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Regioselective 2-Amination of Polychloropyrimidines

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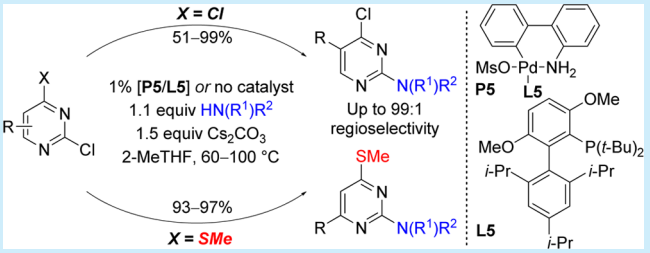
Supporting Information

ABSTRACT: The regioselective amination of substituted di- and trichloropyrimidines affording the 2-substituted products is reported. While aryl- and heteroarylamines require the use of a dialkylbiarylphosphine-derived palladium catalyst for high efficiency, more nucleophilic dialkylamines produce 2-amino-pyrimidines 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 pyridimines,[1] especially 2- and 4-amino-pyrimidines,[2] 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-aminopyridimines 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-dichloropyridimine derivative represents an attractive and potentially generalizable route to access 2- or 4-aminopyridimines. Importantly, the 2- and 4-aminopyridimine 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-aminopyridimine synthesis via palladium-catalyzed amination is the discrimination of the two aryl-chloride bonds in 2,4-dichloropyridimine compounds.[3] A number of previous studies from other laboratories have highlighted the often poor levels of regioselectivity observed when utilizing such an approach.[4,5] Peng recently described the most general reported method for the highly selective synthesis of 4-amino-2-chloropyridimine compounds: a 6-aryl substituent is required for such selectivity (Figure 1).[6] However, no general method for the synthesis of 2-amino-4-chloropyridimine derivatives from 2,4-dichloropyrimidines has been reported to date.[7] This is primarily a consequence of the inherent reactivity of 2,4-dichloropyridimine compounds, which tend to undergo substitution at the more reactive 4-position.[5] We describe herein several strategies to access a variety of 2-amino-4-chloropyridimines 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.[8] Initially,

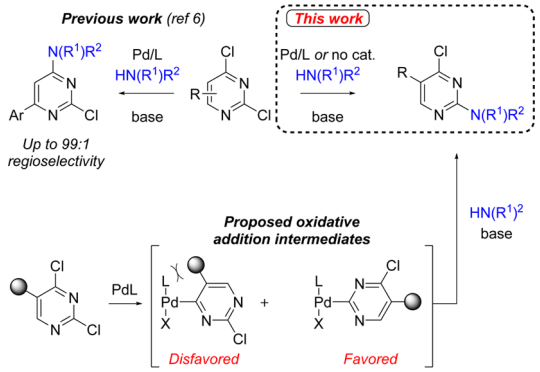


Figure 1. Regioselective amination of substituted 2,4-dichloropyrimidines.

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-dichloropyridimine. No catalyst system was found to override the inherent tendency toward 4-substitution of 2,4-dichloropyridimine. We speculated that placement of a suitable substituent at the 5-position of the pyridimine 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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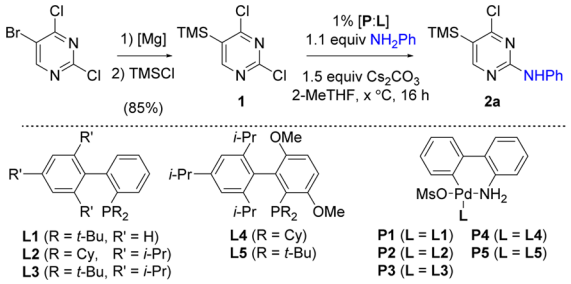
tion of the 5-bromo derivative (85%, Table 1) and began our amination studies.

Table 1. Regioselective Amination of 1 by Aniline[a]



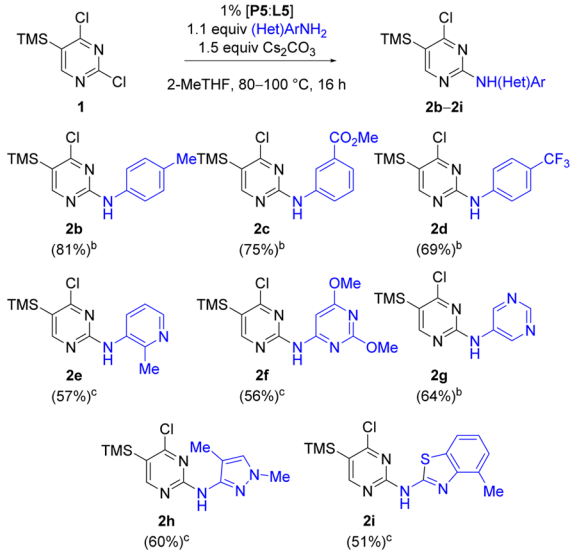
entry	P:L	solvent	temp (°C)	2a yield (%)
1	no catalyst	2-MeTHF	80	22
2	no catalyst	2-MeTHF	100	32
3	P1:L1	2-MeTHF	80	34
4	P2:L2	2-MeTHF	80	39
5	P3:L3	2-MeTHF	80	45
6	P4:L4	2-MeTHF	80	35
7	P5:L5	2-MeTHF	80	83,[b] 78[b,c]
8	P5:L5	THF	80	65
9	P5:L5	CPME	100	73
10	P5:L5	toluene	100	71
11	P5:L5	NMP	60	<3

[a]Reaction conditions unless otherwise noted: **1** (0.25 mmol), aniline (0.28 mmol), Cs_2CO_3 (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 ^{1}H NMR analysis of the crude reaction mixture. [b]Represents isolated yield as an average of two runs. [c]Reactions were run on a 1.0 mmol scale.

Given the susceptibility of electron-deficient pyrimidines such as **1** toward nucleophilic aromatic substitution,[4,5] noncatalyzed amination was first explored. Thus, **1** in combination with Cs_2CO_3 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**[9] 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,[10] 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)[11] 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[a]

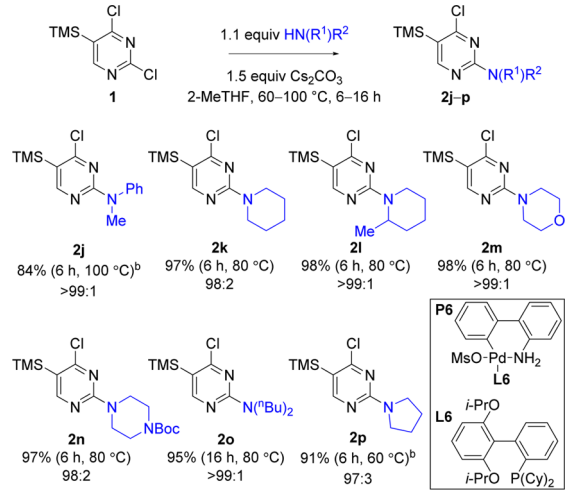


[a]All regioselectivities were >99:1 2-:4-aminated product and were determined by GC analysis of the crude reaction material. Isolated yields are reported and are an average of two runs. [b]Reaction was run at 80 °C. [c]Reaction was run at 100 °C.

(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).[8a,12]

Scheme 2. Noncatalyzed and Palladium-Catalyzed Amination of 1 with Secondary Amines[a]



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

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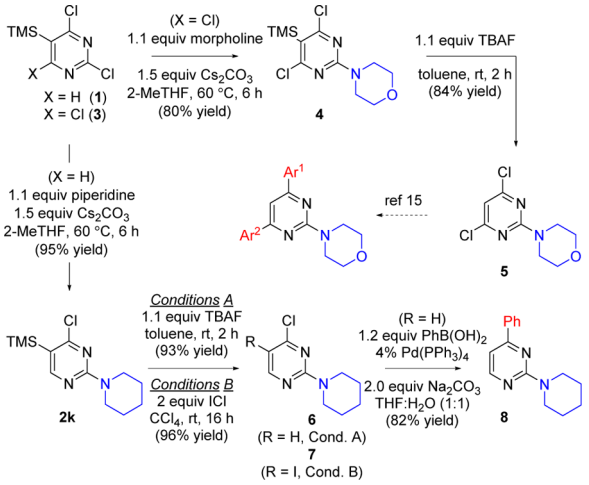
This nucleophilic aromatic substitution protocol was amenable to a broad range of amine coupling partners. Amination of **1** by more nucleophilic piperidine afforded **2k** in excellent yield and regioselectivity (97%, >99:1) in the absence of a palladium catalyst. Additionally, sterically encumbered 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

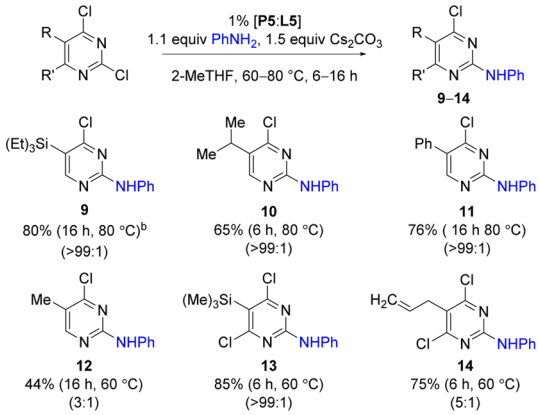


Protodesilylation of **4** produced heterocycle **5** (84%),[14] a dichloropyrimidine that has demonstrated high efficiency in C–C cross-couplings to provide access to 4,6-di(hetero)aryl-2-morpholinopyrimidines.[15]

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 $PhB(OH)_2$ 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_4 (96%).[13]

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

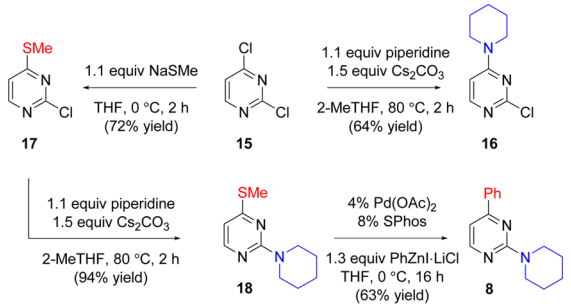
Scheme 4. Regioselective Amination of Substituted Di- and Trichloropyrimidines[a]



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

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.[16] 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).

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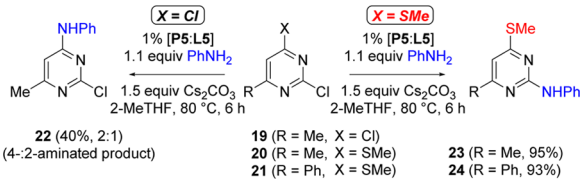

Figure 2. Selective palladium-catalyzed amination of substituted 2-chloro-4-thiomethoxypyrimidines.

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 heteroarylamines 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.

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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