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Communication

C2-Selective Palladium-Catalyzed C−S Cross-Coupling of 2,4-Dihalopyrimidines

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ABSTRACT: Under most conditions, 2,4-dihalopyrimidines undergo substitution reactions at C4. Here we report that Pd(II) precatalysts supported by bulky *N*-heterocyclic carbene ligands uniquely effect C2-selective cross-coupling of 2,4-dichloropyrimidine with thiols. The regioselectivity of this reaction stands in stark contrast to ∼1500 previously reported Pd-catalyzed cross-couplings that favor C4 in the absence of other substituents on the pyrimidine ring. Selectivity in the catalytic system reported herein is extremely sensitive to the structure of the Pd(II) precatalyst, largely due to competing C4-selective nucleophilic aromatic substitution. C2-selectivity is high with most 1° thiols and thiophenols, and a range of substituted dichloropyrimidines can be used. The atypical selectivity of this transformation may facilitate diversity-oriented synthesis, as demonstrated for derivatives of an antiviral agent. Under these conditions, C2—Cl cleavage may not take place through a typical oxidative addition pathway.

Pyrimidines are common motifs in bioactive small molecules such as pharmaceutical drugs and agrichemicals, and are also of value for organic materials.[1−5] The privileged role of pyrimidines in bioactive compounds can be understood by their ubiquity in nature. In particular, nucleobases (the building blocks of DNA) are pyrimidine derivatives. The majority of pyrimidine motifs in small molecule drugs are substituted at both the 2- and the 4-positions.[6] As such, synthetic strategies to functionalize these sites are of high value. Readily available 2,4-dichloropyrimidines are logical precursors to 2,4-difunctionalized derivatives. These substrates typically undergo reaction at C4 to yield Regioisomer B (Scheme 1A) in both cross-coupling and nucleophilic aromatic substitution (S_NAr)[7] reactions. In fact, a survey of the literature indicates that, out of nearly 1500 reported examples, at least 99% of Pd- or Ni-catalyzed C−C, C−N, or C−S cross-couplings of **1** afford Regioisomer B as the major product.[8,9] The handful of reported exceptions lack definitive structural characterization.[10] Thus, obtaining Regioisomer A through the cross-coupling of unsubstituted **1** has not been feasible. Buchwald found that introducing bulky C5-substituents promotes formation of Regioisomer A in Pd-catalyzed and catalyst-free (S_NAr) aminations (Scheme 1B).[11] A removable C5-substituent like TMS presents a useful workaround to the selectivity problem but also introduces additional synthetic steps.

The inability to directly cross-couple at the C2 position of 2,4-dihalopyrimidines without a bulky 5-substituent limits the chemical space that is likely to be targeted during diversity-oriented synthesis, for example, during the development of screening libraries. A catalyst-controlled approach to C2-functionalization would facilitate access to Regioisomer A and, therefore, broaden the landscape of readily accessible pyrimidine derivatives.

We began investigating cross-coupling with thiols, as thiopyrimidines represent a common substitution pattern in druglike compounds (Scheme 1C). Although thiols are good nucleophiles, especially in the presence of base, the uncatalyzed S_NAr reactions of 2,4-dichloropyrimidines with thiols tend to afford C4-substituted products (for example, see ref 12 as well as Table 1, entry 1). Thus, we envisioned that a C2-selective catalytic process for C−S coupling would enable bond construction that was currently not possible to make in a single step. We were further inspired by reports of Pd-catalyzed C−S cross-coupling reactions of other substrates because these often benefit from the use of bulky monodentate ligands.[13−17] We had recently found that bulky monodentate *N*-heterocyclic carbene (NHC) ligands are key to inversion of conventional site selectivity in cross-couplings of other dihalogenated heteroarenes.[18]

PEPPSI-Pd-IPent precatalyst **3** and its analogue **4** were selected for our initial studies (Table 1).[17] Unfortunately, a preference for the conventional C4-functionalized product was observed with both precatalysts (entries 2 and 3). The C4-selectivity using **3** is even higher than that of the Pd-free control reaction (entry 1), suggesting that the selectivity observed with **3** may be due to Pd-catalysis and not to background S_NAr. Interestingly, morpholine complex **4** displayed a weaker preference for C4, leading to more C2 product (**2a**) than the Pd-free control (compare entries 1 and 3). Complex **4** is known to activate more quickly than **3** under

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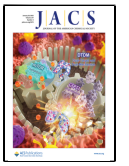

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Scheme 1. Derivatization of 2,4-Dichloropyrimidines[11]

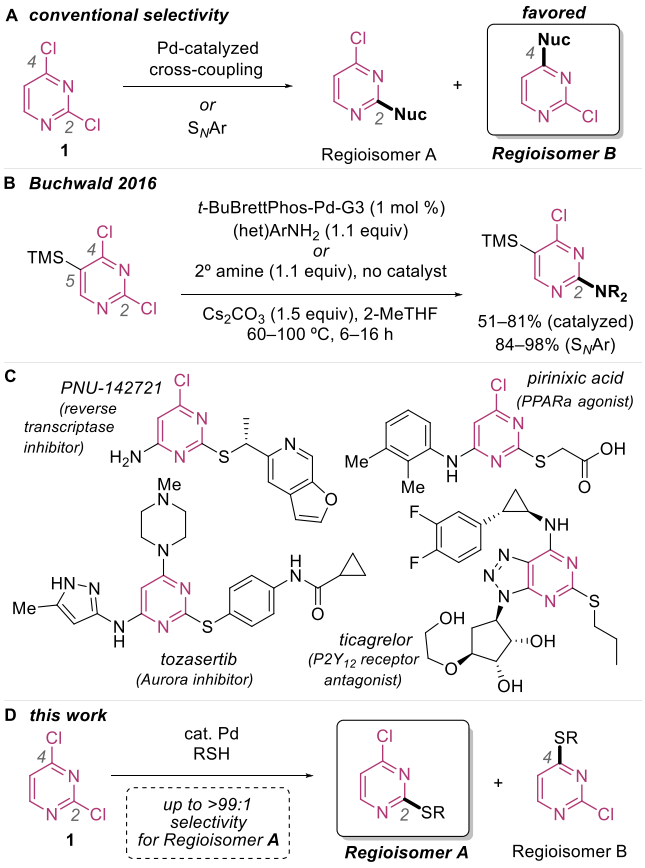
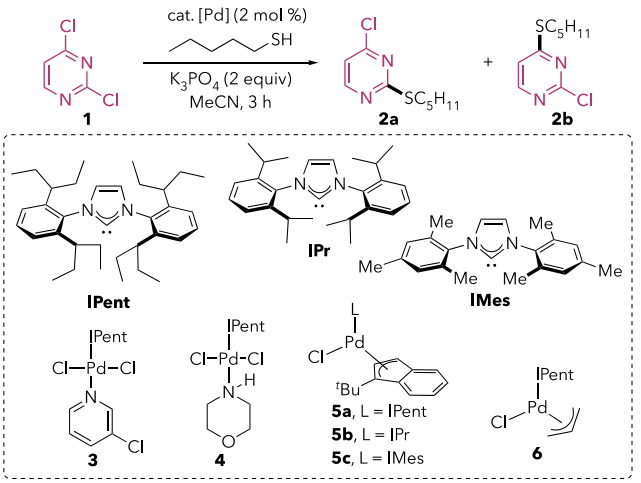


Table 1. Optimization of a C2-Selective Cross-Coupling of 2,4-Dichloropyrimidine[a]



entry	cat.	temp	2a + 2b (%)	2a:2b
1	none	r.t.	82	1:7
2	**3**	r.t.	70	1:22
3	**4**	r.t.	71	1:2
4	**5a**	r.t.	62	14:1
5	**6**	r.t.	50	>99:1
6	**5a**	0 °C	90	>99:1
7	**6**	0 °C	73	77:1
8	none	0 °C	51	1:6
9	**5b**	0 °C	86	25:1
10	**5c**	0 °C	61	3:1

[a]% Product yields and ratios determined by ^{1}H NMR spectroscopy of the crude reaction mixture using mesitylene as an internal standard.

C–S coupling conditions,[17d] which may be relevant to the difference in selectivity between these two precatalysts.

Remarkably, switching to precatalysts ***5a*** *or* ***6****, supported by t-Bu-indenyl*[19] *or allyl ligands,*[20] *led to a complete reversal of selectivity (entries 4–5).* The contrast between **5a**/**6** and the other Pd-IPent precatalysts **3** and **4** is notable, considering that they are all expected to generate 12e^- Pd^0(IPent) as the active catalyst.[21] The selectivity with commercial precatalyst **5a** was further improved by running the reaction at 0 °C, affording almost exclusive selectivity for C2-functionalized product **2a** (entry 6). This temperature effect may be partially due to suppression of background S_NAr, as the Pd-free control reaction is somewhat slower at 0 °C (compare entry 8 with entry 1). *t*-Bu-indenyl precatalysts bearing the smaller NHC ligands IPr and IMes (**5b** and **5c**) also promote unconventional selectivity at C2 (entries 9–10), but the preference is weaker and appears correlated with ligand sterics, where C2 selectivity follows the trend IPent > IPr > IMes. Product **2a** remains the major product in other polar solvents, but **2b** is favored in ethereal solvents (see Table S2).

With **5a** identified as the optimal catalyst based on its selectivity and commercial availability, the scope of this reaction was examined (Figure 1). With other 1° thiols (**7a**-**23a**), high selectivity is maintained in most cases. Esters, amides, and alcohols are tolerated on the thiol reagent (**9a**-**11a**, **13a**-**15a**, and **23a**). These functional groups can be sensitive to $POCl_3$, a chlorinating reagent that would typically be used to install a chloride at the 4-position after constructing the thioether at C2.[22] Synthetically useful, albeit much lower, C2-selectivity was also observed with 2° thiols (**24a**-**26a**), though selectivity was sometimes variable across reaction trials especially on small scales.[23] Notably, for these more hindered thiols, room temperature conditions tended to afford selectivities better than those at 0 °C. A tertiary thiol gave C4-selectivity (**42b**) in a ratio similar to the catalyst-free control, which could indicate that **42b** arises from S_NAr and not from catalysis.

Electron-rich, -neutral, and moderately electron-deficient thiophenols are also effective coupling partners (**27a**-**33a**). An aryl chloride and even an aryl bromide was tolerated on the thiol coupling partner (**32a** and **33a**). However, the reaction favors C4 coupling with a very electron-deficient thiophenol (**43b**). In this case, selectivity mirrors that of the catalyst-free reaction. The increased acidity of an electron-poor thiophenol would lead to a higher concentration of thiolate anion, which may allow S_NAr to outcompete catalysis. Interestingly, it was necessary to change the base to KF and to increase the reaction temperature to 50–80 °C to get high conversion and C2-selectivity with thiophenol reagents (Table S3).

Dibromo- and diiodopyrimidines also react preferentially at C2 (**39a**, **40a**). Unexpectedly, the dibromopyrimidine is less selective than either the dichloro or diiodo analog. Moderate to high C2-selectivity is upheld for a range of substituted 2,4-dichloropyrimidines (**34a**-**38a**). A substrate bearing a bulky C5-substituent[11] gives exclusive C2-selectivity (**38a**), even though the corresponding catalyst-free S_NAr reaction slightly favors C4 (see p. S23). However, the 5-amino analogue of **1** led to exclusive reaction at C4 (**41b**) under both catalytic and catalyst-free conditions. Furthermore, a very electron-deficient pyrimidine, which should be highly activated toward S_NAr, also

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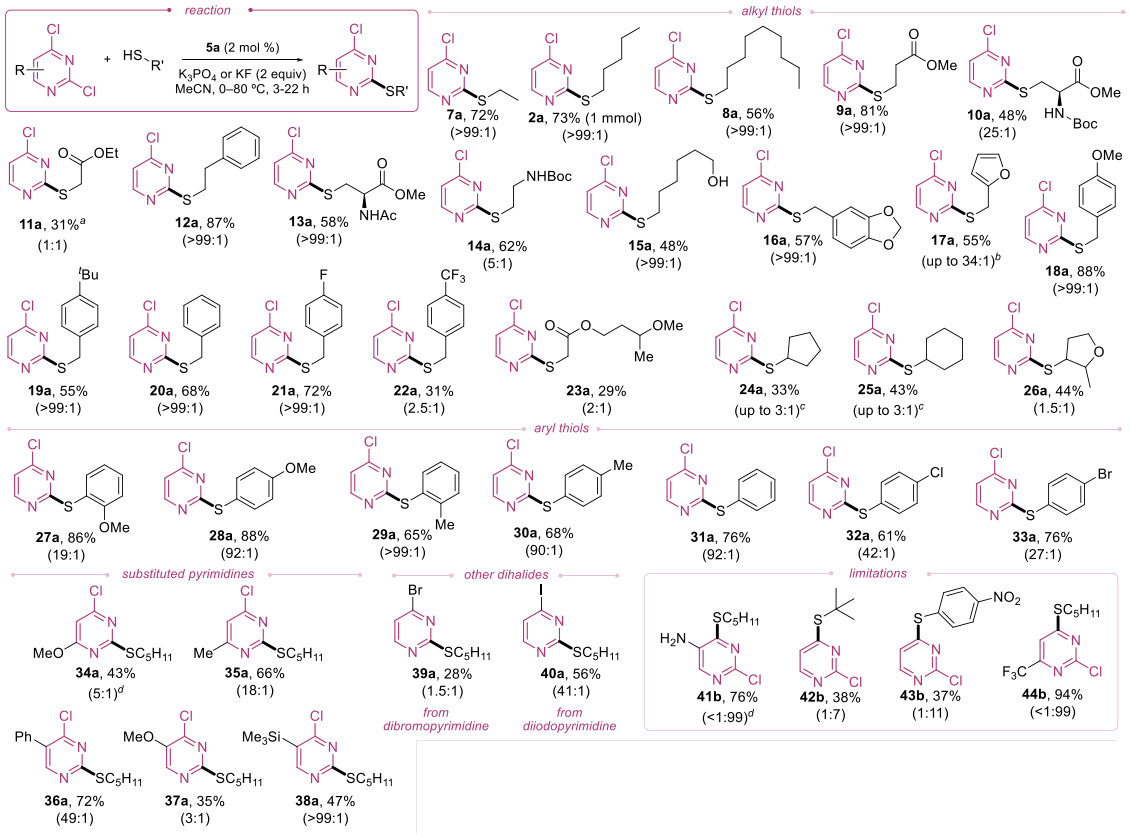
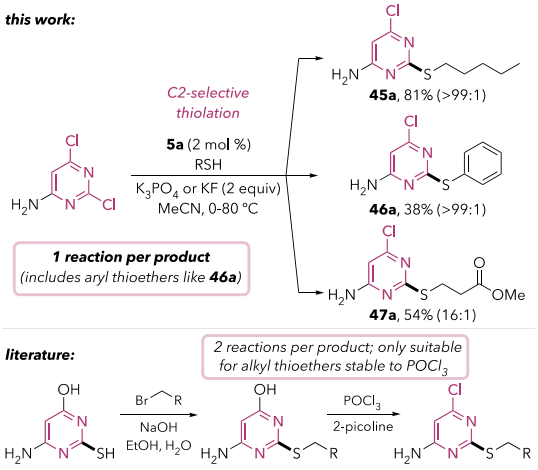


Figure 1. Scope of C2-selective thiolation. Isolated yields of the indicated regioisomer. Ratios represent C2:C4-functionalized products prior to purification based on ^{1}H NMR analysis of the crude reaction. [a]Calculated isolated yield adjusted to account for ~96% purity (isolated product is contaminated by a small amount of C4-functionalized product). Variable selectivity was observed on smaller scale trials with certain thiols: [b]Selectivity as low as 3:1 was observed on a smaller scale. [c]Selectivity as low as 1:3 was observed on a smaller scale. [d]The catalyst-free control (S_NAr) favors the same regiosomer.

gave exclusive C4-selectivity identical to that observed under catalyst-free conditions (**44b**).

To demonstrate the utility of this C2-selective thiolation for divergent synthesis, the reaction was applied toward the preparation of analogues of PNU-142721, a reverse transcriptase inhibitor (Scheme 2).[22,24] 6-Amino-2,4-dichloropyrimidine was compared to the previously reported synthetic methods; the C2-selective thiolation chemistry enables shorter divergent syntheses that avoid the use of $POCl_3$ and enable access to a broader scope of thioethers (Scheme 2).[22,25]

Scheme 2. Divergent Synthesis of Analogues of a Reverse Transcriptase Inhibitor (PNU-142721)



The mechanistic origin of the unusual selectivity afforded by Pd/NHC precatalysts such as **5a** is unclear and is a topic of ongoing study in our lab. We have previously shown that bulky NHC ligands enable inversion of conventional site selectivity in C−C cross-couplings of dichloroheteroarenes **48** and **49** (Figure 2A).[18] The ligand-controlled divergent selectivity with those substrates apparently hinges on the complementary influences of bond strengths and frontier molecular orbital coefficients. With bulky NHC ligands, unconventional selectivity for reaction at the C−Cl bond distal to nitrogen in **48** and **49** is attributed to oxidative addition at monoligated 12e^- PdL. PdL is biased toward reaction at the site with the larger LUMO coefficient (distal to nitrogen for these substrates), due to its preferred oxidative addition mechanism (LUMO pictures in Figure 2A, bottom).[18b,26,27] On the other hand, the site selectivity of bisligated 14e^- PdL_2 tends to trend with bond strength, and conventional selectivity for the weaker C−Cl bond proximal to nitrogen is seen when oxidative addition takes place at 14e^- PdL_2 (BDEs[28] in Figure 2A, top). However, 2,4-dichloropyrimidine **1** does not fit the pattern of **48** and **49**. For substrate **1**, C−Cl bond strengths and LUMO coefficients both favor reaction at the same site (C4), suggesting that both 14e^- and 12e^- Pd would favor the conventional C4 site.

Indeed, DFT calculations indicate that both PdL (L = IPr) and $[Pd(L)(L')]^-$ (L = IPr, L' = SMe) should prefer to insert

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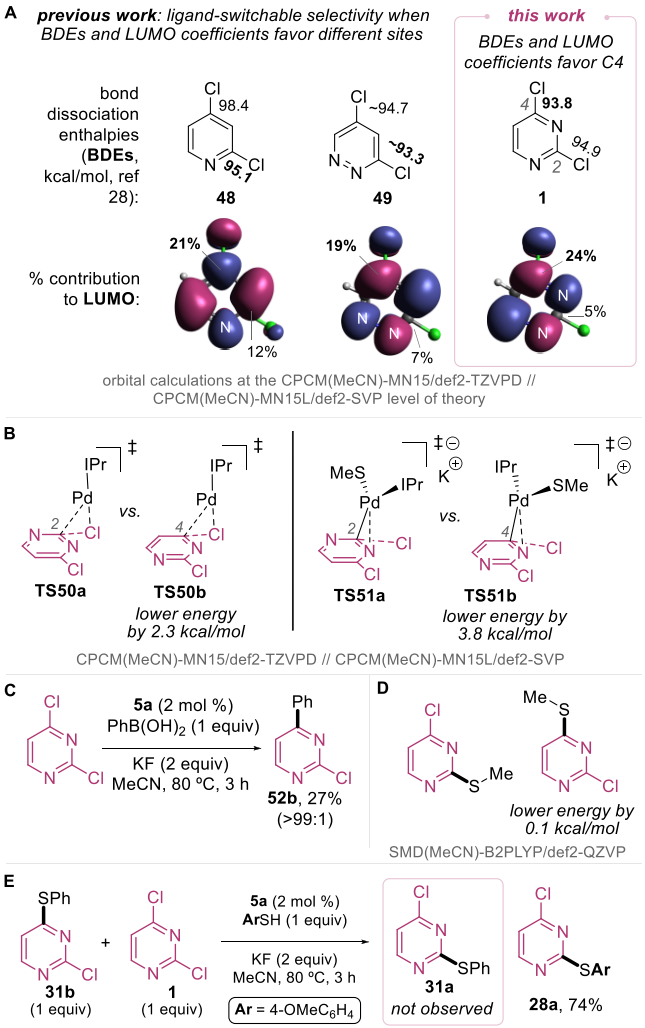

Figure 2. (A) For heteroarenes **48** and **49**, 14e^- Pd favors the site with the weaker C−Cl bond, while 12e^- Pd favors the site with the larger LUMO coefficient. For pyrimidine **1**, both factors favor the same site (C4); (B) DFT calculations suggest that both 12e^- and 14e^- Pd should favor oxidative addition at C4; (C) a Suzuki coupling under conditions analogous to the thiolation reaction favors C4; (D) a C2-functionalized product is not thermodynamically favored based on DFT calculations; (E) C−S coupling is not reversible.

into C4—Cl (Figure 2B, compare **TS50a** with **TS50b** and compare **TS51a** with **TS51b**). This prediction is inconsistent with our experimental results using precatalyst **5a**, although it is consistent with the large body of prior literature describing C4-selective cross-coupling. It appears that the thiol itself is significant to the unique C2 selectivity: a Suzuki cross-coupling using analogous conditions minus the thiol affords a C4-arylated product (Figure 2C). However, the addition of thiophenol to the Suzuki reaction in Figure 2C does not alter the selectivity of arylation (see page S34).

We find no evidence to suggest that the reaction is under thermodynamic control, even under the high-temperature conditions optimized for coupling with aryl thiols. A C2 product is not predicted to be more stable than a C4-substituted regioisomer (Figure 2D). Furthermore, resubjecting C4-coupled products such as **31b** to the catalytic reaction conditions did not result in any isomerization to C2-coupled product **31a**, even in the presence of a chloride source such as **1** (Figure 2E; see also pages S34−S41).

Experimentally evaluating the reversibility of the individual C−Cl oxidative addition step is challenging, in part because Pd(II)(NHC)Ar complexes are generally not isolable.[29,30] However, DFT calculations indicate that C−Cl oxidative addition through transition structures **TS50** or **TS51** should be highly exergonic and thus not reversible at 0 °C ($\Delta G^{\ddagger}$ for C−Cl reductive elimination >30 kcal/mol, see Figures S7 and S8). Thus, it appears that C2-selectivity in the C−S coupling may involve a nontraditional mechanism for C−Cl cleavage.

In summary, we report the first example of the C2-selective cross-coupling of 2,4-dichloropyrimidines that does not rely on substrate control. Palladium complexes containing the IPent ligand are optimal for promoting C2-selectivity, although the selectivity is highly dependent on the structure of the Pd^{II} precatalyst. The C2-selectivity is general for many thiols and substituted 2,4-dihalopyrimidines, but sterically hindered thiols and some substituted pyrimidines favor C4-coupling. In at least some of these cases, C4-selective S_NAr likely outcompetes the desired catalysis. Mechanistic investigation is ongoing, but preliminary studies indicate that the thiol coupling partner is an important element in C2-selectivity, and C−Cl cleavage under the catalytic thiolation conditions is unlikely to take place through a traditional oxidative addition mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c17020.

Experimental and computational details, materials, methods, NMR spectra, and characterization data including regiochemical assignments of products (PDF)

Cartesian coordinates of calculated structures (XYZ)

Accession Codes

Deposition Numbers 2385747−2385752 and 2385780−2385781 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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