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Rapid Access to Kinase Inhibitor Pharmacophores by Regioselective C−H Arylation of Thieno[2,3-*d*]pyrimidine

Shuya Yamada, Kaylin Nicole Flesch, Kei Murakami,* and Kenichiro Itami*

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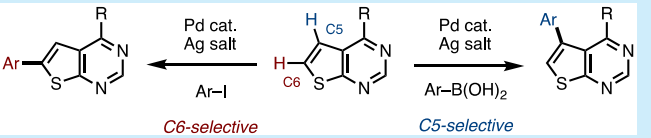
ABSTRACT: Regioselective C−H arylations of thieno[2,3-*d*]-pyrimidine are accomplished under palladium catalysis. Thieno-[2,3-*d*]pyrimidines react with aryl iodides at the C6-position and with aryl boronic acids at the C5-position, showing excellent regioselectivity. Mechanistic investigations indicate that the regioselectivity is controlled by the nature of the palladium catalyst: the cationic palladium favorably arylates the C5-position. The utility of this direct arylation has been highlighted in the streamlined synthesis of kinase inhibitors and their derivatives.



Thieno[2,3-*d*]pyrimidine is one of the most attractive pharmacophores due to its structural similarity to the purine base.[1] This chemical characteristic allows thieno[2,3-*d*]pyrimidine derivatives to bind to the ATP-binding site (hinge region) in protein kinases by mimicking the ATP molecule. Because of the ATP-competitive ability, thieno[2,3-*d*]pyrimidines have gathered much interest as potent kinase inhibitors[2] that are potentially exploited in the development of therapeutic agents.[1c,d] While a number of synthetic derivatives have found versatile biological applications, aryl-substituted thieno[2,3-*d*]pyrimidines have become prominent because of their stability and structural diversity (Figure 1).[3] In addition to the importance of aryl thieno[2,3-*d*]pyrimidine as a promising motif in the field of drug discovery, these heterobiaryl compounds have distinctive biological activity toward animals and plants. Very recently, we discovered a series of bioactive aryl thieno[2,3-*d*]pyrimidines that distinctively affect plant stomatal development.[4] This discovery speaks well for the significance of aryl thieno[2,3-*d*]pyrimidine derivatives for biological study.

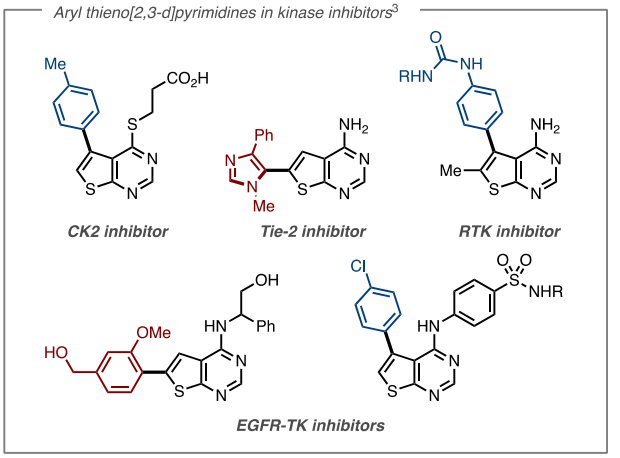


Figure 1. Examples of bioactive aryl thieno[2,3-*d*]pyrimidines.

Despite the prevalence of the aryl thieno[2,3-*d*]pyrimidine framework in bioactive molecules, their synthesis relies on multistep organic reactions (Figure 2a).[1,5] In contrast to the well-established role of benzo[*b*]thiophene in regioselective C−H arylation chemistry,[6,7] the structurally related thieno[2,3-*d*]pyrimidine remains a challenging substrate owing to the existence of electronegative and coordinating nitrogen atoms that decrease its reactivity.[8] Indeed, our early investigations revealed that the aforementioned C−H arylation reactions of benzo[*b*]thiophene[6,7] failed in the case of thieno[2,3-*d*]-pyrimidine (see Supporting Information). In some cases, thieno[2,3-*d*]pyrimidine strongly deactivated the catalysts. The significant yet difficult transformation of thieno[2,3-*d*]-pyrimidine motivated us to develop new regioselective arylation methodologies. Herein, we describe the first example of the palladium-catalyzed regioselective arylation of thieno-[2,3-*d*]pyrimidines (Figure 2b). The reaction selectively proceeds at the C6-position with an aryl iodide and at the C5-position with an aryl boronic acid under palladium catalysis.

To realize the desired arylation with precise control of both C5 and C6 regioselectivities, we optimized the reaction conditions by employing **1a** as a model substrate (Figure 3). After extensive screening (see Supporting Information), we found that the combination of $Pd(PPh_3)_4$/AgOAc and iodobenzene was suitable for C6-arylation, which afforded the corresponding product **2a** in 75% yield. Regarding the C5-

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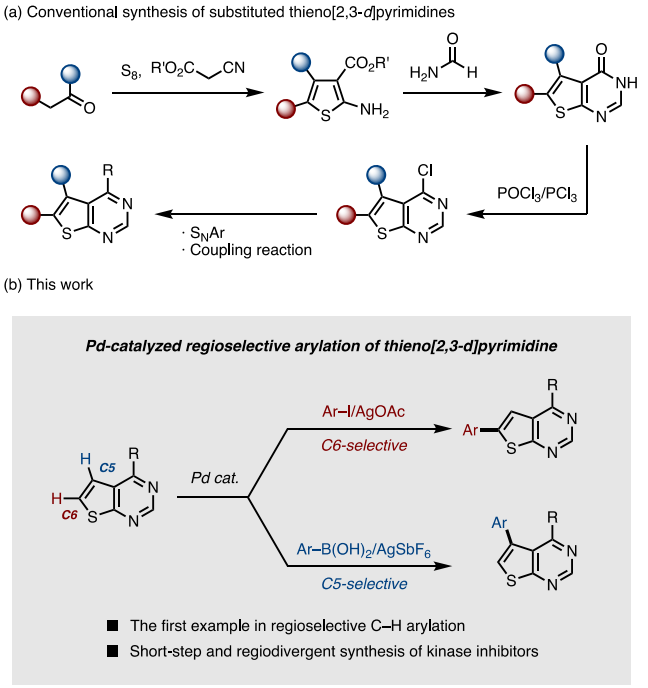


Figure 2. Synthesis of thieno[2,3-*d*]pyrimidines. (a) Multistep reactions. (b) The regioselective arylation method under palladium catalysis.

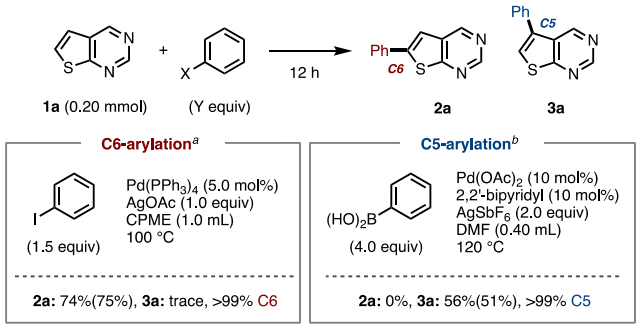


Figure 3. Optimal conditions. [a]NMR yield using 1,1,2,2-tetrachloroethane as the internal standard. [b]GC yield using dodecane as the internal standard. Yields shown in parentheses are isolated yields. CPME = cyclopentyl methyl ether. DMF = *N*,*N*-dimethylformamide.

selective arylation, the use of iodobenzene as an arylating agent gave disappointing results (poor selectivity). Gratifyingly, the oxidative coupling reaction with phenylboronic acid in the presence of $Pd(OAc)_2$/2,2′-bipyridyl/$AgSbF_6$ gave the desired product **3a** in 51% yield with exclusive selectivity. Having achieved the desired regioselectivities, we set the corresponding conditions as optimal.

The proposed catalytic cycles for both direct arylation reactions are shown in Figure 4. The C6-arylation is initiated by the oxidative addition of aryl iodide to palladium(0) species **A** to afford **B**. Transmetalation between **B** and aryl silver species **C**, which is generated from the reaction of **1** with AgOAc, gives intermediate **D**.[9] In the next step, reductive elimination furnishes the corresponding product **2** and regenerates **A**. The C5-arylation cycle begins with the generation of cationic palladium(II) **E** through oxidation by the Ag(I) salt and transmetalation with the arylboronic acid. Thieno[2,3-*d*]pyrimidine **1** can coordinate to this electrophilic **E** to form intermediate **F**. Then, a Heck-type carbopalladation

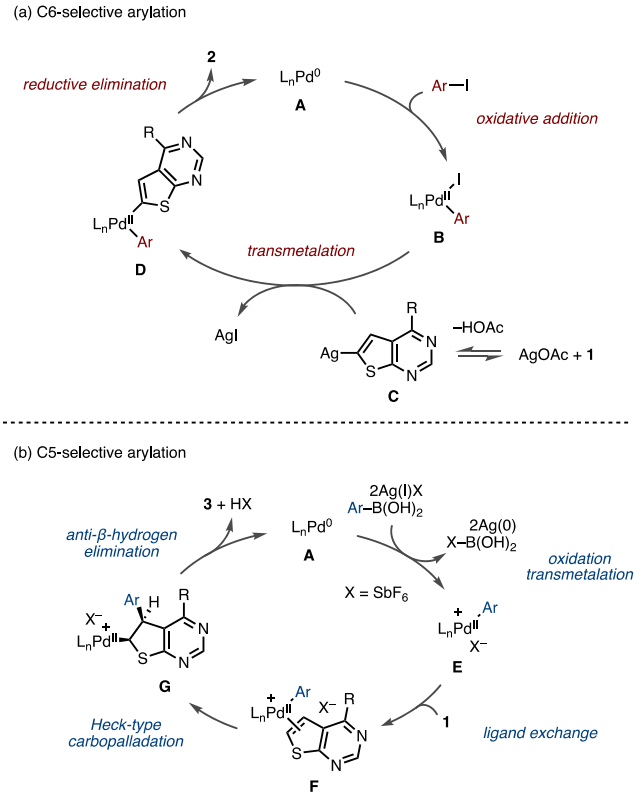
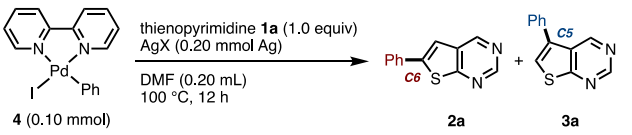


Figure 4. Proposed catalytic cycles for (a) the C6-selective arylation and (b) the C5-selective arylation.

step[7d,10] leads to intermediate **G**. Finally, *anti*-*β*-hydrogen elimination toward **3** completes the catalytic cycle.

To obtain mechanistic insights into the regioselectivity, we investigated the effect of silver(I) salts on the stoichiometric reaction of 2,2′-bipyridyl-coordinated PhPdI complex **4** with **1a** (Figure 5). When $AgSbF_6$, AgOTf, or $AgBF_4$ was utilized,



entry	AgX	2a(%)[a]	3a(%)[a]	C6/C5	pK_a value of HX[b]
1	$AgSbF_6$	0	23	>99% C5	–25
2	AgOTf	0	17	>99% C5	–14
3	$AgBF_4$	0	19	>99% C5	–0.44
4	Ag_2CO_3	4	4	50:50	3.6
5	AgOAc	48	10	83:17	4.76
6	Ag_2O	19	4	83:17	15.7

Figure 5. Silver(I) salt effect on the regioselectivity. [a]NMR yield using 1,1,2,2-tetrachloroethane as the internal standard. [b]Based on the Evans pK_a table[11] except $HSbF_6$[12] and HBF_4.[13]

significant C5-selectivity was observed (entries 1−3). The use of Ag_2CO_3 lowered the selectivity (C6/C5 = 50:50) (entry 4). The use of AgOAc and Ag_2O drastically shifted the selectivity toward C6, providing **2a** as the major product (entries 5 and 6). These outcomes suggest that the presence of a less basic counteranion such as SbF_6^- makes palladium more cationic, leading to C5 selectivity.[10a] The experimental results were consistent with the proposed mechanism.

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After establishing the regioselective catalysis, we turned our attention to the substrate scope under the C6-selective conditions. Coupling reactions of **1** with diverse aryl iodides were feasible, with good functional compatibility (Figure 6).

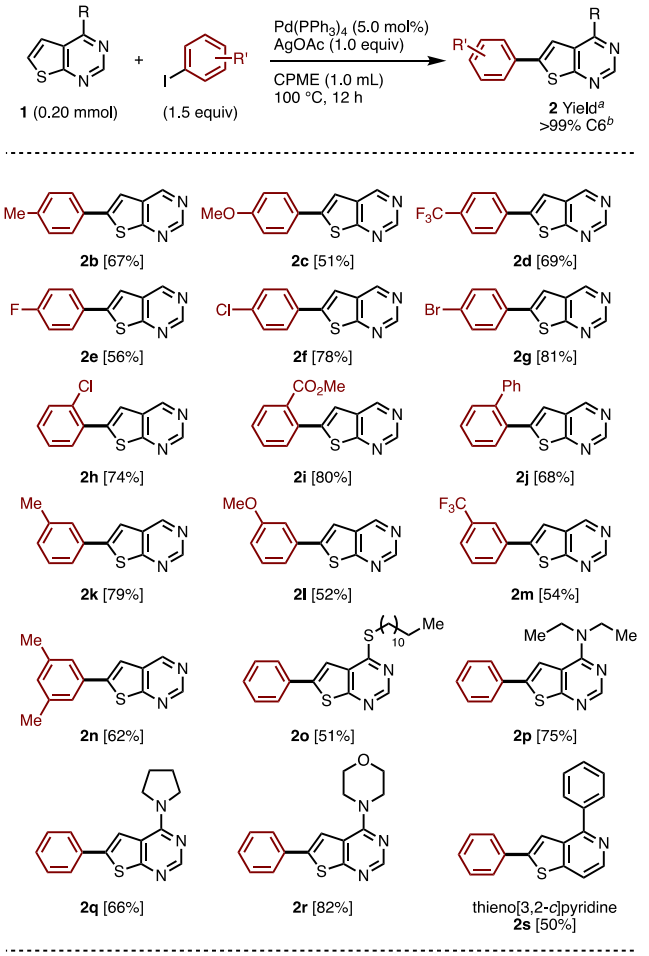

Figure 6. Substrate scope of C6-selective arylation of **1**. [a]Isolated yield. [b]Determined by ^{1}H NMR of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard.

Iodobenzenes with electron-donating groups at the *para*-position efficiently participated in the coupling reaction with **1a**, furnishing **2b** and **2c** in 67% and 51% yields, respectively. Electron-withdrawing groups, including halogens at the *para*-position, were also tolerated (**2d**–**g**), providing further chemical modification sites with traditional transition metal catalysis. Sterically demanding *ortho*-substituents (chloro, ester, and phenyl groups) did not inhibit the arylation (**2h**–**j**). *Meta*-substituted iodobenzenes reacted smoothly, regardless of their electronic properties (**2k**–**n**). Furthermore, the C6-selective catalysis was applied to hetero-substituted thieno[2,3-*d*]-pyrimidines, which are extensively studied as frameworks for anticancer agents.[3] The dodecylsulfanyl group at C4 remained intact, providing the target product **2o** in 51% yield. This reaction was also compatible with amino substituents to provide **2p**–**r** with excellent regioselectivity.[14] Arylation of thieno[3,2-*c*]pyridine, an attractive heterocycle in medicinal chemistry,[15] reacted to afford **2s** in 50% yield. Under the C6-selective conditions, the regioselectivity was not influenced by steric or electronic properties of the coupling agents. To illustrate the synthetic utility of the C6-arylation, we performed the short-step synthesis of the bioactive aryl thieno[2,3-*d*]pyrimidine **2u**, an EGFR-TK inhibitor.[3e,h] The synthesis was accomplished over 3 linear steps: (i) amination of commercial 4-chlorothieno[2,3-*d*]pyrimidine, (ii) C6-selective arylation with retention of the sensitive N–H bond, and (iii) subsequent reduction of two ester groups (Figure 7).

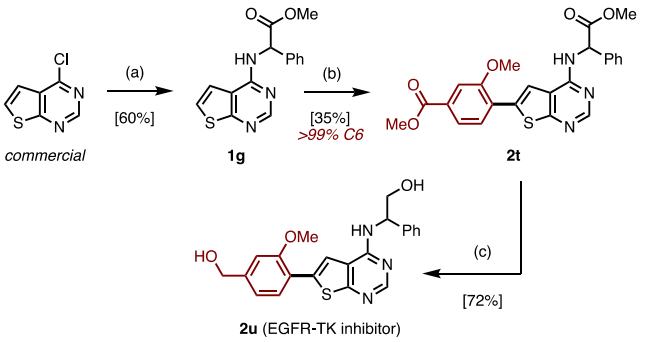

Figure 7. Synthesis of EGFR-TK inhibitor **2u**. (a) 4-Chlorothieno-[2,3-*d*]pyrimidine, 2-phenylglycine methyl ester hydrochloride, K_2CO_3, ^{i}PrOH, 80 °C. (b) Methyl 4-iodo-3-methoxybenzoate, $Pd(PPh_3)_4$, AgOAc, CPME, 100 °C. (c) $LiAlH_4$, THF, 0 °C.

Next, the scope of the C5-selective arylation was investigated (Figure 8). Notably, no C6-arylated regioisomers were detected in the crude mixtures of all reactions. Thieno[2,3-*d*]pyrimidines bearing an aryl group at C4 reacted with phenylboronic acid to give **3b**–**d** in moderate yields, regardless of the electronic properties of the C4-aryl groups. The electron-rich morpholine-substituted thieno[2,3-*d*]pyrimidine

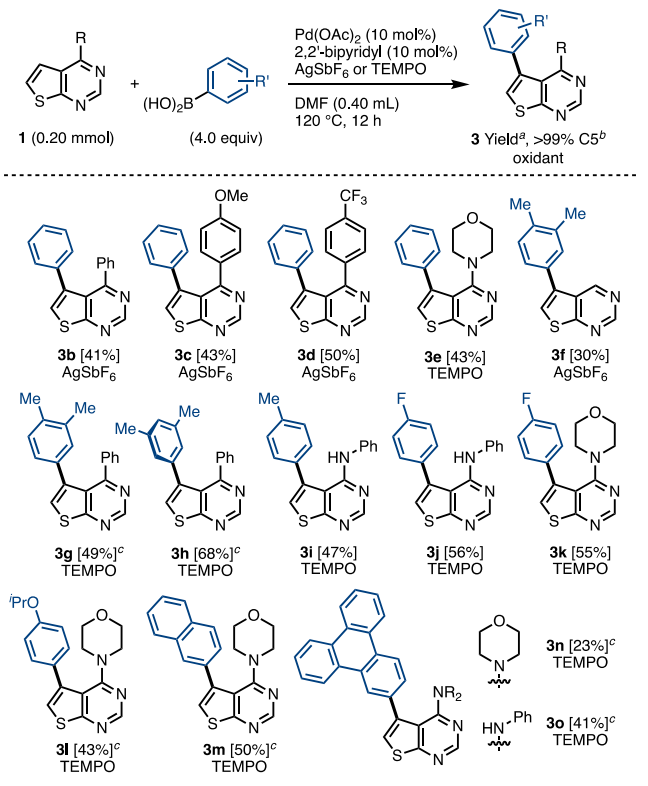

Figure 8. Substrate scope of C6-selective arylation of **1**. [a]Isolated yield. [b]Determined by ^{1}H NMR of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard. [c]18 h.

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1e decomposed under the reaction conditions. Oxidant rescreening revealed that 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)[7b] suppressed substrate decomposition (**3e**). A range of arylboronic acids were then evaluated. The reactions of **1a** or **1h** with dimethylphenylboronic acids furnished the corresponding products (**3f–h**). Substituents at the *para*-position, such as methyl, fluoro, and alkoxy groups, were well tolerated in the reaction with amino-substituted thieno[2,3-*d*]pyrimidines (**3i–3l**). Coupling reactions with extended aromatic systems such as naphthalene or triphenylene groups proceeded to give the target compounds (**3m–3o**). Overall, the reaction successfully inserts versatile aryl units into thieno[2,3-*d*]pyrimidines in a regioselective manner.

To emphasize the synthetic value of direct arylation, we performed the regiodivergent syntheses of a CK2 inhibitor NHTP25 **3q** and its regioisomer **2w**,[3i] employing **1l** as the common starting material. Satisfyingly, C6- and C5-selective arylations of **1l** and subsequent hydrolysis of the ester proceeded smoothly to afford the desired products (Figure 9). Thus, the developed catalysis is more beneficial than the conventional preparation methods and thereby will be a powerful tool in drug discovery.

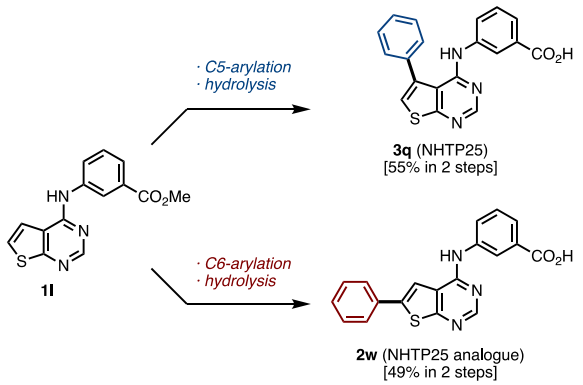

Figure 9. Divergent synthesis of CK2 inhibitors (the detailed reaction conditions are described in the Supporting Information).

In summary, the first regioselective arylations of thieno[2,3-*d*]pyrimidine under palladium catalysis were achieved. Both C6- and C5-selective arylations showed remarkable regioselectivities and a broad substrate scope. This protocol was successfully applied to the short-step preparation of EGFR-TK inhibitor **2u**. The synthetic utility was highlighted by the regiodivergent access to aryl thieno[2,3-*d*]pyrimidines **3p** (NHTP25) and **2w**, which show CK2 inhibitory potency. The installation of aryl groups into the original pharmacophore scaffolds has a potential to dramatically alter their biological activities.[16] For this reason, the rapid synthesis of aryl thieno[2,3-*d*]pyrimidine derivatives with our C–H arylations will be beneficial not only for the target-oriented synthesis but also for the divergent-oriented synthesis to construct a series of novel bioactive candidates. Biological assay of the synthesized aryl thieno[2,3-*d*]pyrimidines is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00143.

Detailed experimental procedures and spectral data for all compounds, including scanned image of ^{1}H, ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Kei Murakami – *Institute of Transformative Bio-Molecules (WPI-ITbM) and Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan*; orcid.org/0000-0001-5405-3069; Email: murakami@chem.nagoya-u.ac.jp

Kenichiro Itami – *Institute of Transformative Bio-Molecules (WPI-ITbM) and Graduate School of Science and JST, ERATO, Itami Molecular Nanocarbon Project, Nagoya University, Chikusa, Nagoya 464-8602, Japan*; orcid.org/0000-0001-5227-7894; Email: itami@chem.nagoya-u.ac.jp

Authors

Shuya Yamada – *Institute of Transformative Bio-Molecules (WPI-ITbM) and Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan*

Kaylin Nicole Flesch – *Institute of Transformative Bio-Molecules (WPI-ITbM) and Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00143

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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