

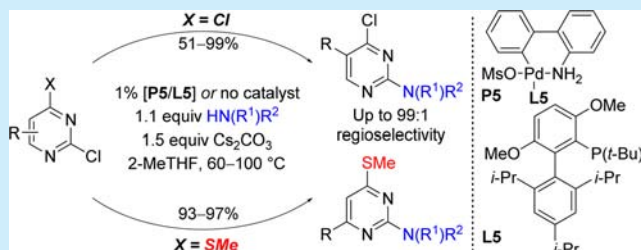
## Regioselective 2-Amination of Polychloropyrimidines

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## S Supporting Information

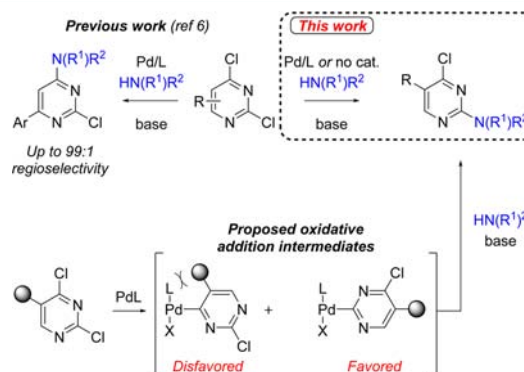
**ABSTRACT:** The regioselective amination of substituted di- and trichloropyrimidines affording the 2-substituted products is reported. While aryl- and heteroaryl amines require the use of a dialkylbiarylphosphine-derived palladium catalyst for high efficiency, more nucleophilic dialkylamines produce 2-aminopyrimidines under noncatalyzed  $S_NAr$  conditions. The key is the use of 5-trimethylsilyl-2,4-dichloropyrimidine as a surrogate for the parent dichloropyrimidine. For more challenging cases, the 2-chloro-4-thiomethoxy analogues were prepared and exclusively afford the desired 2-aminated-4-thiomethoxypyrimidine products.



Polysubstituted pyrimidines,<sup>1</sup> especially 2- and 4-aminopyrimidines,<sup>2</sup> constitute important biological and pharmaceutical compounds that are being increasingly studied in materials research. Yet, despite their demonstrated importance, general methods for the selective preparation of 2- and 4-aminopyrimidines from simple starting materials remain underdeveloped. Our laboratory has long been interested in the use of palladium catalysis for the catalytic formation of carbon–nitrogen bonds, particularly within the context of the selective functionalization of heterocycles. Using this approach, the site-selective coupling between an amine and a 2,4-dichloropyrimidine derivative represents an attractive and potentially generalizable route to access 2- or 4-aminopyrimidines. Importantly, the 2- and 4-aminopyrimidine products accessed by such a strategy contain a reactive aryl-chloride bond that is available for further synthetic manipulation.

The major challenge associated with selective 2- or 4-aminopyrimidine synthesis via palladium-catalyzed amination is the discrimination of the two aryl-chloride bonds in 2,4-dichloropyrimidine compounds.<sup>3</sup> A number of previous studies from other laboratories have highlighted the often poor levels of regioselectivity observed when utilizing such an approach.<sup>4,5</sup> Peng recently described the most general reported method for the highly selective synthesis of 4-amino-2-chloropyrimidine compounds: a 6-aryl substituent is required for such selectivity (Figure 1).<sup>6</sup> However, no general method for the synthesis of 2-amino-4-chloropyrimidine derivatives from 2,4-dichloropyrimidines has been reported to date.<sup>7</sup> This is primarily a consequence of the inherent reactivity of 2,4-dichloropyrimidine compounds, which tend to undergo substitution at the more reactive 4-position.<sup>5</sup> We describe herein several strategies to access a variety of 2-amino-4-chloropyrimidines selectively.

As part of our work on C–N cross-coupling methods, we have developed a family of dialkylbiarylphosphine ligands that have found widespread use in the amination of heterocycles.<sup>8</sup> Initially,



**Figure 1.** Regioselective amination of substituted 2,4-dichloropyrimidines.

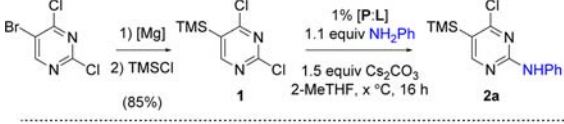
we screened these and other phosphine ligands in an attempt to identify a catalyst system capable of the selective amination at the 2-position of 2,4-dichloropyrimidine. No catalyst system was found to override the inherent tendency toward 4-substitution of 2,4-dichloropyrimidine. We speculated that placement of a suitable substituent at the 5-position of the pyrimidine ring, together with the use of larger dialkylbiarylphosphines, might direct the reaction to the desired 2-position due to these combined steric effects (Figure 1). We reasoned that a 5-trimethylsilyl (TMS) group would be ideal for this substrate-guided approach given (a) its ease of incorporation; (b) its large size and hence its ability to direct reactions away from its adjacent positions; and (c) its ease of removal (vide infra) and thus potential as a traceless directing group. We therefore prepared 2,4-dichloro-5-(trimethylsilyl)pyrimidine (**1**) by simple silyla-

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tion of the 5-bromo derivative (85%, Table 1) and began our amination studies.

Table 1. Regioselective Amination of 1 by Aniline<sup>a</sup>



entry	P:L	solvent	temp (°C)	2a yield (%)
1	no catalyst	2-MeTHF	80	22
2	no catalyst	2-MeTHF	100	32
3	P1:L1	2-MeTHF	80	34
4	P2:L2	2-MeTHF	80	39
5	P3:L3	2-MeTHF	80	45
6	P4:L4	2-MeTHF	80	35
7	P5:L5	2-MeTHF	80	83, <sup>b</sup> 78 <sup>b,c</sup>
8	P5:L5	THF	80	65
9	P5:L5	CPME	100	73
10	P5:L5	toluene	100	71
11	P5:L5	NMP	60	<3

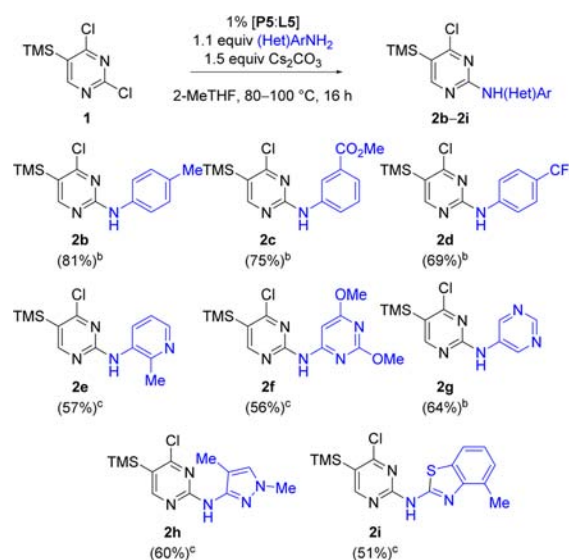
**L1** (R = *t*-Bu, R' = H)    **L4** (R = Cy, R' = *i*-Pr)    **P1** (L = L1)    **P4** (L = L4)  
**L2** (R = Cy, R' = *i*-Pr)    **L5** (R = *t*-Bu)    **P2** (L = L2)    **P5** (L = L5)  
**L3** (R = *t*-Bu, R' = *i*-Pr)    **P3** (L = L3)

<sup>a</sup>Reaction conditions unless otherwise noted: 1 (0.25 mmol), aniline (0.28 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.38 mmol), P (2.5 μmol), L (2.5 μmol), and solvent (0.5 mL). Yields are expressed as an average of two runs and were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>b</sup>Represents isolated yield as an average of two runs. <sup>c</sup>Reactions were run on a 1.0 mmol scale.

Given the susceptibility of electron-deficient pyrimidines such as 1 toward nucleophilic aromatic substitution,<sup>4,5</sup> noncatalyzed amination was first explored. Thus, 1 in combination with Cs<sub>2</sub>CO<sub>3</sub> and aniline in 2-MeTHF gave 2a in low yield at both 80 and 100 °C (Table 1, entries 1 and 2, respectively) with noticeable formation of the minor 4-substituted regioisomer (3–4%). Little improvement was realized with palladium precatalysts P1–P3<sup>9</sup> in conjunction with dialkylbiaryl phosphines L1–L3 (34–35%, entries 3–5). Catalyst system P4:L4, which previously has demonstrated high efficiency in C–N cross-coupling reactions of primary amines,<sup>10</sup> also yielded pyrimidine 2a in low yield (35%, entry 6). The yield was greatly improved with P5 in combination with L5 (*t*BuBrettPhos, 1:1 ratio, 1 mol %), giving 2a in 83% yield with no formation of the 4-substituted product (entry 7) observed. Using P5:L5, no improvement in yield was observed employing other ethereal solvents such as THF or CPME (entries 8 and 9) or aromatic solvents such as toluene (entry 10). More polar solvents (NMP, entry 11)<sup>11</sup> resulted in greatly diminished yields of 2a.

Having identified P5:L5 as a highly active catalyst system for the 2-selective amination of 1, the reactions of a series of other aryl and heteroarylamine cross-coupling amines were evaluated. Amination of 1 with *p*-toluidine under the optimized conditions led to exclusive formation of 2b in high yield (81%, Scheme 1). More electron-deficient arylamines gave the respective 2-substituted products 2c and 2d in reasonable yield (69–75%). Electron-deficient heteroarylamines also served as good cross-coupling partners, resulting in the exclusive formation of the respective 2-aminated products 2e–2g in slightly lower yields

Scheme 1. Regioselective Amination of 1 by Aryl and Heteroarylamines<sup>a</sup>

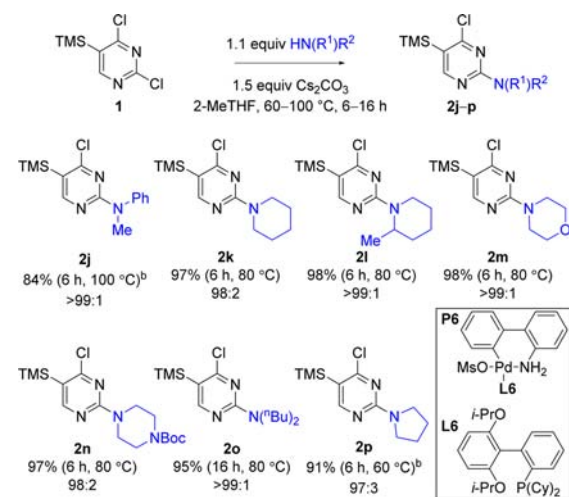


<sup>a</sup>All regioselectivities were >99:1 2-:4-aminated product and were determined by GC analysis of the crude reaction material. Isolated yields are reported and are an average of two runs. <sup>b</sup>Reaction was run at 80 °C. <sup>c</sup>Reaction was run at 100 °C.

(56–64%). Five-membered heterocycles, such as substituted aminopyrazole and aminobenzothiazole, afforded 2h and 2i (60 and 51% yields, respectively) with no formation of regioisomer observed.

When secondary amines were employed as coupling partners, they were found to proceed efficiently under noncatalyzed nucleophilic aromatic substitution conditions. For example, using *N*-methylaniline as a coupling partner without a palladium catalyst afforded 2j in 67% yield (Scheme 2). Addition of P6:L6 (RuPhos) combination provided a minor increase in yield (84%, > 99:1 regioselectivity).<sup>8a,12</sup>

Scheme 2. Noncatalyzed and Palladium-Catalyzed Amination of 1 with Secondary Amines<sup>a</sup>

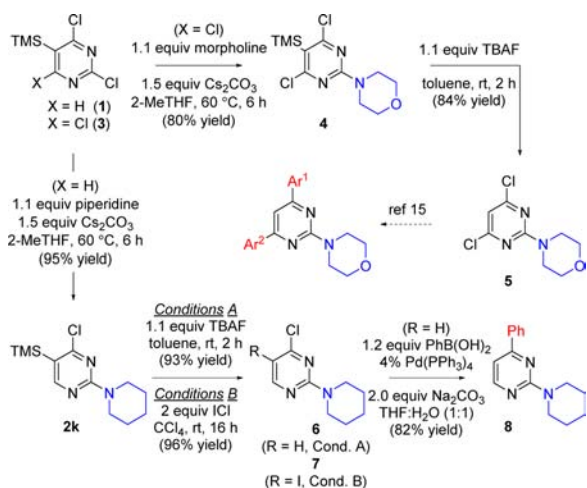


<sup>a</sup>Regioselectivities were determined by GC analysis of the crude reaction material. Isolated yields are reported and are an average of two independent runs. <sup>b</sup>Reaction was run with 1% P6:L6.

This nucleophilic aromatic substitution protocol was amenable to a broad range of amine coupling partners. Amination of **1** by more nucleophilic piperidine afforded **2k** in excellent yield and regioselectivity (97%, >99:1) in the absence of a palladium catalyst. Additionally, sterically encumbered 2-methylpiperidine as well as morpholine, *N*-Boc-protected piperazine, and acyclic *N,N*-dibutylamine produced the respective 2-aminated products **2l–2o** in excellent yields and exceptional levels of regioselectivity (95–98%, 97:3–99:1 2-/4-aminated product). Nucleophilic aromatic substitution by pyrrolidine gave **2p** with slightly diminished regioselectivity (92:8), likely a consequence of its relatively smaller size. The regioselectivity of this transformation was improved to 97:3 (2-/4-aminated product) when **P6:L6** was included in the reaction.

Amination of trichloropyrimidine analogue **3** by morpholine afforded the 2-aminopyrimidine regioisomer **4** in high yield and regioselectivity (80%, >99:1 regioselectivity, Scheme 3).

**Scheme 3. Amination and Subsequent Functional Group Elaboration of 1 and 3**

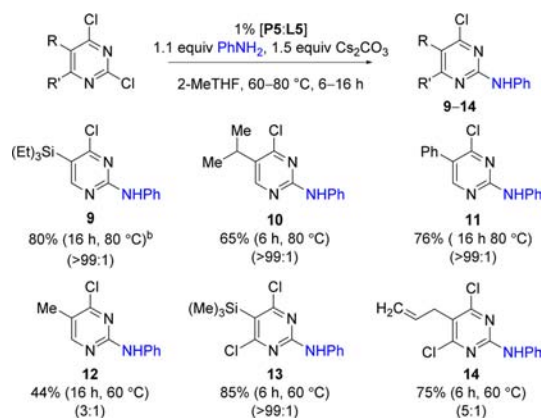


Protodesilylation of **4** produced heterocycle **5** (84%),<sup>14</sup> a dichloropyrimidine that has demonstrated high efficiency in C–C cross-couplings to provide access to 4,6-di(hetero)aryl-2-morpholinopyrimidines.<sup>15</sup>

Additional synthetic utility of the products accessed via this method is also highlighted in Scheme 3. For example, the 5-TMS blocking group used in substrate **2k** was cleanly cleaved by treatment with TBAF (**6**, 93%). Desilylated pyrimidine **6** was then coupled to PhB(OH)<sub>2</sub> to afford **8** (82%), demonstrating the value of this method for accessing 4-aryl-2-aminopyrimidine structures in a regioselective manner. Additionally, **2k** was smoothly converted to the 5-iodopyrimidine analogue **7** by reaction with ICl in CCl<sub>4</sub> (96%).<sup>13</sup>

A variety of other 5-substituted dichloropyrimidines showed the same preference for 2-amination as **1**. For instance, amination of dichloropyrimidines containing 5-TES, *i*-Pr, and Ph substitution with aniline using **P5:L5** gave the respective 2-aminated products **9–11** (65–80%, Scheme 4). A noticeably lower yield and selectivity were observed for the amination of 2,4-dichloro-5-methylpyrimidine (44% and 3:1 2-/4-substituted pyrimidine). The lower yield of **12** is most likely explained by the relatively smaller size of the 5-methyl substituent. Aminated products **13** and **14** were obtained in high yield (75 and 85%, respectively) from 5-substituted trichloropyrimidines. Once

**Scheme 4. Regioselective Amination of Substituted Di- and Trichloropyrimidines<sup>a</sup>**

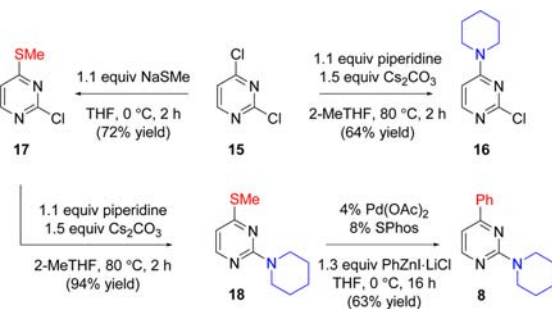


<sup>a</sup>Regioselectivities were determined by GC analysis of the crude reaction material. Isolated yields are reported as an average of two independent runs. <sup>b</sup>Reaction was run with 2% **P5:L5**.

again, lower regioselectivity was observed for 5-allyl-2,4,6-trichloropyrimidine compared to the 5-TMS analogue.

As highlighted by the results with substrates **12** and **14**, relatively smaller 5-substituents on the pyrimidine ring have a detrimental effect on the levels of 2-selectivity in the amination of polychloropyrimidines. In the complete absence of a 5-substituent (**15**), the 4-aminated product **16** predominates (64%), with only 20% of the desired 2-aminated regioisomer formed (Scheme 5).

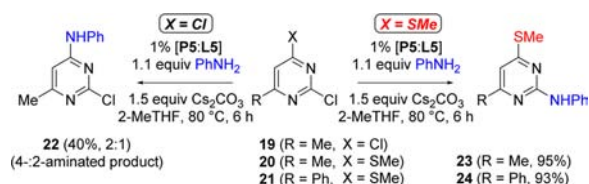
**Scheme 5. Amination of 2-Chloro-4-thiomethoxypyrimidine (17)**



To overcome the inherent preference for 4-substitution of unbiased 2,4-dichloropyrimidines, a thiomethoxy substituent was installed at the 4-position of **15** by nucleophilic aromatic substitution with NaSMe (**17**, 72%, Scheme 5). Numerous examples of metal-mediated aryl- and heteroaryl-SMe activation in C–C cross-coupling led us to believe that we could carry out 2-amination by piperidine followed by palladium-catalyzed C–C cross-coupling at the 4-position.<sup>16</sup> Amination of **17** by piperidine gave 2-amino-4-thiomethoxypyrimidine **18** in excellent yield (94%) followed by conversion to **8** (63%) via palladium-catalyzed C–C cross-coupling.

We also utilized the 4-thiomethoxy-installation strategy for the 2-selective palladium-catalyzed amination of 6-substituted pyrimidine substrates **20** and **21** (products **23** and **24**, Figure 2). Products **23** and **24** were obtained with complete 2-selectivity, as compared to 2,4-dichloropyrimidine substrate **19**, which led to a mixture of the 2- and 4-aminated pyrimidine products (**22**, 40%, 1:2 2-/4-aminopyrimidine).





**Figure 2.** Selective palladium-catalyzed amination of substituted 2-chloro-4-thiomethoxypyrimidines.

In summary, we have developed several effective approaches for the preparation of 2-aminopyrimidines through the amination of substituted polychloropyrimidines and chlorothiomethoxy pyrimidines. Palladium-catalyzed aminations of 5-substituted di- and trichloropyrimidines by aryl and heteroaryl amines afford the 2-substituted products in excellent levels of regioselectivity. More nucleophilic dialkylamines also exhibit 2-amination but do not require a palladium catalyst for a regioselective reaction. For chloropyrimidines without sterically encumbering 5-substituents, an attractive alternative route utilizing readily prepared 2-chloro-4-thiomethoxypyrimidine analogues results in exclusive 2-amination. Taken together, these methods should aid the further development of functionalized 2-aminopyrimidines in application-focused research.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b00799](https://doi.org/10.1021/acs.orglett.6b00799).

Synthetic procedures, characterization of products, and NMR spectra (PDF)

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### Notes

The authors declare the following competing financial interest(s): MIT has patents on some of the ligands and precatalysts described in this work from which S.L.B. as well as former or current co-workers receive royalty payments.

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## ■ REFERENCES

- (1) (a) Malik, I.; Ahmed, Z.; Reimann, S.; Ali, I.; Villinger, A.; Langer, P. *Eur. J. Org. Chem.* **2011**, 2011, 2088. (b) Hadad, C.; Achelle, S.; García-Martínez, J. C.; Rodríguez-López, J. J. *Org. Chem.* **2011**, 76, 3837. (c) Radi, M.; Schenone, S.; Botta, M. *Org. Biomol. Chem.* **2009**, 7, 2841. (d) Ortiz, R. P.; Casado, J.; Hernández, V.; López, V. T.; Navarrete, J. A. L.; Ratner, M. A.; Facchetti, A.; Marks, T. *Chem. - Eur. J.* **2009**, 15, 5023. (e) Achelle, S.; Ramondence, Y.; Marsais, F.; Plé, N. *Eur. J. Org. Chem.* **2008**, 2008, 3129. (f) Itami, K.; Yamazaki, D.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2004**, 126, 15396. (g) Hughes, G.; Wang, C.; Batsanov, A. S.; Fern, M.; Frank, S.; Bryce, M. R.; Perepichka, I. F.; Monkman, A. P.; Lyons, B. P. *Org. Biomol. Chem.* **2003**, 1, 3069. (h) Undeim, K.; Benneche, T. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Scriben, E. F. V., Eds.; Elsevier: Oxford, U.K., 1996; Vol. 6, pp 93–231 and references cited therein.

- (2) (a) Selvam, T. P.; James, C. R.; Dniandev, P. V.; Valzita, S. K. *Res. Pharm.* **2012**, 2, 1. (b) Tavares, F. X.; Boucheron, J. A.; Dickerson, S. H.; Griffin, R. J.; Preugschat, F.; Thomson, S. A.; Wang, T. Y.; Zhou, H. – Q. *J. Med. Chem.* **2004**, 47, 4716. (c) Fabbro, D.; Ruetz, S.; Buchdunger, E.; Cowan-Jacob, S. W.; Fendrich, G.; Liebetanz, J.; Mestan, J.; O'Reilly, T.; Traxler, P.; Chaudhuri, B.; Fretz, H.; Zimmermann, J.; Meyer, T.; Caravatti, G.; Furet, P.; Manley, P. W. *Pharmacol. Ther.* **2002**, 93, 79–98 and references cited therein.

- (3) For reviews on regioselective cross-couplings of polyhalogenated heterocycles, see: (a) Rossi, R.; Bellina, F.; Lessi, M. *Adv. Synth. Catal.* **2012**, 354, 1181. (b) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, 36, 1036. (c) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, 61, 2245.

- (4) For recent examples, see: (a) Joubran, L.; Jackson, W. R.; Campi, E. M.; Robinson, A. J.; Wells, B. A.; Godfrey, P. D.; Callaway, J. K.; Jarrot, B. *Aust. J. Chem.* **2003**, 56, 597. (b) Montebugni, D.; Bravo, P.; Corradi, E.; Dettori, G.; Mioskowski, C.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2002**, 58, 2147. (c) Luthin, D. R.; Hong, Y.; Tompkins, E.; Anderes, K. L.; Paderes, G.; Kraynov, E. A.; Castro, M. A.; Nared-Hood, K. D.; Castillo, R.; Gregory, M.; Vazir, H.; May, J. M.; Anderson, M. B. *Bioorg. Med. Chem. Lett.* **2002**, 12, 3635. (d) Schomaker, J. M.; Delia, T. J. *J. Heterocycl. Chem.* **2000**, 37, 1457.

- (5) Recent computational work has sought to explain the observed preference for coupling at the 4-chloro position, see: (a) Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, 131, 6632. (b) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, 129, 12664.

- (6) Peng, Z. – H.; Journet, M.; Humphrey, G. *Org. Lett.* **2006**, 8, 395.

- (7) For the regioselective preparation of 2-aminopyrimidines via amination by N-substituted cyclic amines with POCl<sub>3</sub>, see: (a) Yoshida, K.; Taguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 919. (b) Yoshida, K.; Tanaka, T.; Ohtaka, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1279.

- (8) (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, 2, 27. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, 47, 6338. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, 41, 1461.

- (9) For the preparation of precatalysts P1–P5, see: (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, 4, 916. (b) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, 15, 2876.

- (10) (a) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, 2, 57. (b) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, 130, 13552.

- (11) Catalyzed or uncatalyzed aminations carried out in more polar solvents such as NMP resulted in desilylation as well as decomposition of 1. The same observation was made when aminations were carried out with relatively stronger bases such as LDA and LiHMDS.

- (12) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, 131, 5766.

- (13) Farha, O. K.; Yazaydin, A. Ö.; Eryazici, I.; Malliakas, C. D.; Hauser, B. G.; Kanatzidis, M. G.; Nguyen, S. T.; Snurr, R. Q.; Hupp, J. T. *Nat. Chem.* **2010**, 2, 944.

- (14) Desilylation of 4 in THF with TBAF resulted in substantial amounts of nucleophilic aromatic substitution, affording the respective fluorinated pyrimidine product. Using a less polar solvent such as toluene circumvented this issue.

- (15) (a) Martínez, M. M.; Pérez-Caaveiro, C.; Peña-López, M.; Sarandeses, L. A.; Sestelo, J. P. *Org. Biomol. Chem.* **2012**, 10, 9045. (b) Liu, M.; Su, S. – J.; Jung, M. – C.; Qi, Y.; Zhao, W. – M.; Kido, J. *Chem. Mater.* **2012**, 24, 3817.

- (16) For recent examples of C–C cross-coupling via metal-mediated C–S activation of aryl and heteroaryl thioethers, see: (a) Lee, K.; Counciller, C. M.; Stambuli, J. P. *Org. Lett.* **2009**, 11, 1457. (b) Metzger, A.; Melzig, L.; Despotopoulou, C.; Knochel, P. *Org. Lett.* **2009**, 11, 4228. (c) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* **2003**, 5, 4349. (d) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, 4, 979. and references cited therein. For reviews, see: (e) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, 42, 599. (f) Modha, S. G.; Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, 42, 5042.