as the coupling partner to produce the desired products **3h** (ref. 6) and **3i** (ref. 6) in 57% and 62% yields, respectively. We also investigated the reaction with aliphatic amines as the coupling partners. When the reaction of DHPM **1a** with *n*-PrNH<sub>2</sub> was performed the desired product **3j** was produced in only 24% yield. This unacceptable low yield motivated us to determine the reaction conditions using  $\text{Cu}(\text{OAc})_2$ ,  $\text{K}_3\text{PO}_4$ , ethylene glycol and 4 Å molecular sieves in *i*-PrOH, under which the desired product **3j** was obtained in 57% yield. Thus, the reaction conditions were



**Scheme 2** Scope of the reaction with respect to amine. Reaction conditions: DHPM **1a** (0.25 mmol), amine **2** (0.38 mmol),  $\text{Cu}(\text{OAc})_2$  (0.50 mmol), LiHMDS (0.38 mmol) in DMF (1.5 mL) at 100 °C for 18–24 h under Ar. <sup>a</sup> $\text{Cu}(\text{OAc})_2$  (0.50 mmol),  $\text{K}_3\text{PO}_4$  (0.50 mmol), ethylene glycol (0.50 mmol), *i*-PrOH (1.5 mL) and 4 Å molecular sieves.

applied to the reactions with other aliphatic amines. When secondary amines, morpholine and pyrrolidine, were reacted, the corresponding products **3k** (ref. 4e) and **3l** (ref. 4b) were produced in 64% and 65% yields, respectively.<sup>24</sup>

We assessed the scope of the reaction with respect to the DHPM substrate by varying substituents at the C4 to C6 positions (Scheme 3). The reaction of the DHPM possessing no substituents at the C5 and C6 positions with aniline gave the desired product **4a** (ref. 25) in 36% yield. A *t*-butoxycarbonyl group at the C5 position resulted in pyrimidine **4b** (ref. 7) in 33% yield in the reaction with aniline; much lower yield compared with ethoxycarbonyl group (**3a**, 88% yield) might be attributed to decomposition of the *t*-butoxycarbonyl group under the reaction conditions. We also investigated the effects of substituents at C4 aryl by varying the *para* substituent and observed no distinct preference of the reaction toward either electron-donating or electron-withdrawing substituents. When tolyl, 4-fluorophenyl, and 4-bromophenyl groups at the C4 position of DHPM were examined for the reaction with *p*-toluidine or aniline, the corresponding products **4c–e** (ref. 6) were obtained in good yields. DHPM with no substituents at the C4

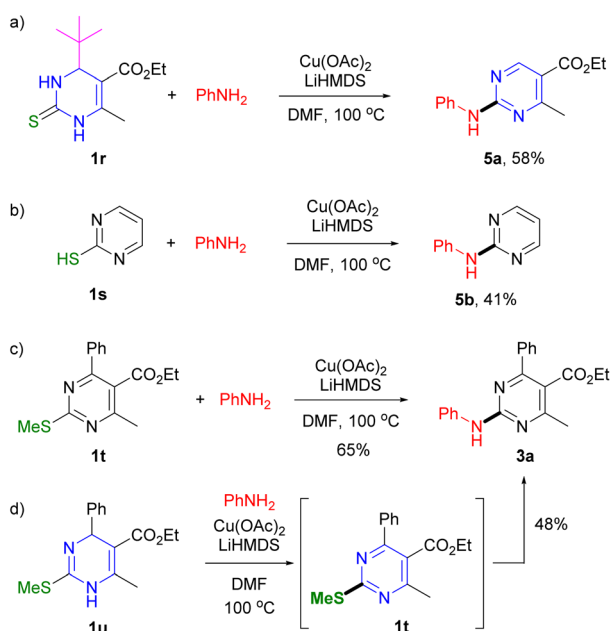


**Scheme 3** Scope of the reaction with respect to DHPM and amine. Reaction conditions: DHPM **1** (0.25 mmol), amine **2** (0.38 mmol),  $\text{Cu}(\text{OAc})_2$  (0.50 mmol), and LiHMDS (0.38 mmol) in DMF (1.5 mL) at 100 °C for 18–24 h under Ar. <sup>a</sup> $\text{Cu}(\text{OAc})_2$  (0.50 mmol),  $\text{K}_3\text{PO}_4$  (0.50 mmol), and ethylene glycol (0.50 mmol) in *i*-PrOH (1.5 mL) and 4 Å molecular sieves. <sup>b</sup> $\text{CuTC}$  (0.75 mmol) and  $\text{Cs}_2\text{CO}_3$  (0.75 mmol) in 1,4-dioxane (1.5 mL) under air.

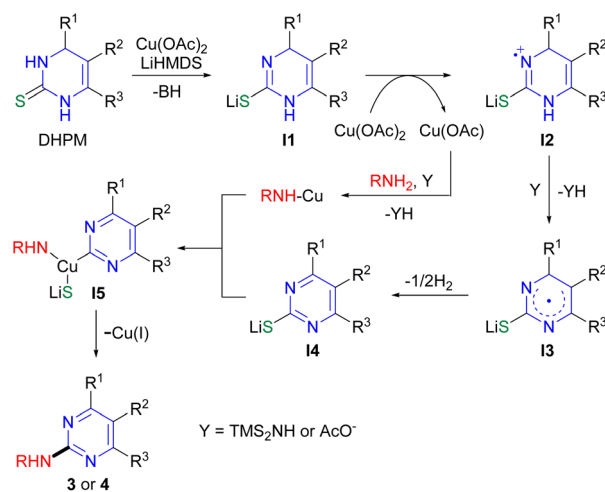


position yielded the desired product **4f** in 54% yield in the reaction with 4-fluoroaniline. Substituent *n*-propyl or *i*-propyl group at the C6 position, which gave pyrimidine **4g** or **4h**, respectively, in good yield in the reaction with 4-fluoroaniline, was compatible with the reaction method. The phenyl group at the C6 position also gave the desired product **4i** (ref. 26) or **4j** in 64–67% yields when coupling with *n*-BuNH<sub>2</sub> under the conditions for aliphatic amines. Tolyl and phenyl groups at the C4 and C6 positions, respectively, were also compatible substituents in the reaction with morpholine to generate **4k**. Next, we attempted the reaction of DHPM with indole to produce 2-indolylpyrimidine, which was not successful in the previous Pd-catalyzed/Cu-mediated reaction.<sup>7</sup> We found that the reaction of **1a** with indole in the presence of CuTC and Cs<sub>2</sub>CO<sub>3</sub> in 1,4-dioxane at 100 °C under air provided the desired product **4l** (ref. 27) in 48% yield.

To understand the mode of the reaction, control experiments were performed. When DHPM **1r** containing *t*-butyl group at the C4 position was reacted with aniline, the debutylated product **5a**,<sup>28</sup> was produced as the major product (Scheme 4a). As described in previous reports regarding the oxidative dehydrogenation (aromatization) and the oxidative dehydrosulfurative cross-coupling reactions of DHPM derivatives possessing the C4 *t*-Bu group, published by others and us, these results support the involvement of a radical intermediate in the aromatization process.<sup>16,19,29,30</sup> When the reaction of 2-mercaptopyrimidine **1s** with aniline was performed, the desired pyrimidine **5b** (ref. 31) was obtained (Scheme 4b), consistent with the proposition that the C–S single bond generated after deprotonation is involved in the reaction of DHPM. Pyrimidinyl thioether **1t** (ref. 32) and dihydropyrimidinyl thioether **1u**,<sup>4b</sup> which provide the same product **3a**, were also compatible with the reaction method (Scheme 4c and d). We found that the reaction of **1u** proceeded



Scheme 4 Control experiments.



Scheme 5 A plausible reaction mechanism.

*via* aromatization to yield pyrimidine **1t** as an intermediate in advance of C–N coupling.

Based on the results, a plausible mechanism of the reaction is proposed as shown in Scheme 5. The reaction could proceed *via* the generation of dihydropyrimidine **11** possessing C–S single bond after deprotonation and coordination to Cu, which then undergoes aromatization to yield pyrimidine **14** likely *via* the generation of radical species **13**.<sup>29b</sup> Radical **13** could arise from nitrogen radical cation **12** formed from **11** by single electron transfer. Oxidative addition of pyrimidine **14** to Cu(I)NHR produced from the amine and Cu(I) species could afford Cu(III) complex **15**,<sup>20</sup> which is then transformed to 2-aminopyrimidine **3** or **4** by reductive elimination.

In summary, we have developed a Cu-promoted oxidative dehydrosulfurative C–N cross-coupling reaction of DHPMs with amines to produce 2-aryl(alkyl)aminopyrimidine derivatives. To our knowledge, this is the first use of thiono substrate as an arylating partner in the Cu-promoted C–N cross-coupling reaction. The reaction proceeded well with various DHPMs and aryl amines or aliphatic amines as coupling partners, providing efficient access to biologically and pharmacologically important 2-aryl(alkyl)aminopyrimidines with rapid diversification.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- (a) M. Lagoja, *Chem. Biodiversity*, 2005, **2**, 1–50; (b) *Pharmaceutical Substances: Synthesis, Patents, Applications*,





- ed. A. Kleemann and J. Engel, Thieme, Stuttgart, Germany, 2001.
- 2 (a) L. Yet. *Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis*, John Wiley & Sons, Inc., New Jersey, USA, 2018, ch. 7, pp. 237–283; (b) S. Kumar and B. Narsimhan, *Chem. Cent. J.*, 2018, **12**, 38.
- 3 (a) S. D. Gilbert, S. J. Mediatore and R. T. Batey, *J. Am. Chem. Soc.*, 2006, **128**, 14214–14215; (b) B. Puffer, C. Kreutz, U. Rieder, M. O. Ebert, R. Konrat and R. Micura, *Nucleic Acids Res.*, 2009, **37**, 7728–7740.
- 4 For selected examples, see: (a) F.-A. Kang, J. Kodah, Q. Guan, X. Li and W. V. Murray, *J. Org. Chem.*, 2005, **70**, 1957–1960; (b) M. Matloobi and C. O. Kappe, *J. Comb. Chem.*, 2007, **9**, 275–284; (c) X.-C. Wang, G.-J. Yang, Z.-J. Quan, P.-Y. Ji, J.-L. Liang and R.-G. Ren, *Synlett*, 2010, 1657–1660; (d) X.-C. Wang, G.-J. Yang, X.-D. Jia, Z. Zhang, Y.-X. Da and Z.-J. Quan, *Tetrahedron*, 2011, **67**, 3267–3272; (e) K. Singh, K. Singh, B. Wan, S. Franzblau, K. Chibale and J. Balzarini, *Eur. J. Med. Chem.*, 2011, **46**, 2290–2294; (f) Q. Yang, Z. Quan, S. Wu, B. Du, M. Wang, P. Li, Y. Zhang and X. Wang, *Tetrahedron*, 2015, **71**, 6124–6134; (g) L. A. Ho, C. L. Raston and K. A. Stubbs, *Eur. J. Org. Chem.*, 2016, **2016**, 5957–5963; (h) T.-T. Li, C. Pannecouque, E. De Clercq, C.-L. Zhuang and F.-E. Chen, *Molecules*, 2020, **25**, 1581; (i) M. Huang, Y. Huang, J. Guo, L. Yu, Y. Chang, X. Wang, J. Luo, Y. Huang, Z. Tu, X. Lu, Y. Xu, Z. Zhang, Z. Zhang and K. Ding, *Eur. J. Med. Chem.*, 2021, **211**, 113023; (j) J. Y. Lee, Y. S. Shin, S. Jeon, S. I. Lee, S. Noh, J.-E. Cho, M. S. Jang, S. Kim, J. H. Song, H. R. Kim and C. M. Park, *Bioorg. Med. Chem. Lett.*, 2021, **39**, 127885.
- 5 Other strategy to 2-aminopyrimidines using three-component reaction with aldehydes,  $\beta$ -ketonitriles and substituted guanidines: C. Val, A. Crespo, V. Yaziji, A. Coelho, J. Azuaje, A. E. Maatougui, C. Carbajales and E. Sotelo, *ACS Comb. Sci.*, 2013, **15**, 370–378.
- 6 The route involving 2-NH<sub>2</sub>-pyrimidine intermediates for the C-N cross-coupling: Y. Zhang, Z.-J. Quan, H.-P. Gong, Y.-X. Da and Z. Zhang, *Tetrahedron*, 2015, **71**, 2113–2118.
- 7 N. H. T. Phan, H. Kim, H. Shin, H.-S. Lee and J.-H. Sohn, *Org. Lett.*, 2016, **18**, 5154–5157.
- 8 (a) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131; (b) *Copper Catalysis in Organic Synthesis*, ed. G. Anilkumar and S. Saranya, Wiley-VCH Verlag GmbH & Co., Weinheim, Germany, 2020.
- 9 (a) H. Rao and H. Fu, *Synlett*, 2011, 745–769; (b) C. Sambiagio, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Soc. Rev.*, 2014, **43**, 3525–3550; (c) S. Thapa, B. Shrestha, S. K. Gurung and R. Giri, *Org. Biomol. Chem.*, 2015, **13**, 4816–4827; (d) J. Jiang, L. Du and Y. Ding, *Mini-Rev. Org. Chem.*, 2020, **17**, 26–46.
- 10 (a) S. U. Tekale, V. B. Jadhav, V. P. Pagore, S. S. Kauthale, D. D. Gaikwad and R. P. Pawar, *Mini-Rev. Org. Chem.*, 2013, **10**, 281–301; (b) P. Bichler and J. A. Love, *Top. Organomet. Chem.*, 2010, **31**, 39–64; (c) H. Lin and D. Sun, *Org. Prep. Proced. Int.*, 2013, **45**, 341–394; (d) Q. Zeng, L. Zhang and Y. Zhou, *Chem. Rec.*, 2018, **18**, 1278–1291.
- 11 D. M. T. Chan, K. L. Monaco, R.-P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933–2936.
- 12 D. A. Evans, J. L. Katz and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937–2940.
- 13 P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941–2944.
- 14 (a) J. X. Qiao and P. Y. S. Lam, *Synthesis*, 2011, 829–856; (b) K. S. Rao and T.-S. Wu, *Tetrahedron*, 2012, **68**, 7735–7754; (c) I. Munir, A. F. Zahoor, N. Rasool, S. A. R. Naqvi, K. M. Zia and R. Ahmad, *Mol. Diversity*, 2019, **23**, 215–259; (d) J.-Q. Chen, J.-H. Li and Z.-B. Dong, *Adv. Synth. Catal.*, 2020, **362**, 3311–3331; (e) A. Vijayan, D. N. Rao, K. V. Radhakrishnan, P. Y. S. Lam and P. Das, *Synthesis*, 2021, **53**, 805–847.
- 15 (a) G. I. Elliott and J. P. Konopelski, *Tetrahedron*, 2001, **57**, 5683–5705; (b) J.-P. Finet, A. Y. Fedorov, S. Combes and G. Boyer, *Curr. Org. Chem.*, 2002, **6**, 597–626; (c) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400–5449.
- 16 (a) H. Kim, J. Lee, H. Shin and J.-H. Sohn, *Org. Lett.*, 2018, **20**, 1961–1965; (b) J. Lee, Y. Kwon, D.-C. Lee and J.-H. Sohn, *RSC Adv.*, 2021, **11**, 36821–36825.
- 17 For recent selected reviews, see: (a) K. Singh and K. Singh, *Adv. Heterocycl. Chem.*, 2012, **105**, 223–308; (b) Suresh and J. S. Sandhu, *ARKIVOC*, 2012, 66–133; (c) R. V. Patil, J. U. Chavan, D. S. Dalal, V. S. Shinde and A. G. Beldar, *ACS Comb. Sci.*, 2019, **21**(3), 105–148.
- 18 Since Kappe's seminal work, five- or six-membered thiono substrates, such as thioamides, thiourethanes, and thioureas, have been utilized as electrophilic partners in Pd-catalyzed/Cu-mediated dehydrosulfurative C–C cross-couplings with boronic acids, stannanes, siloxanes, or terminal alkynes, as a notable extension of the Liebeskind–Srogl reaction. For the representative examples, see: (a) A. Lengar and C. O. Kappe, *Org. Lett.*, 2004, **6**, 771–774; (b) H. Prokopcova and C. O. Kappe, *J. Org. Chem.*, 2007, **72**, 4440–4448; (c) S. Silva, B. Sylla, F. Suzenet, A. Tatibouët, A. P. Rauter and P. Rollin, *Org. Lett.*, 2008, **10**, 853–856; (d) S. Silva, S. Tardy, S. Routier, F. Suzenet, A. Tatibouët, A. P. Rauter and P. Rollin, *Tetrahedron Lett.*, 2008, **49**, 5583–5586; (e) N. Arshad, J. Hashim and C. O. Kappe, *J. Org. Chem.*, 2009, **74**, 5118–5121; (f) X. Guinchard and E. Roulland, *Org. Lett.*, 2009, **11**, 4700–4703; (g) Q. Sun, F. Suzenet and G. Guillaumet, *J. Org. Chem.*, 2010, **75**, 3473–3476; (h) Q. Sun, F. Suzenet and G. Guillaumet, *Tetrahedron Lett.*, 2012, **53**, 2694–2698; (i) Z.-J. Quan, W. H. Hu, X. D. Jia, Z. Zhang, Y.-X. Da and X.-C. A. Wang, *Adv. Synth. Catal.*, 2012, **354**, 2939–2948; (j) Z. F. Yan, Z.-J. Quan, Y.-X. Da, Z. Zhang and X.-C. Wang, *Chem. Commun.*, 2014, **50**, 13555–13558; (k) Y. Wu, Y. Xing, J. Wang, Q. Sun, W. Kong and F. Suzenet, *RSC Adv.*, 2015, **5**, 48558–48562; (l) W. Zou, Z. Huang, K. Jiang, Y. Wu, Y. Xue, F. Suzenet, Q. Sun and G. Guillaumet, *Tetrahedron*, 2017, **73**, 5485–5492; (m) O. V. Maltsev, A. Pöthig and L. Hintermann, *Org. Lett.*, 2014, **16**, 1282–1285.



- 19 We previously demonstrated that DHPMs are suitable substrates for Liebeskind–Srogl-type Pd-catalyzed/Cu-mediated dehydrosulfurative C–C, C–N and C–O cross-couplings: (a) H. Kim, N. H. T. Phan, H. Shin, H.-S. Lee and J.-H. Sohn, *Tetrahedron*, 2017, **73**, 6604–6613; (b) H. Yang, N. S. L. Pham, H. Shin and J.-H. Sohn, *Bull. Korean Chem. Soc.*, 2020, **41**, 881–883; (c) N. S. L. Pham, H. Shin, J. Y. Kang and J.-H. Sohn, *J. Org. Chem.*, 2020, **85**, 5087–5096; (d) N. H. T. Phan, J. Lee, H. Shin and J.-H. Sohn, *J. Org. Chem.*, 2021, **86**, 5423–5430.
- 20 A Cu-promoted C–N cross-coupling of disulfide substrate prepared from DHPM was reported by Quan and Wang: K.-J. Wei, Z. Quan, Z. Zhang, Y. Da and X. Wang, *Org. Biomol. Chem.*, 2016, **14**, 2395–2398.
- 21 C. K. Khatri, S. M. Potadar and G. U. Chaturbhuj, *Tetrahedron Lett.*, 2017, **58**, 1778–1780.
- 22 The reaction of 1.00 g of **1a** with aniline provided the desired product **3a** in 79% yield.
- 23 Z. Quan, F. Jing, Z. Zhang, Y. Da and X. Wang, *Chin. J. Chem.*, 2013, **31**, 1495–1502.
- 24 The reaction with acyclic secondary amine such as dibutylamine or dicyclohexylamine provided only a trace amount of the desired 2-aminopyrimidine product.
- 25 Y. F. Liu, Y. J. Bai, J. Zhang, Y. Y. Li, J. P. Jiao and X. L. Qi, *Eur. J. Org. Chem.*, 2007, **36**, 6084–6088.
- 26 J. J. V. Eynde, N. Labuche, Y. V. Haverbeke and L. Tietze, *ARKIVOC*, 2003, **15**, 22–28.
- 27 H. P. Gong, Z. J. Quan and X. C. Wang, *Appl. Organomet. Chem.*, 2016, **30**, 949–953.
- 28 A. Porcheddu, G. Giacomelli, L. De Luca and A. M. A. Ruda, *J. Comb. Chem.*, 2004, **6**, 105–111.
- 29 (a) K. Yamamoto, Y. G. Chen and F. G. Buono, *Org. Lett.*, 2005, **7**, 4673–4676; (b) B. Han, R. F. Han, Y. W. Ren, X. Y. Duan, Y. C. Xu and W. Zhang, *Tetrahedron*, 2011, **67**, 5615–5620.
- 30 We attempted to trap the radical species using radical scavengers, such as TEMPO, BHT, or 1,1-diphenylethylene but could not obtain the pyrimidine-radical scavenger adduct, presumably due to the faster aromatization than the intermolecular adduct formation.
- 31 L. B. Delvos, J. M. Begouin and C. Gosmini, *Synlett*, 2011, **16**, 2325–2328.
- 32 N. N. Karade, S. V. Gampawar, N. P. Tale and S. B. Kedar, *J. Heterocycl. Chem.*, 2010, **47**, 740–744.

