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Regioselective synthesis of benzimidazole thiophene inhibitors of polo-like kinase 1

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ABSTRACT

A regioselective synthesis of novel 1-(2-thienyl)-benzimidazole inhibitors of polo-like kinase 1 is described. Amination of substituted 2-iodo or -bromo nitrobenzenes with a 2-aminothiophene derivative catalyzed by Pd_2dba_3 and XANTPHOS in the presence of excess Cs_2CO_3 afforded good yields of the coupled products. Subsequent reduction and cyclization of these intermediates provided the desired benzimidazole compounds.

Polo-like kinase (PLK) belongs to a family of highly conserved serine/threonine kinases that regulate multiple critical processes during mitosis.[1] The unique role of PLK in the cell cycle has prompted the pharmaceutical industry to explore development of small molecule inhibitors of PLK as a therapy for the treatment of cancer.[2,3] Recently, we have discovered a novel class of inhibitors of the polo-like kinase 1 (PLK1) represented by the generic structure **1** (Fig. 1).[4]

A key challenge surrounding these compounds has been their efficient synthesis. Our original synthetic route involved a non-regioselective addition of a substituted benzimidazole **2** to the enone **3** (Scheme 1).[4b,5] In the early stages of our lead optimization program, this methodology offered a facile entry into 1-(2-thienyl)-benzimidazoles necessary for a rapid build-up of structure-activity relationships around the benzimidazole core. As we became interested in specific substitution patterns, however, we required a more efficient route to specific regioisomers. Herein, we report a convenient solution to this regiochemical problem utilizing a palladium-catalyzed amination reaction.

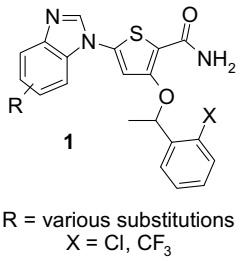
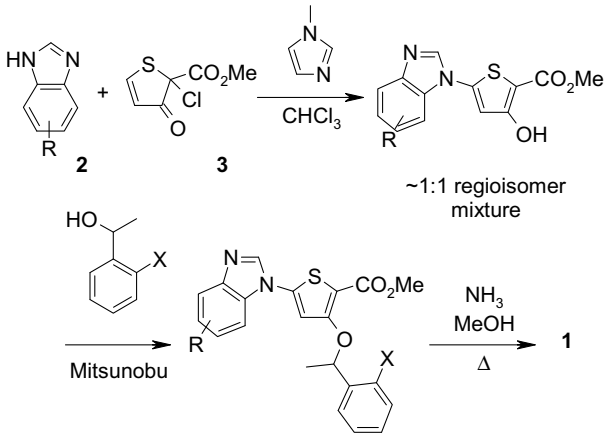


Figure 1. Generic structure of PLK1 inhibitors.



Scheme 1. Non-regioselective route to compounds of structure **1**.

In seeking a solution to this regiochemical impasse, we focused on N-substituted 2-nitroanilines such as **4** as the immediate synthetic precursors to the ultimate benzimidazole targets. In this system, the two nitrogen atoms are differentiated by oxidation state

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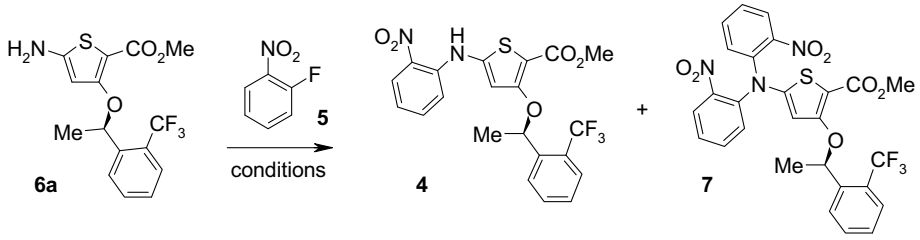
(and thus nucleophilicity), providing a viable solution to the problem of regioselectivity. The subsequent reduction and cyclization of substituted 2-nitroanilines to the corresponding benzimidazoles are well-precedented;[6] these operations may also conveniently be carried out in a one-pot transformation.[7] The most straightforward route to **4** would entail conjugate addition of a nitroaniline to the enone **3**. In practice, however, such reactions gave no products under a variety of conditions (data not shown), presumably due to the poor nucleophilicity of nitroanilines. We then attempted to form the key aniline bond via a nucleophilic aromatic substitution (S_NAr) reaction of 2-fluoronitrobenzene (**5**) with 2-aminothiophene **6a**[8] (Table 1). Unfortunately, this model reaction proceeded inefficiently under a variety of conditions, giving at best only 34% isolated yield of **4** (Entry 7). The frequently observed side product **7** (arising via addtion of **4**–**5**) further complicated the reaction profile.

Reasoning that perhaps the poor nucleophilicity of **6a** was the culprit in this transformation, we next explored a variety of Pd- and Cu-catalyzed aminations between **6a** and 2-iodonitrobenzene **8** (Table 2).[9] The combination of a Pd_2dba_3 catalyst and XANTPHOS ligand, previously utilized in a single instance for an aminothiophene substrate,[10] proved uniquely effective in catalyzing this process. In contrast to many published procedures, it was beneficial to run this particular reaction in the presence of 5 equiv of base (Cs_2CO_3) to obtain optimal yields (Table 2, compare entries 9 and 10). A full equivalent of base is likely consumed in the deprotona-

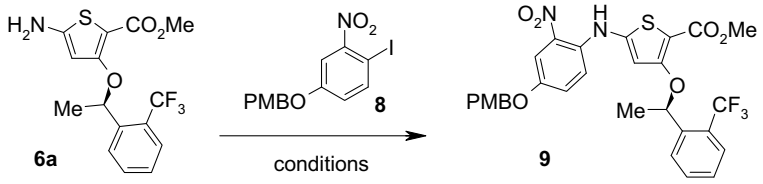
Table 1
S_NAr reaction between **5** and **6a**[a]



Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	**4** (%)	**7** (%)
1	K_2CO_3 (2.5)	MeCN	60	19	11	0
2	K_2CO_3 (2.0)[b]	DMSO	80	18	0	19
3	KHMDS (3.0)	THF	0 to rt	20	0	0
4	PS-TBD (2.5)	MeCN	60	19	0	0
5	LiOH (2.5)	DMF	60	19	0	20
6	LiOH (2.0)[b]	DMF	60	18	17	43
7	LiOH (5.1)	DMF	rt to 30	72	34[c]	0
8	*i*-Pr_2NEt	DMF	200[d]	10 min	0	0
9	DBU (2.0)[e]	neat	80[d]	1	0	0

[a] All reactions used 1 equiv of **6a**, 2.0 equiv of **5** at a substrate concentration of 0.1 M in the indicated solvent. All yields are isolated yields of the indicated products.
[b] 1.1 equiv. of **5.**
[c] 26% Recovered **6a**.
[d] Microwave heating.
[e] 1.0 equiv. of **5**.

Table 2
Optimization of Pd- or Cu-catalyzed amination of **8** with **6a**



Entry	Cat. (mol %)	L (mol %)	Solvent	Base (equiv)	Temp (°C)	Time (h)	Yield[a]
1	[b] (2)	None	PhMe	NaOMe/Et_3N (2.0/0.5)	60	22	<10
2	Pd_2dba_3 (2.5)	[c] (5)	PhMe	NaO*t*-Bu (2.4)	rt	26	19
3	$PdCl_2dppf$ (5)	dppf (15)	THF	NaO*t*-Bu (2.5)	100	26	0
4	Pd_2dba_3 (0.5)	[d] (2)	DME	K_3PO_4 (2.8)	80	18	0
5	Pd_2dba_3 (0.5)	[e] (2)	DME	K_3PO_4 (2.8)	80	18	0
6	Pd_2dba_3 (1)	X-Phos (8)	*t*-BuOH	K_2CO_3 (5.0)	80	16	19
7	$Pd(OAc)_2$ (3)	BINAP (4.5)	PhMe	Cs_2CO_3 (2.8)	100	17	0
8	$CuBr(PPh_3)_3$ (20)	None	PhMe	Cs_2CO_3 (3.0)	110	24	0
9	Pd_2dba_3 (2)	XANTPHOS (4.4)	1,4-Dioxane	Cs_2CO_3 (1.4)	60	18	59
10	Pd_2dba_3 (2)	XANTPHOS (4.4)	1,4-Dioxane	Cs_2CO_3 (5.0)	60	16.5	78

[a] Isolated yield.
[b] Acetato(2′-di-*t*-butylphosphino-1,1′-biphenyl-2-yl)palladium (II).
[c] 1,1′-Bis(di-*t*-butylphosphino)ferrocene.
[d] 2-(Dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl.
[e] 2-(Dicyclohexylphosphino)biphenyl.

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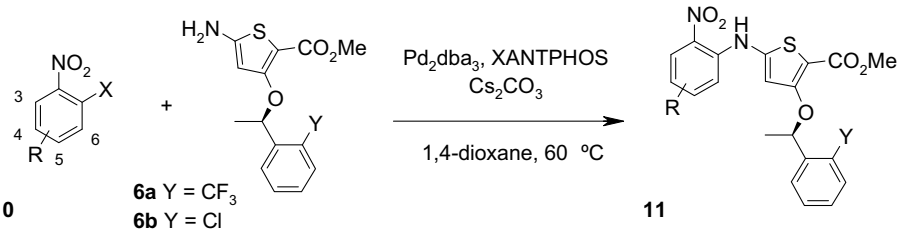
Table 3
Substrate scope of palladium-catalyzed amination between **6** and **10**[a]



Entry	R	X	Y	Time (h)	Product	Yield (%)
1	4-OPMB	I	CF_3	16.5	**11a**	78
2[b]	4-Br	Br	CF_3	1.75	**11b**	61
3[c]	4-CN	Cl	CF_3	24	**11c**	67
4	5-OPMB	Br	CF_3	24	**11d**	74
5	5-OCF_3	Br	CF_3	15.5	**11e**	79
6	5-$CH(OMe)_2$	Br	CF_3	18	**11f**	81
7	4-$O(CH_2)_2$TMS, 5-Cl	Br	Cl	20	**11g**	44
8	4-Br, 5-OPMB	Br	Cl	~18	**11h**	37
9	5-CH_2OPiv	OTf	CF_3	2	**11i**	dec
10	6-Me	Br	CF_3	24	**11j**	dec
11	3-Me	Br	CF_3	17	**11k**	dec

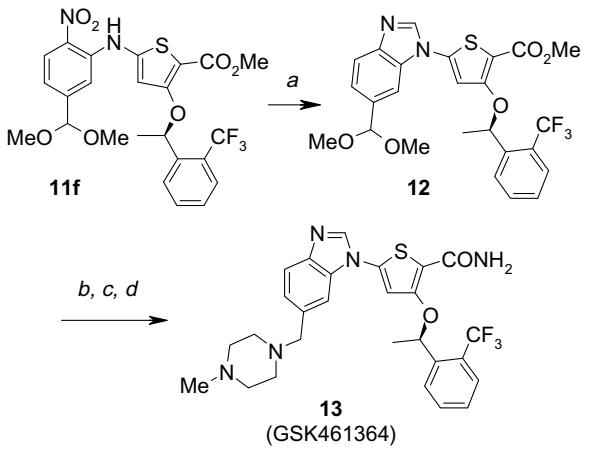
[a] Standard conditions: Pd_2dba_3 (2 mol %), XANTPHOS (4.4 mol %), **6** (1.05 equiv), **10** (1.0 equiv), Cs_2CO_3 (5.0 equiv), 1,4-dioxane (0.25 M concentration). All compounds had satisfactory ^{1}H NMR and HPLC/MS analyses.
[b] Toluene was used as solvent.
[c] 1.4 equiv Cs_2CO_3, 0.10 M concentration.

tion of **9**, whose aniline N–H has a substantially enhanced acidity due to the electron-withdrawing substitutions of and attachment to two aromatic rings.

With the optimal conditions now in hand, we explored the substrate scope of this process (Table 3).[11] A variety of coupling partners **10** reacted with **6** to provide the desired products **11** in good yields. Both electron-donating and electron-withdrawing substituents are tolerated (entries 1–5), as are alcohols and aldehydes suitably protected for further elaborations (entries 1, 4, 6–8). Substrates containing potentially labile protons (e.g., aldehydes, phenols, and amides) underwent extensive decomposition (data not shown). Aryl iodides and bromides are both useful coupling partners, and in one sufficiently electron-deficient case (entry 3), an aryl chloride could be used. Reaction with a triflate substrate (entry 9) was unsuccessful, presumably due to competitive hydrolysis of the triflate moiety by adventitious water present in the reaction medium. It was even possible to selectively couple a dibromo substrate (entries 2, 8) by taking advantage of the activating effects of the neighboring nitro group. Methyl substitution *ortho* to the halide (entry 10) was not tolerated, presumably due to increased steric hindrance. Interestingly, methyl substitution *ortho* to the nitro group (entry 11) was also not tolerated, leading instead to substrate decomposition.

The products listed in Table 3 could then be readily converted to the corresponding benzimidazoles. For example, **11f** was reduced and cyclized in one pot[7] to benzimidazole **12** by hydrogenation over sulfided platinum on carbon in trimethyl orthoformate (Scheme 2). Benzimidazole **12** was further transformed in three steps (acetal deprotection, reductive amination, and ester aminolysis) to amide **13** (GSK461364). Compound **13**, a potent, kinase- and PLK isoform-selective human PLK1 inhibitor with an IC_{50} of 3 nM, has been selected as a clinical candidate for the treatment of cancer.[4c]

In summary, we have developed an efficient method for the regioselective synthesis of 1-(2-thienyl)benzimidazoles via a palladium-catalyzed amination reaction.[12] The use of XANTPHOS as ligand was uniquely effective in this setting, showing a generality for this substrate class beyond a previously reported isolated



Scheme 2. Synthesis of **13** (GSK461364). Reagents and conditions: (a) H_2 (50 psi), Pt(S)/C (5 mol %), PPTS (10 mol %), $HC(OMe)_3$, rt, 3 h. (b) PPTS (10 mol %), acetone, water, rt, 2 h (58%, 2 steps). (c) *N*-methylpiperazine, AcOH, $Na(AcO)_3BH$, DCE, rt, 1.5–3 h (93%). (d) 7 N NH_3 in MeOH, sealed tube, 70 °C, 40–48 h (89%).

example.[10] The structure-activity relationships of the benzimidazoles **1** as PLK1 inhibitors, leading to the identification of **13** (GSK461364), will be the subject of further communications.

Supplementary data

Experimental procedures for the synthesis of aminothiophene **6** and substrates **10a**, **10d**, **10f–i**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.077.

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11. *Typical experimental procedure*: To an oven-dried round-bottomed flask under N_2 were added Pd_2dba_3 (3.7 mg, 0.0040 mmol), XANTPHOS (5.1 mg, 0.0088 mmol), aminothiophene **6a** (72 mg, 0.21 mmol), iodobenzene **8** (77 mg, 0.20 mmol), Cs_2CO_3 (326 mg, 1.00 mmol), and 1,4-dioxane (0.80 mL, degassed by sparging with N_2 for 1 h). The flask was evacuated and refilled with nitrogen (3×), then heated to 60 °C for 16.5 h. The reaction was then cooled to room temperature, diluted with THF (10 mL), filtered to remove solids (washing with another 10 mL THF), and concentrated. Purification by flash column chromatography (10–40% ethyl acetate/hexanes) afforded 94 mg (78%) of the coupled product **9** as a dark red foam, >95% HPLC/MS purity. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.42 (br s, 1H), 7.90 (d, 1H, J = 8.3 Hz), 7.72 (d, 1H, J = 3.0 Hz), 7.61 (m, 2H), 7.42–7.34 (m, 3H), 7.25 (d, 1H, J = 9.1 Hz), 7.12 (m, 1H), 6.93 (m, 2H), 6.35 (s, 1H), 5.71 (q, 1H, J = 6.2 Hz), 4.99 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 1.72 (d, 3H, J = 6.2 Hz); MS (ESI): 625.17 $[M+Na]^+$; HRMS (ESI) calcd for $C_{29}H_{26}F_3N_2O_7S$ $[M+H]^+$ 603.1413, found 603.1409.
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