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The First Catalytic Direct C–H Arylation on C2 and C3 of Thiophene Ring Applied to Thieno-Pyridines, -Pyrimidines and -Pyrazines

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Received: 13 March 2018; Accepted: 28 March 2018; Published: 30 March 2018

Abstract: A practical one-pot procedure for the preparation of diverse thieno[3,2-*d*]pyrimidines is reported here for the first time. This two-step process via C–H activation in position C-2 of thiophene led to the development of an improved methodology for the synthesis of numerous compounds. This new methodology is an efficient alternative to the conventional methods currently applied. The C–H activation of the thiophene C-3 position was also achieved and can be selective. The optimized conditions can also be applied to thienopyridines and thienopyrazines.

Keywords: C–H activation; regioselectivity; thienopyridines; thienopyrimidines; thienopyrazines

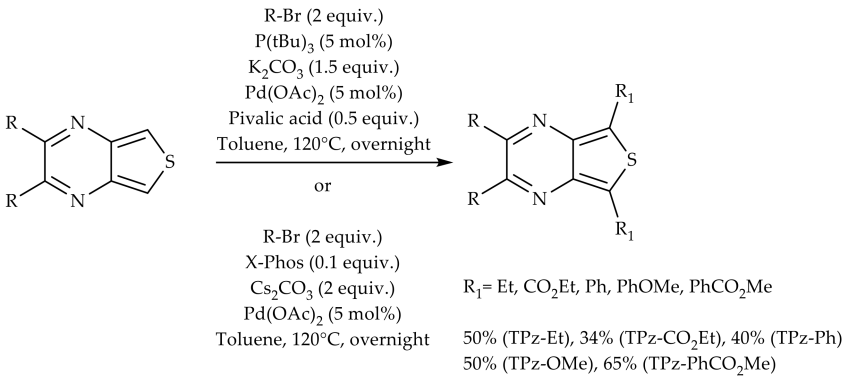
1. Introduction

The direct functionalization of C–H bonds in catalytic coupling reactions is considered to be a significant step to achieve molecular diversity and great progress has already been made in this field. Furthermore, environmentally benign, operationally simple, and robust reactions, particularly those employing heterogeneous catalysts, are of significant interest to the chemical industry. The direct palladium-catalyzed C–H activation of heteroaromatic compounds has recently been extensively studied. The main challenge of this approach is the control of regioselectivity with heterocyclic substrates containing multiple C–H bonds that may have similar reactivities [1–6]. Thienopyridines, thienopyrimidines, and thienopyrazines are sulfur-containing heterocyclic molecules that, when functionalized, are often incorporated into important molecular scaffolds used in materials science and in particular in biology and medicine [7]. To the best of our knowledge, however, no studies have yet been reported on the C–H activation of the thiophene ring in thieno[3,2-*b*]pyridines, thieno[3,2-*d*]pyrimidines, and thieno[2,3-*b*]pyrazines. The present study explores this topic.

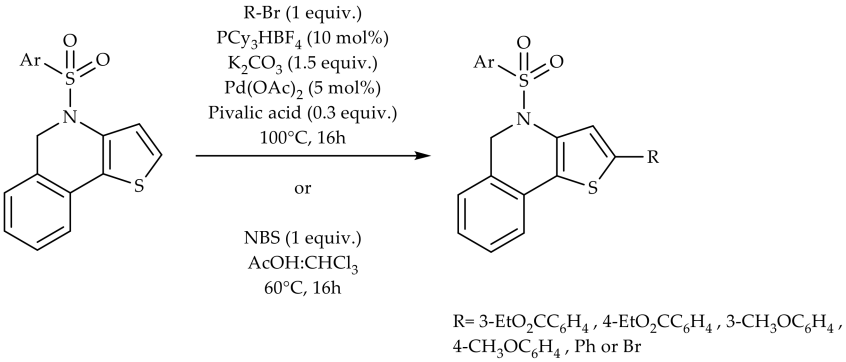
A study of the literature revealed that only three teams have worked on the C–H activation of thieno[3,4-*b*]pyrazine, 2,3-thienoisoquinolines, and 3,4-thienoisoquinolines (Schemes 1–3).

McNamara et al. [8] presented the synthesis of a series of thieno[3,4-*b*]pyrazine derivatives as fluorescent compounds through the direct palladium-catalyzed activation of the C–H bonds of thiophene using $Pd(OAc)_2$ with X-Phos or $PtBu_3$ as ligands. Moderate yields were achieved, with some variation depending on the reagents (Scheme 1).

In 2014, Chen et al. [9] developed a synthetic route on 2,3-thienoisoquinoline-phenylsulfamide which was successfully functionalized with phenyl, 3-$EtO_2CC_6H_4$, 4-$EtO_2CC_6H_4$, 3-$CH_3OC_6H_4$, and 4-$CH_3OC_6H_4$ bromides employing a C–H activation reaction on position 5 of the thiophene moiety. Yields ranged from 25% to 86% (Scheme 2).

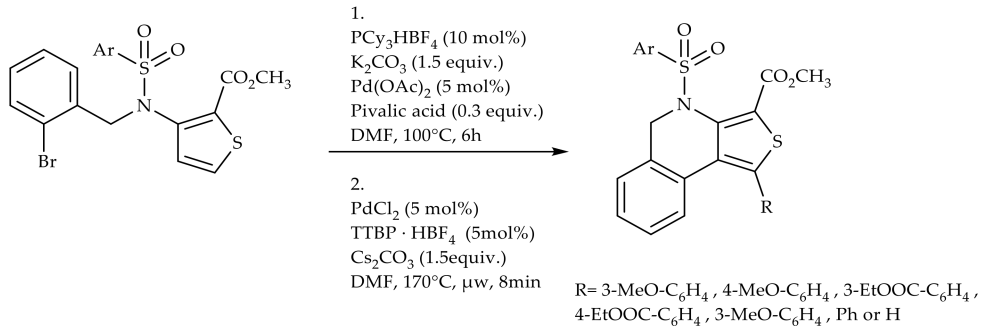


Scheme 1. McNamara et al.'s work (2016).



Scheme 2. Chen et al.'s work (2014).

Wong and Forngione [10] reported the synthesis of a unique class of highly functionalized 3,4-thienoisoquinolines via an efficient double C-H palladium-catalyzed one-pot activation using $Pd(OAc)_2$, PCy_3 HBF_4, PivOH, and K_2CO_3 in DMF at 100 °C for 6 h in good yields (Scheme 3).



Scheme 3. Wong and Forngione's work (2012).

2. Results and Discussion

Pursuing our previous work [11] on various annelated sulfur-containing heterocycles, where we investigated the functionalization of the C3 position of the thiophene ring in several thieno-pyridines, -pyrimidines, and -pyrazines (Figure 1) using C3-bromoderivatives and various boronic acids in optimized Suzuki conditions, we worked on a Pd-catalyzed direct arylation to generate diversity.

Herein we report our investigation of the development of efficient Pd-catalyzed direct arylation on position C-3 of the thiophene ring from the thieno-pyridines, -pyrimidines, and -pyrazines presented in Figure 1. In a first attempt, the thienoderivatives 1 and 4 were reacted using the conditions already described by our team for the Pd-catalyzed direct arylation of pyrazolo[1,5-*a*]pyrimidine [12].

Unfortunately, these conditions did not yield the expected products (Table 1). The thienoderivatives 1 and 4 in presence of 1.5 equivalent of 1-iodo-4-methoxybenzene, $Pd(OAc)_2$ (10% mol), $P(tBu)_3$ (20% mol), and cesium carbonate (2 equiv.) in toluene after 48 h at 110 °C led only to recovery of the starting material and no trace of the expected product was detected. The use of $P(Cy)_3HBF_4$ as ligand did not lead to any improvement even when the reaction time was increased up to 70 h (Scheme 4).

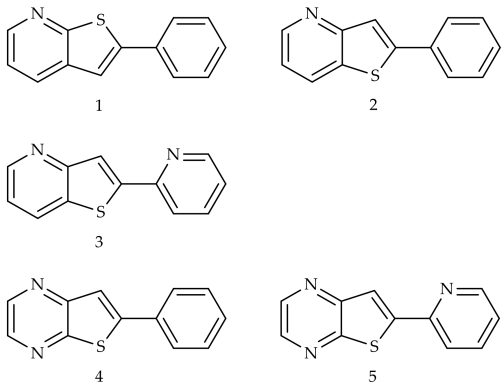


Figure 1. Thienopyridines and thienopyrazines used in first attempts of Pd-catalyzed direct arylation.

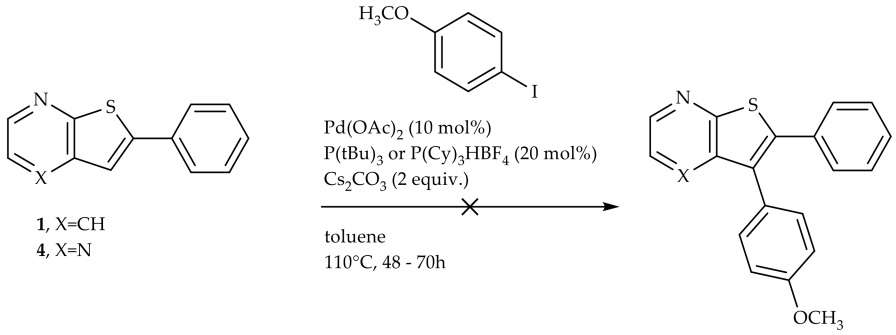
Table 1. Optimization of direct C–H arylation in position 3 of the 2-phenylthieno[3,2-*b*]pyridine **2.**

Entry	$Pd(OAc)_2$ (mol %)	Ligand (mol %)	Cu (equiv.)	Base (equiv.)	Solvent	Br–X (1 equiv.)	Time (h)	*T* (°C)	Yield [a] (%)
1	(10)	-	CuI (20)	K_2CO_3 (2)	Toluene	Bromo benzene	24	120	0
2	(10)	-	$Cu(OAc)_2$ (20)	K_2CO_3 (2)	Toluene	Bromo benzene	24	120	0
3	(10)	-	CuI (20)	KOAc (2)	Toluene	Bromo benzene	24	120	0
4	(10)	-	$Cu(OAc)_2$ (20)	KOAc (2)	Toluene	Bromo benzene	24	120	0
5	(5)	P(*t*-Bu)$_2$ $MeHBF_4$ (10)	-	K_2CO_3 (1)	DMA	Bromo benzene	24	120	7
6	(1)	P(*t*-Bu)$_2$ $MeHBF_4$ (3)	-	K_2CO_3 + AgOTf (0.2) + (0.1)	DMA	Bromo benzene	24	145	0
7	(5)	P(*t*-Bu)$_2$ $MeHBF_4$ (10)	-	K_2CO_3 (1)	DMA	1-bromo-4-methyl benzene	96	120	26
8	(5)	P(*t*-Bu)$_2$ $MeHBF_4$ (10)	-	K_2CO_3 (1)	DMA	1-bromo-4-(trifluoro methyl) benzene	96	120	20
9	(1)	-	-	KOAc (2)	DMA	Bromo aceto phenone	24	150	0

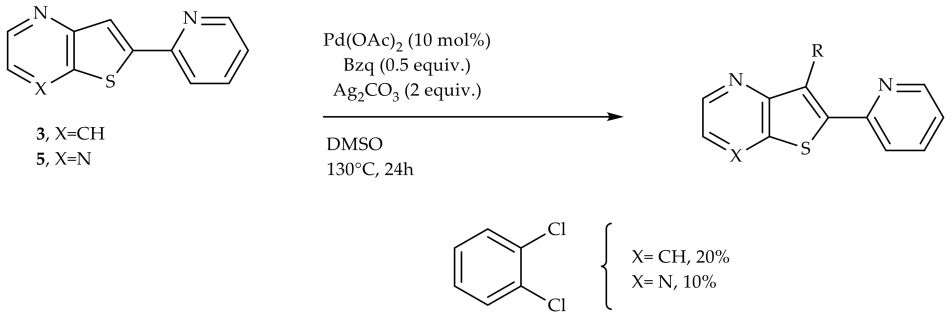
[a] Isolated yield after column chromatography.

Applying the conditions reported by Hull and Sanford [13] on thienoderivatives **3** and **5** was likewise unsuccessful. This methodology involves the direct oxidative coupling of two arene C–H substrates with a very large excess of one of them. The use of $Pd(OAc)_2$ in presence of Ag_2CO_3 as base and benzoquinone Bzq as oxidant in DMSO at 130 °C with 100 equivalents of 1,2-dichlorobenzene did not yield the expected compound after 16 h, and once

again only the starting material was recovered. After 24 h of reaction time 20% of the expected compound was obtained from 2-(pyridin-2-yl)thieno[3,2-*b*]pyridine **3** and 10% from 6-(pyridin-2-yl)thieno[2,3-*b*]pyrazine **5**. When 100 equivalents of 1,2-dimethoxybenzene, nitrobenzene, methoxybenzene, or 1,3-dimethoxy-2-nitrobenzene were used in the same conditions, only the starting material was recovered and no product was detected. Although the product was obtained with a very low yield in two cases, given the large quantity of one of the reagents that had to be used in this method, we made no further attempts to optimize the conditions in terms of time or other factors (Scheme 5).



Scheme 4. Pd-catalyzed direct arylation on position C-3 of the thiophene ring from the thieno-pyridines and -pyrazines.



Scheme 5. Results of conditions reported by Hull and Sanford on thienoderivatives.

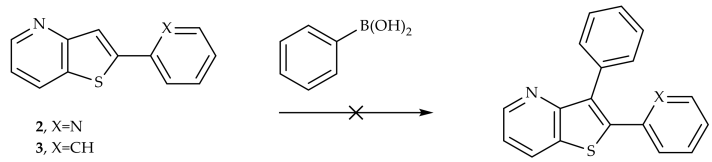
The work by Wei et al. [14] and Yang et al. [15] reported procedures for Pd-catalyzed direct arylation with aryl boronic acids which were applied to our thienoderivatives **2** and **3** using phenyl boronic acid but yet again, the reaction was unsuccessful (Scheme 6).

One of the other possible options was to use aryl bromides [16,17]. The 2-phenylthieno[3,2-*b*]pyridine **2** was chosen for these experiments and was reacted with various amounts of $Pd(OAc)_2$, K_2CO_3, or KOAc as base, with or without ligands in different solvents. The results are summarized in Table 1. In entries 1 to 4 copper was added as co-catalyst without any improvement, while in entries 5 to 8 P(*t*-Bu)$_2$MeHBF$_4$ was used as ligand with which the best yield was obtained (Table 1, Entry 7, yield 26%).

Despite several attempts, however, we did not manage to exceed a 26% yield. Using a different strategy, with 4-chlorothieno[3,2-*d*]pyrimidine **6** as starting material in the conditions reported by Hull and Sanford [13], also proved unsuccessful (Scheme 7).

To avoid a possible interaction of the chlorine atom in the Pd-catalyzed direct arylation (Scheme 7), it was substituted by various amines, generating a new series of potentially biologically active molecules. This new strategy is shown in Scheme 8. After adding one chain by SnAr, the scope

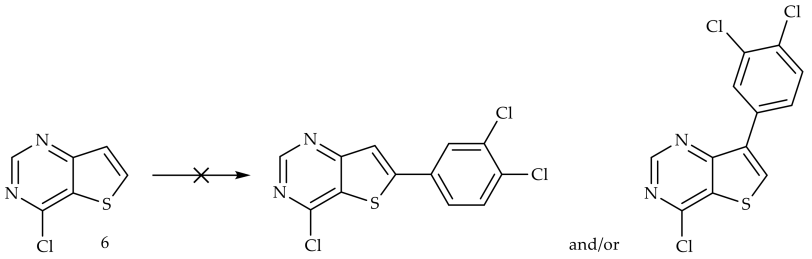
of the reactivity and regioselectivity of Pd-catalyzed direct arylation in positions 2 or 3 of the thiophene moiety was evaluated.



2, X=N
3, X=CH

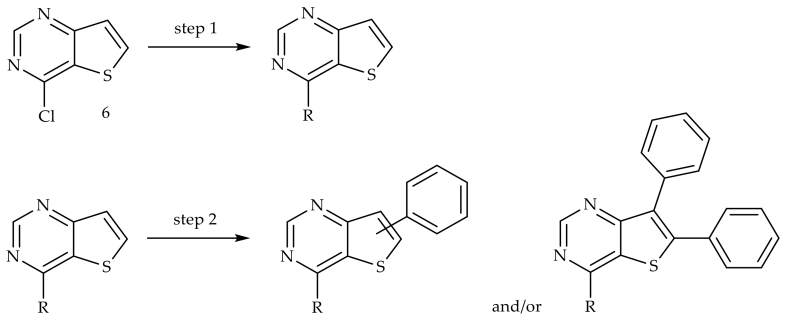
1) $Pd(OAc)_2$ (5 mol%), Ag_2CO_3 (2 equiv.), K_2CO_3 (0.5 equiv.), p-toluic acid (0.3 equiv.), DMA, 16h, 110 °C: no reaction
2) $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1 mol%), TFA, 63h, r.t.: no reaction
3) $Pd(OAc)_2$ (10 mol%), AcOH, 24h, r.t.: no reaction

Scheme 6. Results of conditions reported by Wei et al. and Yang et al. on thienoderivatives.



Conditions: $Pd(OAc)_2$ (10 mol%), Benzoquinone (0.5 equiv.), Ag_2CO_3 (2 equiv.), DMSO, 16h, 130ºC.

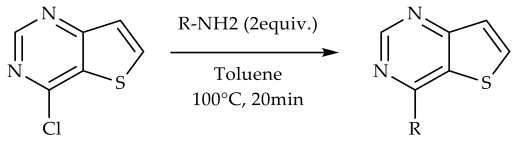
Scheme 7. C–H activation from 4-chlorothieno[3,2-*d*]pyrimidine using conditions reported by Hull and Sanford.



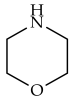
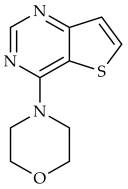
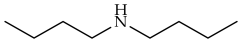
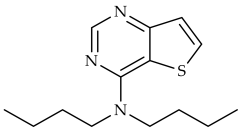
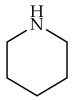
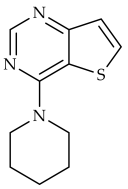
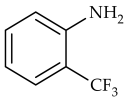
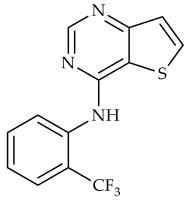
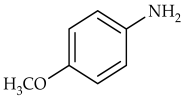
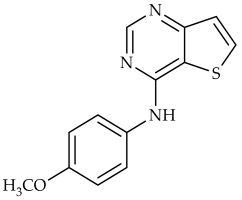
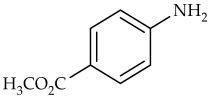
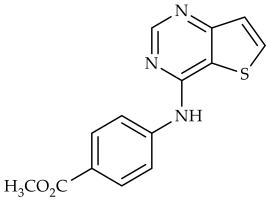
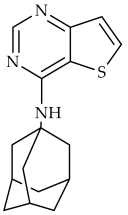
Scheme 8. New synthesis strategy.

Several strategies to conduct an SnAr reaction of 4-chlorothieno[3,2-*d*]pyrimidine using amino derivatives are reported in the literature [18–22]. With a view to developing procedures with the lowest possible environmental impact, we tested the use of PEG 400 as solvent. This compound, like the other heterocyclic scaffolds, underwent the SnAr reaction using amines and produced good yields in only 5 min [23], but our goal was to diversify our core structure by C–H activation which tried using Polyethylene glycol 400 as solvent without success in a one-pot process. We therefore decided, in the present work, to use toluene with various amines to generate precursors of C–H catalyzed cross-coupling. In these conditions all the expected substituted 4-amino-thieno[3,2-*d*]pyrimidine compounds were successfully synthesized in good yields of 60% to 96%. The lowest yield was obtained for the deactivated aniline substituted in the *ortho* position by the electro-withdrawing trifluoromethyl group (Table 2).

Table 2. SnAr substitution of chlorine on the six-membered ring by various amines.



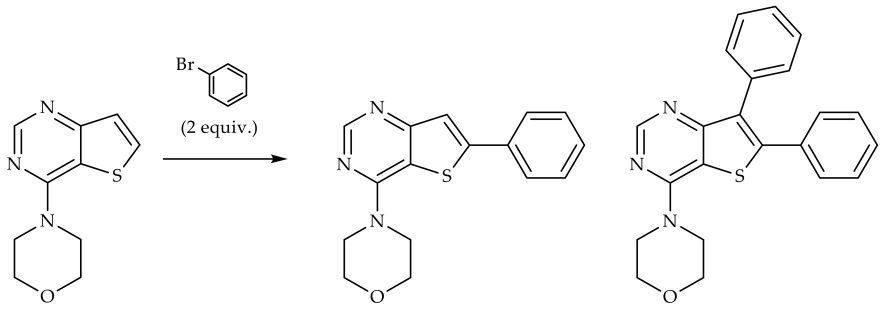
6

Entry	Amine Reagent	Product	Yield [a]
1			**7**, 86%
2			**8**, 96%
3			**9**, 82%
4			**10**, 60%
5			**11**, 86%
6			**12**, 67%
7			**13**, 68%

[a] Isolated yield after column chromatography.

Optimization of the Pd-catalyzed direct arylation and its regioselectivity in position C-2 was achieved starting from 4-(thieno[3,2-*d*]pyrimidin-4-yl)morpholine **7** using bromobenzene and by varying the amount of $Pd(OAc)_2$ with or without ligand, and the type and amount of K_2CO_3 or KOAc as base. Various solvents and temperatures were also tested, as summarized in Table 3.

Table 3. Optimization of the C–H activation with regioselectivity in position C-2 of 4-(thieno[3,2-*d*] pyrimidin-4-yl)morpholine **7.**



7 **14** **15**

Entry	Pd Catalyst (equiv.)	Ligand (mol %)	Base (equiv.)	Solvent	Time (h)	*T* (°C)	Yield [a] (%)	
							14	**15**
1	$Pd(OAc)_2$ (20%)	-	K_2CO_3 (4)	Toluene	46	140	64	31
2	$Pd(OAc)_2$ (10%)	PCy_3 (20)	K_2CO_3 (2)	Dioxane	46	130	50	44
3	$Pd(OAc)_2$ (10%)	TTBP · HBF_4 (20)	K_2CO_3 (2)	Toluene	46	130	81	9
4	$Pd(OAc)_2$ (10%)	Phenantroline (20)	K_3PO_4/K_2CO_3 (1)/(1)	DMA	46	140	22	0
5	$Pd(OAc)_2$/ Bu_4NBr (20%)/(2)	-	KOAc (6)	DMF	24	80	26	0
6	$Pd(OAc)_2$/ Bu_4NBr (20%)/(2)	-	KOAc (6)	Water	24	80	0	0
7	$Pd(OAc)_2$ (10%)	TTBP · HBF_4 (20)	K_2CO_3 (2)	Toluene	46	100	72	0

[a] Isolated yield after column chromatography.

The desired compound was obtained in moderate to good yields in presence of $Pd(OAc)_2$ with K_2CO_3 in toluene (Table 3, Entries 1 and 3) and the presence of ligand increased the regioselectivity (Table 3, Entries 3–4). When the reaction was performed in water no results were obtained and only the starting material was recovered (Table 3, entry 6). The temperature had a pronounced effect on regioselectivity: when 4-(thieno[3,2-*d*]pyrimidin-4-yl)morpholine was stirred using $Pd(OAc)_2$, TTBP · HBF_4 as ligand, K_2CO_3 in toluene at 100 °C, complete regioselectivity was obtained.

This process proved to be a good alternative to the most commonly used synthetic routes [24–29] (Figure 2).

Based on our results (Table 3, Entry 7) the scope and limitations of the one pot SnAr–Pd-catalyzed direct arylation on 4-chlorothieno[3,2-*d*]pyrimidine **6** were assessed using several bromo-benzenes (Table 4).

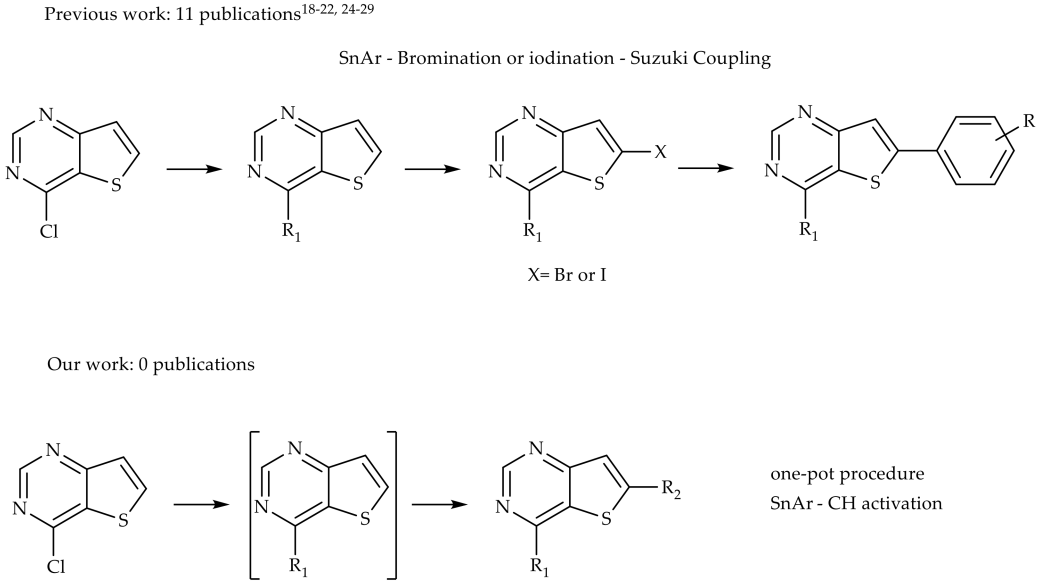
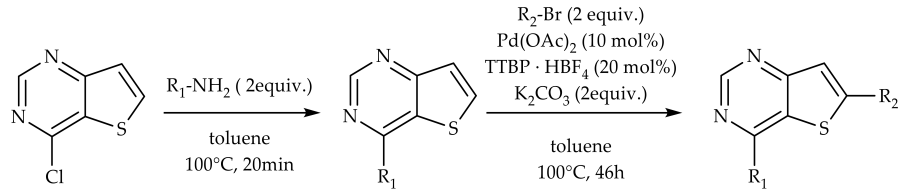


Figure 2. Literature and previous work.

Table 4. Scope and limitations of the one pot SnAr-Pd-catalyzed direct arylation from 4-chlorothieno [3,2-*d*]pyrimidine **6**.



6

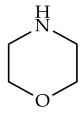
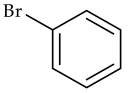
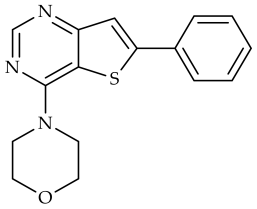
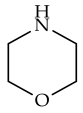
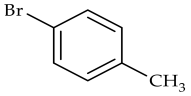
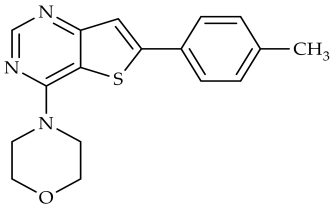
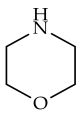
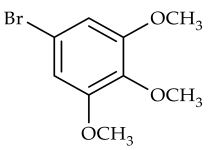
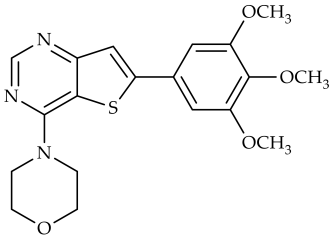
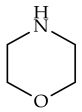
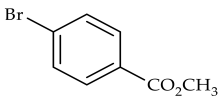
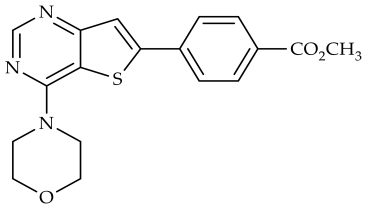
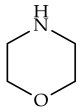
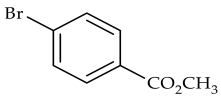
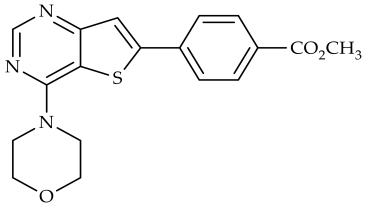
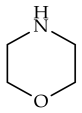
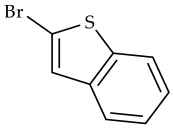
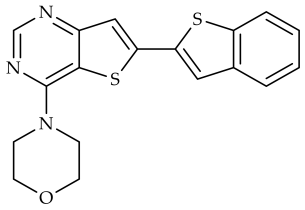
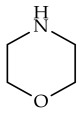
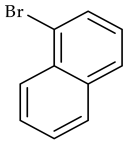
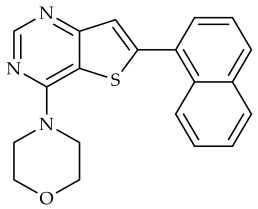
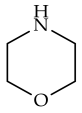
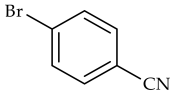
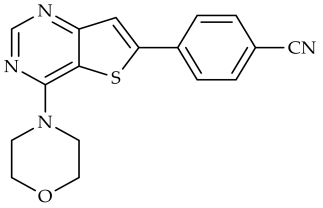
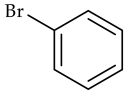
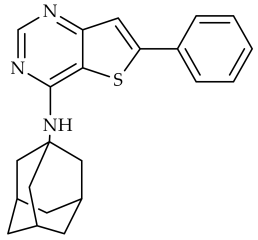
Entry	Amine Reagent	R_2-Br	Product	Yield [a]
1				**14**, 70%
2				**16**, 58%
3				**17**, 63%

Table 4. *Cont.*

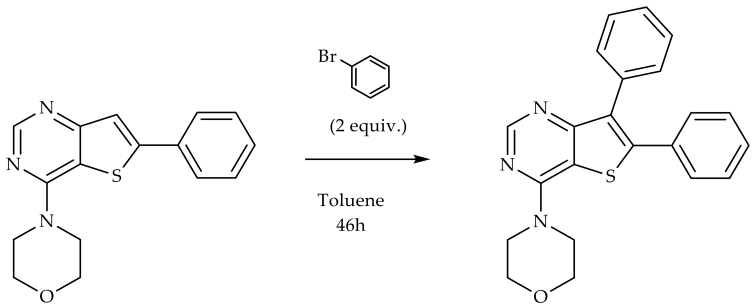
Entry	Amine Reagent	R_2-Br	Product	Yield [a]
4				**18**, 61%
5				**19**, 54%
6				**20**, 43%
7				**21**, 84%
8				**22**, 55%
9				**23**, 67%

[a] Isolated yield after column chromatography.

Several 2-aryl-thieno[3,2-*d*]pyrimidine compounds amino-substituted in position 4 were synthesized in moderate to excellent yields, demonstrating the generalizability of this method. From these results, we started to develop the Pd-catalyzed direct C–H activation on position C-3 of the thiophene moiety. This was studied from compound **14** using bromobenzene (2 equiv.), different amounts of $Pd(OAc)_2$ and K_2CO_3 with or without ligand, in toluene at different temperatures (Table 5). The desired product was obtained in moderate yields (Table 5, Entries 1–3). A temperature between

130–140 °C induced activation in the C-3 position, but when the reaction was performed at 100 °C, direct C–H activation did not take place (Table 5, Entry 4).

Table 5. Optimization of the C–H activation at position C-3 of 4-(6-phenylthieno[3,2-*d*]pyrimidin-4-yl)morpholine **14**.



14 **15**

Entry	Pd Catalyst (mol %)	Ligand (mol %)	Base (equiv.)	*T* (°C)	Yield [a] (%)
1	$Pd(OAc)_2$ (20)	-	K_2CO_3 (4)	140	55
2	$Pd(OAc)_2$ (10)	TTBP·HBF_4 (20)	K_2CO_3 (2)	130	49
3	$Pd(OAc)_2$ (10)	PCy_3 (20)	K_2CO_3 (2)	130	34
4	$Pd(OAc)_2$ (10)	TTBP ·HBF_4 (20)	K_2CO_3 (2)	100	0

[a] Isolated yield after column chromatography.

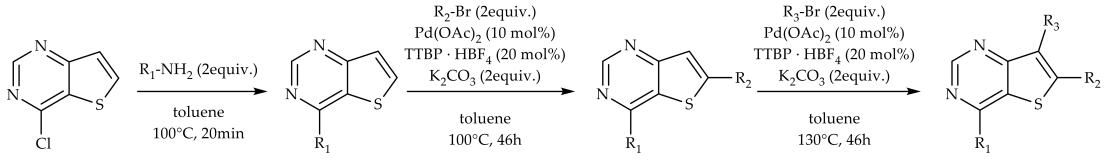
The scope and limitations of the one-pot reaction were then explored. We started with morpholine; then bromobenzene was used for the Pd-catalyzed C–H activation on the C-2 position, and for the last step, the Pd-catalyzed C–H activation on the C-3 position, bromobenzene and bromobenzonitrile were tested. The conditions of entry 2 (Table 5) were chosen even though they required a ligand because the reaction can be carried out with a smaller amount of base and at a lower temperature, which may be important for some sensitive reagents. These conditions appeared to be a good compromise. The results obtained for the one-pot three-step activation are summarized in Table 6.

For these two examples of one-pot three-step SnAr, C–H activation in C-2 then C–H activation in C-3 positions, we were able to obtain the expected compounds with reasonable yields. This method is also a valid alternative to standard synthetic strategies. To validate our Pd-catalyzed C–H arylation conditions on a large panel of heterocycles possessing a thiophene moiety we chose two compounds used at the beginning of this work, and investigated the scope and limitations first on the 2-phenylthieno[3,2-*b*]pyridine core structure (Table 7) and then on the 6-phenyl thieno[2,3-*b*]pyrazine, a heterocycle known to have a particularly low reactivity (Table 8) [11].

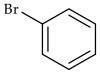
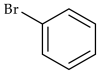
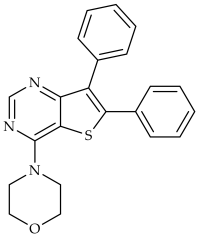
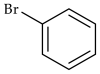
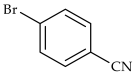
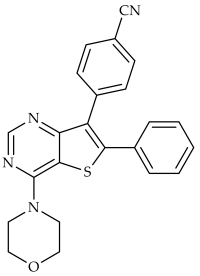
Six different 3-aryl-2-phenylthienopyridines (**25**–**29**) were synthesized in moderate to good yields (41 to 91%) by direct Pd-catalyzed C–H arylation in C-3 position.

Several 5-aryl-6-phenylthieno[2,3-*b*]pyrazines (**30**–**32**) were synthesized in moderate yields, which demonstrated the generality and the feasibility of this method. As expected from the latest results of our team, the pyrazine showed lower yields than the pyridine. These results (Tables 7 and 8) represented an improvement and a good alternative to the most commonly used synthetic routes [11,24–29].

Table 6. One pot three-step selective SnAr, Pd-catalyzed C–H activation on the C-2 then on the C-3 positions of the thiophene moiety.

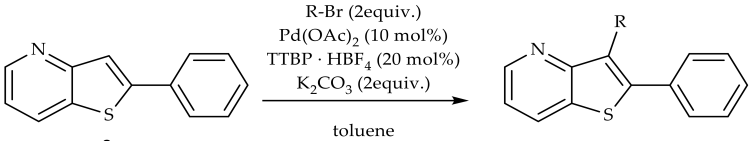


6

Entry	Amine	R_2-Br	R_3-Br	Product	Yield [a]
1					**15**, 48%
2					**24**, 36%

[a] Isolated yield after column chromatography.

Table 7. Pd-catalyzed C–H arylation in position C-3 of the 2-phenylthieno[3,2-*b*]pyridine **2**.



2

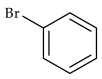
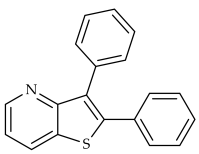
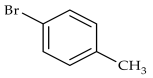
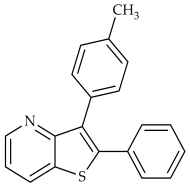
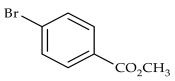
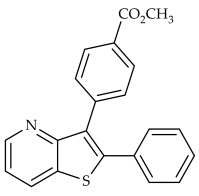
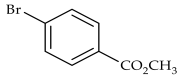
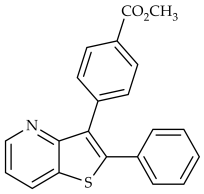
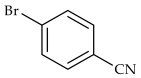
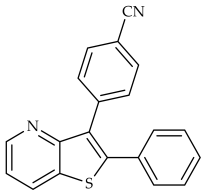
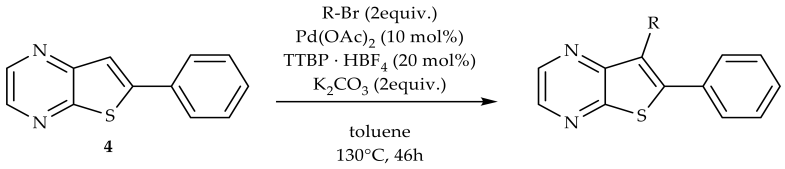
Entry	R-Br	Product	Yield [a]
1			**25**, 91%
2			**26**, 65%
3			**27**, 89%

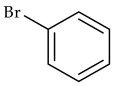
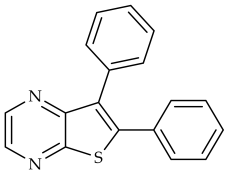
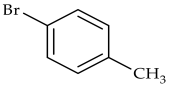
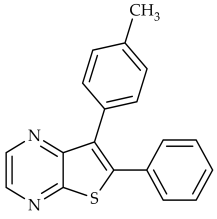
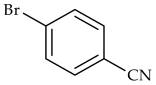
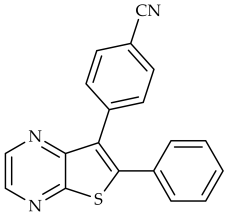
Table 7. *Cont.*

Entry	R-Br	Product	Yield [a]
4			**28**, 41%
5			**29**, 84%

[a] Isolated yield after column chromatography.

Table 8. Pd-catalyzed C–H arylation in C-3 of the 6-phenyl thieno[2,3-*b*]pyrazine **4**.



Entry	R-Br	Product	Yield [a]
1			**30**, 47%
2			**31**, 31%
3			**32**, 38%

[a] Isolated yield after column chromatography.

3. Conclusions

In summary, we have disclosed a convenient one-pot synthesis of thieno-pyridine, -pyrimidine, and -pyrazine scaffolds. The conditions reported make this methodology an interesting alternative to conventional routes, as it avoids the bromination, iodination, or chlorination processes generally used to synthesize various annelated sulfur-containing heterocycles.

Supplementary Materials: Supplementary materials are available online at http://www.mdpi.com/2073-4344/8/4/137/s1.

Acknowledgments: We acknowledge the Region Centre for financial support.

Author Contributions: Joana F. Campos and Sabine Berteina-Raboin conceived and designed the experiments. Joana F. Campos performed the experiments. Maria-João R. P. Queiroz participated in analyzing the data. Joana F. Campos and Sabine Berteina-Raboin analyzed the data and wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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