A Straightforward One-Step Access to Ticlopidine Derivatives Arylated at the C5-Position of the Thienyl Ring via Pd-Catalyzed Direct Arylations

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A straightforward one step access to Ticlopidine derivatives arylated at the C5-position of the thienyl ring *via* Pd-catalyzed direct arylations

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Abstract: The reactivity of Ticlopidine, which belongs to the thienopyridine drug family, in Pd-catalyzed C-H bond functionalization was investigated. The use of a palladium-diphosphine catalyst associated to potassium acetate base in *N*,*N*-dimethylacetamide was found to promote the regioselective arylation at the C5-position of the Ticlopidine thienyl ring with aryl bromides in high yields. In the course of this reaction, no dechlorination or debenzylation of the 2-chlorobenzyl group of Ticlopidine was observed. A wide variety of substituents on the aryl bromide was tolerated such as nitro, nitrile, acetyl, propionyl, benzoyl, ester, chloro, fluoro or trifluoromethyl. Bromopyridines and bromoquinolines were also successfully employed. This methodology gives a one step access to arylated Ticlopidine derivatives from commercially available compounds *via* a straightforward C-H bond functionalization procedure. Therefore, it provides a very appealing method to build a library of compounds containing a Ticlopidine unit.

Several thienopyridine derivatives exhibit very important biological properties.[1] For example, Ticlopidine, Clopidogrel and Prasugrel (Fig. 1), are drugs employed as platelet aggregation inhibitors. It should be mentioned that Clopidogrel belong to the world health organization's list of essential medicines. Prasugrel, which bears a substituent at thienyl C5-position exhibits a similar activity than Clopidogrel. Therefore, the discovery of straightforward methods for the introduction of functional groups at C5-position of the thienyl moiety of thienopyridine derivatives is an important research area in pharmaceutical chemistry.

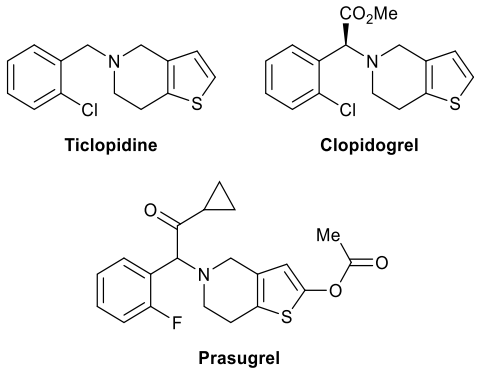
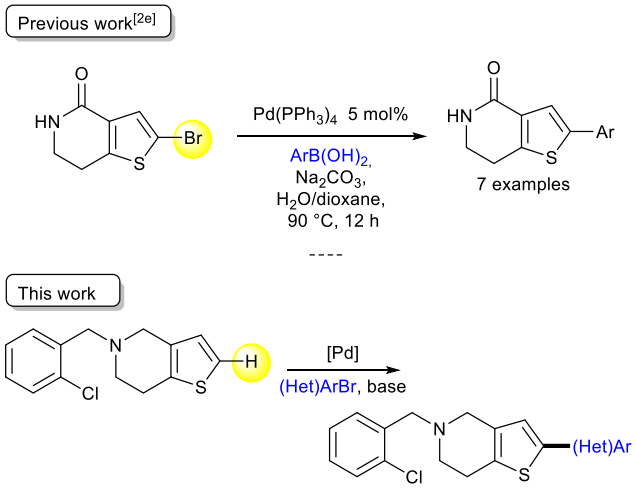


Figure 1. Structures of Ticlopidine, Clopidogrel and Prasugrel.

To our knowledge, the synthesis of Ticlopidine derivatives bearing an aryl substituent at the C5-position of the thienyl ring has not been described yet. Moreover, currently only a few methods for the synthesis of related arylated thienopyridines have been reported. In most cases, a Suzuki type coupling reaction between halothiophenes and arylboronic acids was employed.[2] For example, Wipf et al. recently reported the coupling of a 2-bromo-6,7-dihydrothieno[3,2-*c*]pyridinone with a set of arylboronic acids (Scheme 1, top). [2e]

The late stage C-H bond functionalization of drugs represents a straightforward method for the fast screening of the biological properties of compounds containing a bioactive unit. Since the report by Ohta et al. in 1985 on the Pd-catalyzed arylation of 5-membered ring heteroarenes including thiophenes, *via* a C-H bond functionalization,[3,4] this coupling reaction has been applied to a wide variety of thiophene derivatives.[5] However, to our knowledge, the direct arylation of the C5-position of the thienyl ring of Ticlopidine has not been reported so far (Scheme 1, bottom).

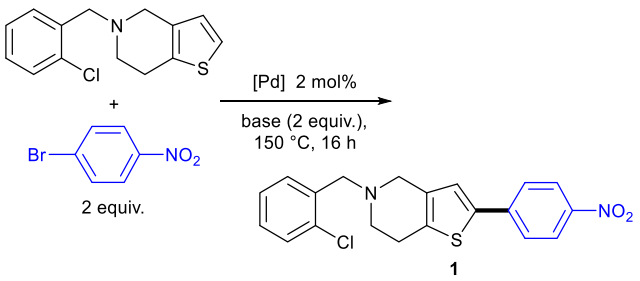


Scheme 1. Access to arylated thienopyridine derivatives.

Herein, we report conditions for the one step access to Ticlopidine derivatives arylated at the C5-position of the thienyl ring, *via* a C-H bond functionalization which are tolerant to the C-Cl bond and benzyl moiety of Ticlopidine.

Based on our previously reported conditions for the Pd-catalyzed direct arylation of thiophenes,[6a] or 2*H*-indazoles,[6b] we first employed 2 mol% $Pd(OAc)_2$ or $PdCl_2$ catalysts with KOAc (2 equiv.) as the base in DMA (*N*,*N*-dimethylacetamide) at 150 °C to promote the arylation of Ticlopidine with 4-bromonitrobenzene. However, under these reaction conditions, a partial conversion of the aryl bromide was obtained and the formation of some unidentified side-products was also observed; whereas the target product **1** was obtained in moderate yields (43% and 40%) (Table 1, entries 1 and 2). In order to improve the conversion of 4-bromonitrobenzene, the more thermally stable catalyst $PdCl(C_3H_5)(dppb)$[7,8] was employed. Under the same reaction conditions, a complete conversion of the aryl bromide was observed, and the desired arylated Ticlopidine derivative **1** was isolated in 78% yield (Table 1, entry 3). Moreover, under these conditions, no dechlorination or debenzylation of the 2-chlorobenzyl unit of Ticlopidine was observed.

Table 1. Influence of the reaction conditions for palladium-catalyzed direct coupling of Ticlopidine with 4-bromonitrobenzene.[a]



Entry	Catalyst	Base	Solvent	Conv. (%)	Yield in **1**
1	$Pd(OAc)_2$	KOAc	DMA	62	43
2	$PdCl_2$	KOAc	DMA	58	40
3	$PdCl(C_3H_5)(dppb)$	KOAc	DMA	100	78
4	$PdCl(C_3H_5)(dppb)$	NaOAc	DMA	<20	<10
5	$PdCl(C_3H_5)(dppb)$	Na_2CO_3	DMA	<20	<10
6	$PdCl(C_3H_5)(dppb)$	K_2CO_3	DMA	<20	<10
7	$PdCl(C_3H_5)(dppb)$	KOAc	DMF	32	17
8	$PdCl(C_3H_5)(dppb)$	KOAc	xylene	<10	-
9	$PdCl(C_3H_5)(dppb)$	KOAc	CPME[b]	<10	-
10	$PdCl(C_3H_5)(dppb)$	KOAc	DMA	57	46[c]

[a] Ticlopidine (1 mmol), 4-bromonitrobenzene (2 mmol), base (2 mmol), catalyst (0.02 mmol), under argon, 16 h, 150 °C, isolated yields. [b] cyclopentyl methyl ether. [c] 120 °C.

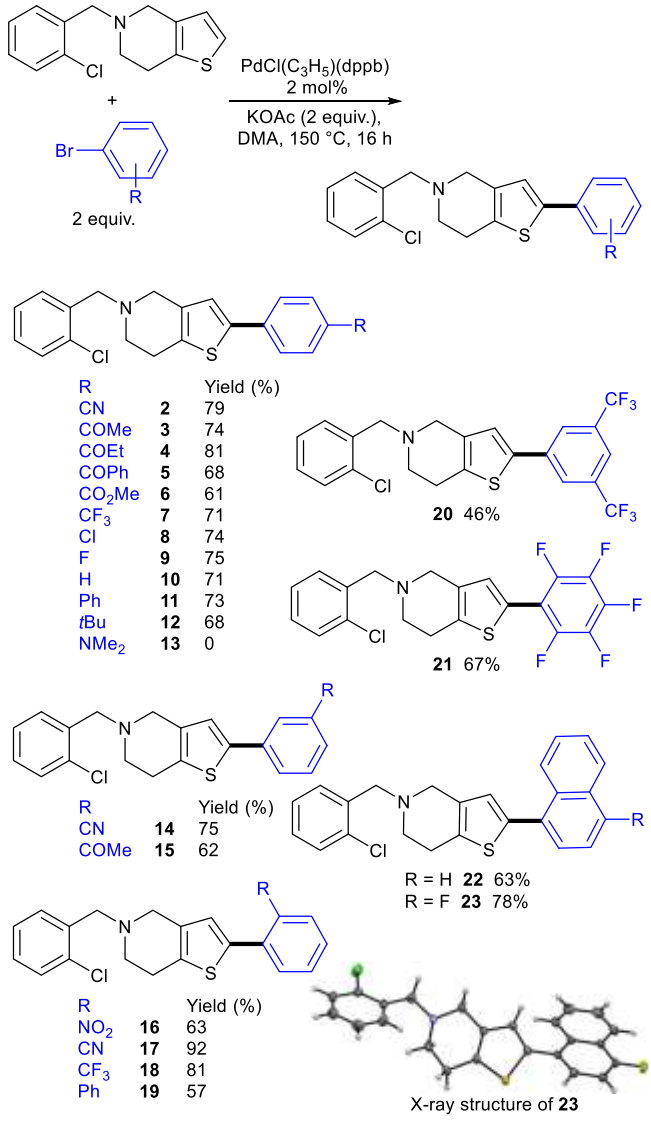
The use of NaOAc, Na_2CO_3 or K_2CO_3 as the reaction bases was ineffective, as in all cases, the product **1** was obtained in <10% yield (Table 1, entries 4-6). The influence of the solvent was also examined. Reaction performed in DMF, xylene or cyclopentyl methyl ether gave **1** in lower yields than in DMA (Table 1, entries 7-9). The reaction performed in DMA at a lower temperature (120 °C instead of 150 °C) using 2 mol% of $PdCl(C_3H_5)(dppb)$ catalyst afforded **1** in only 46% yield due to a poor conversion of 4-bromonitrobenzene (Table 1, entry 10).

Then, the scope of this reaction was studied. First, a set of *para*-substituted aryl bromides was reacted with Ticlopidine using 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst, KOAc as the base in DMA at 150 °C (Scheme 2). The electron-withdrawing *para*-substituents nitrile, acetyl, propionyl, benzoyl, ester and trifluoromethyl on the aryl bromide were tolerated affording the target products **2**-**7** in 61-81% yields. Good yields in coupling products **8** and **9** were obtained from 4-chloro- and 4-fluoro-substituted aryl bromides.

The 5-arylthiophene derivatives **10**-**12** were also obtained in high yields with bromobenzene, 4-bromobiphenyl and the electron-rich 4-*tert*-butylbromobenzene. Conversely, with the more electron-rich 4-bromo-*N*,*N*-dimethylaniline, no formation of the target product **13** was observed, and this aryl bromide was

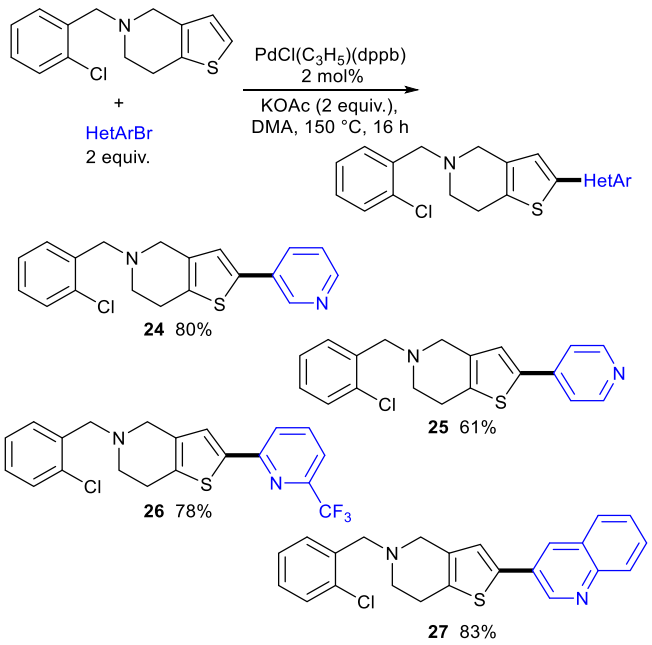
recovered. The *meta*-substituted 3-bromobenzonitrile and 3-bromoacetophenone also led to the formation of the desired arylated Ticlopidine derivatives **14** and **15** in good yields. With more sterically hindered *ortho*-substituted aryl bromides, such as 2-bromonitrobenzene, 2-bromobenzonitrile and 2-bromobenzotrifluoride, the arylated Ticlopidine derivatives **16**-**18** were obtained in 63-92% yields.

(Poly)fluoro-substituted biphenyls are very important units in both bio- and material-chemistry. Therefore, we also studied the reactivity of 3,5-bis(trifluoromethyl)bromobenzene, bromopentafluorobenzene and 4-bromo-1-fluoronaphthalene for this coupling reaction. The expected products **20**, **21** and **23** were obtained in moderate to good yields. The structure of **23** was confirmed by X-ray analysis. With all these aryl bromides, complete regioselectivities in favor of the arylation at the C5-position of the thienyl ring of Ticlopidine were observed.



Scheme 2. Synthesis of arylated Ticlopidine derivatives.

N-containing 6-membered ring heterocycles can be found in many important drugs. Therefore, the reactivity of 3- and 4-bromopyridines and also 3-bromoquinoline for Ticlopidine thienyl ring arylation was also studied (Scheme 3). In all cases, the desired coupling products **24**, **25** and **27** were obtained in high yields. 2-Bromo-6-(trifluoromethyl)pyridine was also reactive affording the expected coupling product **26** in 78% yield.



Scheme 3. Synthesis of heteroarylated Ticlopidine derivatives.

In summary, under appropriate reaction conditions, the Pd-catalyzed C-H bond functionalization of Ticlopidine allows to prepare arylated Ticlopidine derivatives in only one step. The compounds arylated at the C5-position of the Ticlopidine thienyl ring were generally obtained in very high regioselectivities and in good yields using $PdCl(C_3H_5)(dppb)$ as air-stable catalyst, KOAc as inexpensive base and aryl bromides as easily available aryl sources. Moreover, no dechlorination or debenzylation of the 2-chlorobenzyl unit of Ticlopidine was observed under these reaction conditions. This reaction tolerates several useful functional groups on the aryl bromide such as nitro, nitrile, acetyl, propionyl, benzoyl, ester, chloro, fluoro or trifluoromethyl and also the *N*-containing heteroaryl bromides 3- or 4-bromopyridines and 3-bromoquinoline. This synthetic scheme is more simple than the previously reported Suzuki coupling employed in the scheme 1 for the preparation of related compounds, as there is no need to introduce a bromo-substituent on the thienyl ring and as there this coupling does not require the use of arylboronic acids. Therefore, this late stage functionalization methodology provides a straightforward access to (hetero)arylated Ticlopidine derivatives with various substituents allowing an easy tuning of the biological properties.

Experimental Section

General. All reactions were performed in Schlenk tubes under argon. DMA analytical grade was not distilled before use. Potassium acetate 99+ was used. Commercial Ticlopidine hydrochloride (>98%) was treated by a KOH solution, extracted and dried before use. The aryl bromides were used without purification. ^{1}H (400 MHz), ^{13}C (100 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (^{1}H: 7.26 and ^{13}C: 77.16). Flash chromatography was performed on silica gel (230-400 mesh).

Preparation of the $PdCl(C_3H_5)$(dppb) catalyst: [8] An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure for the synthesis of the arylated Ticlopidine derivatives: As a typical experiment, the reaction of the aryl bromide (2 mmol), Ticlopidine (0.264 g, 1 mmol), KOAc (0.196 g, 2 mmol) at 150 ºC during 16 h in DMA (2 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon afford the corresponding arylation product after evaporation of the solvent and purification on silica gel.

5-(2-Chlorobenzyl)-2-(4-nitrophenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (1)

From 4-bromonitrobenzene (0.404 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **1** was obtained in 78% (0.299 g) yield as a yellow solid: mp 144-146 °C. ^{1}H NMR (400 MHz, CDCl3): δ 8.20 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.31-7.22 (m, 2H), 7.11 (s, 1H), 3.87 (s, 2H), 3.67 (s, 2H), 2.97-2.91 (m, 4H). ^{13}C NMR (100 MHz, CDCl3): δ 146.3, 140.8, 138.7, 137.0, 135.9, 135.8, 134.3, 130.6, 129.5, 128.3, 126.8, 125.3, 124.3, 124.0, 58.4, 52.7, 50.4, 25.9. Elemental analysis: calcd (%) for $C_{20}H_{17}ClN_2O_2S$ (384.88): C 62.41, H 4.45; found: C 62.14, H 4.20.

4-(5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)benzonitrile (2)

From 4-bromobenzonitrile (0.364 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **2** was obtained in 79% (0.288 g) yield as a white solid: mp 161-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 4H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.33–7.22 (m, 2H), 7.11 (s, 1H), 3.87 (s, 2H), 3.67 (s, 2H), 2.97-2.91 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 138.9, 136.1, 135.8, 135.6, 134.3, 132.6, 130.6, 129.5, 128.3, 126.7, 125.5, 123.4, 118.9, 110.1, 58.4, 52.7, 50.4, 25.7. Elemental analysis: calcd (%) for $C_{21}H_{17}ClN_2S$ (364.89): C 69.13, H 4.70; found: C 69.24, H 4.48.

1-(4-(5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)phenyl)ethan-1-one (3)

From 4-bromoacetophenone (0.398 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **3** was obtained in 74% (0.283 g) yield as a yellow solid: mp 109-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.32–7.22 (m, 2H), 7.09 (s, 1H), 3.88 (s, 2H), 3.67 (s, 2H), 2.97-2.91 (m, 4H), 2.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 140.1, 139.0, 135.9, 135.5, 135.4, 134.3, 130.7, 129.5, 129.0, 128.3, 126.7, 125.1, 122.9, 58.4, 52.8, 50.5, 26.5, 25.7. Elemental analysis: calcd (%) for $C_{22}H_{20}ClNOS$ (381.92): C 69.19, H 5.28; found: C 69.30, H 5.01.

1-(4-(5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)phenyl)propan-1-one (4)

From 4-bromopropiophenone (0.426 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **4** was obtained in 81% (0.321 g) yield as a white solid: mp 115-117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.32–7.22 (m, 2H), 7.07 (s, 1H), 3.87 (s, 2H), 3.67 (s, 2H), 3.03 (q, *J* = 7.6 Hz, 2H), 2.97-2.91 (m, 4H), 1.26 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 140.1, 138.8, 136.0, 135.4, 135.3, 135.2, 134.3, 130.6, 129.5, 128.7, 128.3, 126.8, 125.1, 122.8, 58.5, 52.9, 50.5, 31.7, 25.8, 8.3. Elemental analysis: calcd (%) for $C_{23}H_{22}ClNOS$ (395.95): C 69.77, H 5.60; found: C 69.79, H 5.47.

(4-(5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)phenyl)(phenyl)methanone (5)

From 4-bromobenzophenone (0.522 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **5** was obtained in 68% (0.302 g) yield as a yellow solid: mp 119-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.78 (m, 4H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.61 (t, *J* = 8.2 Hz, 2H), 7.58-7.54 (m, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.32–7.22 (m, 2H), 7.08 (s, 1H), 3.87 (s, 2H), 3.67 (s, 2H), 2.97-2.90 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 140.1, 138.6, 137.8, 136.0, 135.7, 135.5, 135.4, 134.3, 132.3, 131.0, 130.7, 129.9, 129.5, 128.4, 128.3, 126.8, 124.9, 122.9, 58.5, 52.9, 50.6, 25.8. Elemental analysis: calcd (%) for $C_{27}H_{22}ClNOS$ (443.99): C 73.04, H 4.99; found: C 73.12, H 5.14.

Methyl 4-(5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)benzoate (6)

From methyl 4-bromobenzoate (0.430 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **6** was obtained in 61% (0.243 g) yield as a white solid: mp 105-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.32-7.21 (m, 2H), 7.06 (s, 1H), 3.94 (s, 3H), 3.87 (s, 2H), 3.66 (s, 2H), 2.97-2.91 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 140.2, 138.9, 136.0, 135.4, 135.2, 134.3, 130.6, 130.2, 129.5, 128.4, 128.3, 126.7, 125.0, 122.8, 58.4, 52.8, 52.0, 50.5, 25.7. Elemental analysis: calcd (%) for $C_{22}H_{20}ClNO_2S$ (397.92): C 66.41, H 5.07; found: C 66.02, H 5.19.

5-(2-Chlorobenzyl)-2-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (7)

From 1-bromo-4-(trifluoromethyl)benzene (0.450 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **7** was obtained in 71% (0.290 g) yield as a yellow solid: mp 104-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.55 (m, 5H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.32-7.21 (m, 2H), 7.04 (s, 1H), 3.88 (s, 2H), 3.69 (s, 2H), 2.97-2.91 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.4. ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 138.0, 136.0, 135.4, 135.1, 134.2, 130.7, 129.5, 128.8 (q, *J* = 32.5 Hz), 128.3, 126.8, 125.8 (q, *J* = 3.8 Hz), 125.4, 124.2 (q, *J* = 271.9 Hz), 122.7, 58.6, 53.0, 50.6, 25.9. Elemental analysis: calcd (%) for $C_{21}H_{17}ClF_3NS$ (407.88): C 61.84, H 4.20; found: C 61.99, H 4.38.

5-(2-Chlorobenzyl)-2-(4-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (8)

From 1-bromo-4-chlorobenzene (0.382 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **8** was obtained in 74% (0.277 g) yield as a yellow solid: mp 83-85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.30-7.22 (m, 2H), 6.93 (s, 1H), 3.87 (s, 2H), 3.66 (s, 2H), 2.97-2.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 136.0, 135.1, 134.3, 133.8, 133.2, 132.8, 130.6, 129.5, 128.9, 128.3, 126.7, 126.6, 121.7, 58.4, 52.9, 50.6, 25.7. Elemental analysis: calcd (%) for $C_{20}H_{17}Cl_2NS$ (374.32): C 64.17, H 4.58; found: C 64.34, H 4.29.

5-(2-Chlorobenzyl)-2-(4-fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (9)

From 1-bromo-4-fluorobenzene (0.350 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **9** was obtained in 75% (0.268 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.4 Hz, 1H), 7.51 (dd, *J* = 7.4, 5.4 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 2H), 6.88 (s, 1H), 3.87 (s, 2H), 3.66 (s, 2H), 2.97-2.88 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -115.1. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (d, *J* = 246.7 Hz), 140.6, 136.2, 135.1, 134.4, 133.4, 131.1 (d, *J* = 3.4 Hz), 130.7, 129.6, 128.4, 127.2 (d, *J* = 8.0 Hz), 126.9, 121.4, 115.8 (d, *J* = 21.8 Hz), 58.6, 53.0, 50.7, 25.7. Elemental analysis: calcd (%) for $C_{20}H_{17}ClFNS$ (357.87): C 67.12, H 4.79; found: C 67.39, H 4.84.

5-(2-Chlorobenzyl)-2-phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (10)

From bromobenzene (0.314 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **10** was obtained in 71% (0.241 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.45-7.20 (m, 6H), 6.97 (s, 1H), 3.88 (s, 2H), 3.66 (s, 2H), 2.97-2.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 136.1, 135.0, 134.7, 134.3, 133.4, 130.7, 129.5, 128.8, 128.2, 127.1, 126.8, 125.5, 121.3, 58.5, 53.0, 50.7, 25.7. Elemental analysis: calcd (%) for $C_{20}H_{18}ClNS$ (339.88): C 70.68, H 5.34; found: C 70.94, H 5.70.

2-([1,1'-Biphenyl]-4-yl)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (11)

From 4-bromobiphenyl (0.466 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **11** was obtained in 73% (0.304 g) yield as a yellow solid: mp 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.56 (m, 7H), 7.51-7.45 (m, 2H), 7.45-7.34 (m, 2H), 7.32-7.21 (m, 2H), 7.01 (s, 1H), 3.89 (s, 2H), 3.69 (s, 2H), 2.97-2.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 140.6, 139.9, 136.1, 135.1, 134.3, 133.7, 133.5, 130.6, 129.5, 128.8, 128.2, 127.5, 127.3, 126.9, 126.7, 125.8, 121.3, 58.5, 53.0, 50.7, 25.7. Elemental analysis: calcd (%) for $C_{26}H_{22}ClNS$ (415.98): C 75.07, H 5.33; found: C 74.79, H 5.51.

2-(4-(*tert*-Butyl)phenyl)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (12)

From 1-bromo-4-*tert*-butylbenzene (0.426 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **11** was obtained in 68% (0.269 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.46-7.40 (m, 3H), 7.34-7.22 (m, 2H), 6.95 (s, 1H), 3.90 (s, 2H), 3.70 (s, 2H), 2.97-2.90 (m, 4H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 141.7, 136.2, 134.9, 134.3, 132.8, 132.0, 130.7, 129.5, 128.2, 126.8, 125.7, 125.3, 120.9, 58.5, 53.0, 50.7, 34.6, 31.3, 25.7. Elemental analysis: calcd (%) for $C_{24}H_{26}ClNS$ (395.99): C 72.80, H 6.62; found: C 73.00, H 6.87.

3-(5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)benzonitrile (14)

From 3-bromobenzonitrile (0.364 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **14** was obtained in 75% (0.274 g) yield as a yellow solid: mp 109-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.6, 1.6 Hz, 1H), 7.31-7.21 (m, 2H), 6.98 (s, 1H), 3.86 (s, 2H), 3.65 (s, 2H), 2.96-2.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 136.0, 135.9, 135.5, 135.2, 134.3, 130.7, 130.1, 129.6, 129.5, 129.4, 128.6, 128.3, 126.8, 122.7, 118.6, 113.1, 58.5, 52.8, 50.5, 25.8. Elemental analysis: calcd (%) for $C_{21}H_{17}ClN_2S$ (364.89): C 69.13, H 4.70; found: C 69.00, H 4.51.

1-(3-(5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)phenyl)ethan-1-one (15)

From 3-bromoacetophenone (0.398 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **15** was obtained in 62% (0.237 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.32-7.22 (m, 2H), 7.04 (s, 1H), 3.88 (s, 2H), 3.68 (s, 2H), 2.97-2.91 (m, 4H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 140.3, 137.7, 136.0, 135.2, 134.3, 134.2, 130.6, 129.8, 129.5, 129.1, 128.3, 126.9, 126.7, 125.0, 122.1, 58.4, 52.9, 50.6, 26.7, 25.7. Elemental analysis: calcd (%) for $C_{22}H_{20}ClNOS$ (381.92): C 69.19, H 5.28; found: C 69.08, H 5.33.

5-(2-Chlorobenzyl)-2-(2-nitrophenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (16)

From 2-bromonitrobenzene (0.404 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **16** was obtained in 63% (0.243 g) yield as a yellow solid: mp 119-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.6 Hz, 1H), 7.59-7.50 (m, 3H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.32-7.21 (m, 2H), 6.74 (s, 1H), 3.86 (s, 2H), 3.64 (s, 2H), 2.97-2.89 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 136.0, 134.9, 134.3, 134.2, 131.9, 131.8, 130.7, 129.5, 128.5, 128.3, 128.2, 126.8, 125.4, 123.7, 58.5, 52.8, 50.5, 25.6. Elemental analysis: calcd (%) for $C_{20}H_{17}ClN_2O_2S$ (384.88): C 62.41, H 4.45; found: C 62.17, H 4.54.

2-(5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl)benzonitrile (17)

From 2-bromobenzonitrile (0.364 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **17** was obtained in 92% (0.336 g) yield as a yellow solid: mp 129-131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.59-7.54 (m, 3H), 7.41 (d, *J* = 7.6, 1.6 Hz, 1H), 7.37-7.21 (m, 4H), 3.87 (s, 2H), 3.69 (s, 2H), 2.98-2.89 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 136.6, 136.2, 135.9, 135.4, 134.3, 132.9, 130.7, 129.5, 129.2, 128.3, 127.1, 126.8, 125.8, 119.0, 109.4, 58.5, 52.8, 50.5, 25.7. Elemental analysis: calcd (%) for $C_{21}H_{17}ClN_2S$ (364.89): C 69.13, H 4.70; found: C 69.36, H 4.40.

5-(2-Chlorobenzyl)-2-(2-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (18)

From 1-bromo-2-(trifluoromethyl)benzene (0.450 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **18** was obtained in 81% (0.330 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.57-7.37 (m, 4H), 7.32-7.21 (m, 2H), 6.76 (s, 1H), 3.88 (s, 2H), 3.69 (s, 2H), 2.98-2.91 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.2. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 136.1, 134.7, 134.4, 134.2 (q, *J* = 1.9 Hz), 134.1, 133.3, 131.4 (q, *J* = 1.1 Hz), 130.9, 129.6, 128.9 (q, *J* = 29.9 Hz), 128.4, 127.8, 126.9, 126.5 (q, *J* = 5.5 Hz), 126.2 (q, *J* = 2.6 Hz), 124.1 (q, *J* = 272.9 Hz), 58.6, 53.1, 50.7, 25.6. Elemental analysis: calcd (%) for $C_{21}H_{17}ClF_3NS$ (407.88): C 61.84, H 4.20; found: C 61.71, H 4.02.

2-([1,1'-Biphenyl]-2-yl)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (19)

From 2-bromobiphenyl (0.466 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **19** was obtained in 57% (0.237 g) yield as a yellow solid: mp 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.8 Hz, 2H), 7.50-7.20 (m, 11H), 6.38 (s, 1H), 3.83 (s, 2H), 3.54 (s, 2H), 2.88-2.84 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 140.5, 136.1, 134.2, 133.9, 133.8, 133.4, 130.9, 130.7, 130.3, 129.7, 129.4, 128.2, 128.1, 127.5, 127.4, 126.9, 126.7, 125.1, 58.5, 53.0, 50.6, 25.5. Elemental analysis: calcd (%) for $C_{26}H_{22}ClNS$ (415.98): C 75.07, H 5.33; found: C 75.36, H 5.27.

2-(3,5-Bis(trifluoromethyl)phenyl)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (20)

From 1,3-bis(trifluoromethyl)-5-bromobenzene (0.586 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **20** was obtained in 46% (0.219 g) yield as a yellow solid: mp 97-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 2H), 7.74 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.41 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.32-7.21 (m, 2H), 7.11 (s, 1H), 3.89 (s, 2H), 3.68 (s, 2H), 2.99-2.92 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.1. ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.7, 136.0, 135.8, 135.7, 134.3, 132.2 (q, *J* = 33.3 Hz), 130.7, 129.5, 128.4, 126.8, 125.0 (m), 123.5, 123.2 (q, *J* = 272.8 Hz), 120.2 (m), 58.4, 52.7, 50.5, 25.8. Elemental analysis: calcd (%) for $C_{22}H_{16}ClF_6NS$ (475.88): C 55.53, H 3.39; found: C 55.50, H 3.68.

5-(2-Chlorobenzyl)-2-(perfluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (21)

From bromopentafluorobenzene (0.494 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **21** was obtained in 67% (0.288 g) yield as a white solid: mp 134-136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.30-7.22 (m, 2H), 7.15 (s, 1H), 3.88 (s, 2H), 3.70 (s, 2H), 3.01-2.91 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -140.2 (dd, *J* = 22.0, 6.9 Hz), -156.7 (t, *J* = 22.2 Hz), -162.3 (td, *J* = 21.4, 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (dm, *J* = 253.0 Hz), 139.5 (dm, *J* = 253.0 Hz), 137.8 (dm, *J* = 253.0 Hz), 137.2 (t, *J* = 3.7 Hz), 135.8, 134.4, 134.3, 130.7, 129.5, 128.5 (t, *J* = 4.3 Hz), 128.4, 126.8, 123.5 (m), 110.3 (dd, *J* = 15.4, 4.1 Hz), 58.4, 52.7, 50.4, 25,5. Elemental analysis: calcd (%) for $C_{20}H_{13}ClF_5NS$ (429.83): C 55.89, H 3.05; found: C 55.71, H 2.79.

5-(2-Chlorobenzyl)-2-(naphthalen-1-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (22)

From 1-bromonaphthalene (0.414 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **22** was obtained in 63% (0.246 g) yield as a yellow solid: mp 119-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.1Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.58-7.48 (m, 4H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.34-7.22 (m, 2H), 6.89 (s, 1H), 3.92 (s, 2H), 3.75 (s, 2H), 3.03-2.95 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 136.1, 134.3, 134.2, 134.0, 133.9, 132.8, 131.8, 130.7, 129.5, 128.3, 128.2, 128.1, 127.9, 126.8, 126.3, 126.0, 125.9, 125.6, 125.2, 58.6, 53.2, 50.8, 25.7. Elemental analysis: calcd (%) for $C_{24}H_{20}ClNS$ (389.94): C 73.93, H 5.17; found: C 74.20, H 4.89.

5-(2-Chlorobenzyl)-2-(4-fluoronaphthalen-1-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (23)

From 1-bromo-4-fluoronaphthalene (0.450 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **23** was obtained in 78% (0.318 g) yield as a yellow solid: mp 169-171 °C. ^{1}H NMR (400 MHz, DMSOd_6): δ 8.22 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.72-7.63 (m, 2H), 7.58 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.52 (dd, *J* = 8.0, 5.6 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.40-7.28 (m, 3H), 6.97 (s, 1H), 3.81 (s, 2H), 3.61 (s, 2H), 2.93-2.84 (m, 4H). ^{19}F NMR (376 MHz, DMSOd_6): δ -122.9. ^{13}C NMR (100 MHz, DMSOd_6): δ 158.1 (d, *J* = 251.5 Hz), 137.3, 136.3, 135.1, 134.3, 133.8, 132.7 (d, *J* = 4.8 Hz), 131.3, 129.8, 129.2, 129.0 (d, *J* = 4.3 Hz), 128.3, 128.2 (d, *J* = 8.5 Hz), 127.6, 127.4, 126.6, 125.9, 123.5 (d, *J* = 16.4 Hz), 120.7 (d, *J* = 5.4 Hz), 109.9 (d, *J* = 20.1 Hz), 58.4, 52.9, 50.7, 25.6. Elemental analysis: calcd (%) for $C_{24}H_{19}ClFNS$ (407.93): C 70.66, H 4.69; found: C 70.90, H 4.98.

5-(2-Chlorobenzyl)-2-(pyridin-3-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (24)

From 3-bromopyridine (0.316 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **24** was obtained in 80% (0.273 g) yield as a yellow solid: mp 91-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, *J* = 1.9 Hz, 1H), 8.45 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.29-7.16 (m, 3H), 6.93 (s, 1H), 3.82 (s, 2H), 3.60 (s, 2H), 2.92-2.83 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 146.5, 137.5, 136.0, 135.3, 134.7, 134.3, 132.3, 130.6, 130.6, 129.5, 128.3, 126.8, 123.6, 122.4, 58.5, 52.8, 50.5, 25.8. Elemental analysis: calcd (%) for $C_{19}H_{17}ClN_2S$ (340.87): C 66.95, H 5.03; found: C 66.67, H 4.79.

5-(2-Chlorobenzyl)-2-(pyridin-4-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (25)

From 4-bromopyridine (0.316 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **25** was obtained in 61% (0.208 g) yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 5.8 Hz, 2H), 7.57 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.41-7.37 (m, 3H), 7.31-7.19 (m, 2H), 7.15 (s, 1H), 3.87 (s, 2H), 3.67 (s, 2H), 2.98-2.89 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 141.6, 138.2, 136.3, 135.9, 135.6, 134.3, 130.6, 129.5, 128.3, 126.8, 123.6, 119.4, 58.5, 52.8, 50.5, 25.8. Elemental analysis: calcd (%) for $C_{19}H_{17}ClN_2S$ (340.87): C 66.95, H 5.03; found: C 66.74, H 5.15.

5-(2-Chlorobenzyl)-2-(6-(trifluoromethyl)pyridin-2-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (26)

From 2-bromo-6-(trifluoromethyl)pyridine (0.452 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **26** was obtained in 78% (0.319 g) yield as a yellow solid: mp 124-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (t, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.36 (s, 1H), 7.30-7.18 (m, 2H), 3.88 (s, 2H), 3.58 (s, 2H), 2.98-2.89 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -68.3. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 148.1 (q, *J* = 34.6 Hz), 140.2, 137.9, 137.8, 136.0, 135.4, 134.4, 130.8, 129.6, 128.4, 126.9, 124.6, 121.1 (q, *J* = 274.3 Hz), 120.9, 117.8 (q, *J* = 2.9 Hz), 58.5, 52.9, 50.6, 25.9. Elemental analysis: calcd (%) for $C_{20}H_{16}ClF_3N_2S$ (408.87): C 58.75, H 3.94; found: C 58.89, H 4.11.

5-(2-Chlorobenzyl)-2-(quinolin-3-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (27)

From 3-bromoquinoline (0.416 g, 2 mmol) and Ticlopidine (0.264 g, 1 mmol), **27** was obtained in 83% (0.324 g) yield as a yellow solid: mp 107-109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (d, *J* = 2.2 Hz, 1H), 8.17 (d, *J* = 1.8 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.61-7.52 (m, 2H), 7.40 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.31-7.19 (m, 2H), 7.12 (s, 1H), 3.86 (s, 2H), 3.68 (s, 2H), 2.98-2.89 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 147.1, 137.9, 136.0, 135.5, 134.9, 134.3, 130.6, 130.6, 129.5, 129.3, 129.1, 128.3, 128.0, 127.8, 127.8, 127.2, 126.8, 122.7, 58.5, 52.9, 50.6, 25.8. Elemental analysis: calcd (%) for $C_{23}H_{19}ClN_2S$ (390.93): C 70.67, H 4.90; found: C 70.7451 H 5.05.

For 5-(2-chlorobenzyl)-2-(4-fluoronaphthalen-1-yl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**23**): CCDC number 1951275.

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References:

[1] a) A. K. Jacobson, *Best. Pract. Res. Clin. Haematol.* **2004**, *17*, 55-64; b) G. Montalescot, S. D. Wiviott, E. Braunwald, S. A. Murphy, C. M. Gibson, C. H. McCabe, E. M. Antman, *Lancet* **2009**, *373*, 723-731; c) W. J. M. Dewilde, T. Oirbans, F. W. A. Verheugt, J. C. Kelder, B. J. G.

L. De Smet, J.-P. Herrman, T. Adriaenssens, M. Vrolix, A. A. C. M. Heestermans, M. M. Vis, J. G. P. Tijsen, A. W. van't Hof, J. M. ten Berg, *Lancet* **2013**, *381*, 1107-1115.

[2] a) M. Lindvall, C. McBride, M. McKenna, T. G. Gesner, A. Yabannavar, K. Wong, S. Lin, A. Walter, C. M. Shafer, *ACS Med. Chem. Lett.* **2011**, *2*, 720-723; b) X. Cao, Z. Sun, Y. Cao, R. Wang, T. Cai, W. Chu, W. Hu, Y. Yang, *J. Med. Chem.* **2014**, *57*, 3687-3706; c) J. M. Salamoun, K. E. McQueeney, K. Patil, S. J. Geib, E. R. Sharlow, J. S. Lazo, P. Wipf, *Org. Biomol. Chem.* **2016**, *14*, 6398-6402; d) S. Zhou, Y. Duan, J. Wang, J. Zhang, H. Sun, H. Jiang, Z. Gu, J. Tong, J. Li, J. Li, H. Liu, *Eur. J. Med. Chem.* **2017**, 448-464; e) N. R. Tasker, E. J. Rastelli, I. K. Blanco, J. C. Burnett, E. R. Sharlow, J. S. Lazo, P. Wipf, *Org. Biomol. Chem.* **2019**, *17*, 2448-2466.

[3] a) Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara, M. Shimizu, *Heterocycles*, **1985**, *23*, 2327-2333; b) A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles*, **1990**, *31*, 1951-1958.

[4] For reviews on metal-catalyzed C-H bond functionalization: a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174-238; b) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200-205; c) B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949-957; d) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269-10310; e) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; f*)* X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115; g) G. P. Chiusoli, M. Catellani, M. Costa, E. Motti, N. Della Ca, G. Maestri, *Coord. Chem. Rev.* **2010**, *254*, 456-469; h) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236-10254; i) R. Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal.* **2014**, *356*, 17-117; j) T. Gensch, M. J. James, T. Dalton, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 2296-2306; k) X. Shi, A. Sasmal, J.-F. Soulé, H. Doucet, *Chem. Asian J.* **2018**, *13*, 143-157; l) S. Mao, H. Li, X. Shi, J.-F. Soulé, H. Doucet, *ChemCatChem*, **2019**, *11*, 269-286; m) W. Hagui, H. Doucet, J.-F. Soulé, *Chem* **2019**, *5*, 2006-2078.

[5] For selected examples of Pd-catalyzed direct C2-arylations of thiophenes: a) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn* **1998**, *71*, 467-473; b) L. Lavenot, C. Gozzi, K. Ilg, I. Orlova, V. Penalva, M. Lemaire, *J. Organomet. Chem.* **1998**, *567*, 49-55; c) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286-5287; d) R. V. Smaliy, M. Beauperin, H. Cattey, P. Meunier, J.-C. Hierso, J. Roger, H. Doucet, Y. Coppel, *Organometallics* **2009**, *28*, 3152-3160; e) K. Beydoun, H. Doucet, *ChemSusChem* **2011**, *4*, 526-534; f) S. Mao, X. Shi, J.-F. Soulé, H. Doucet Adv. Synth. Catal. **2018**, *360*, 3306-3317.

[6] a) K. Beydoun, M. Zaarour, J. A. G. Williams, H. Doucet, V. Guerchais, *Chem. Commun.* **2012**, *48*, 1260-1262; b) F. Belkessam, A. Mohand, J.-F. Soulé, H. Doucet, *ChemCatChem* **2017**, *9*, 2239-2249.

[7] W. Hagui, N. Besbes, E. Srasra, T. Roisnel, J.-F. Soulé, H. Doucet, *Org. Lett.* **2016**, *18*, 4182-4185.

[8] T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.* **2003**, *687*, 365-376.

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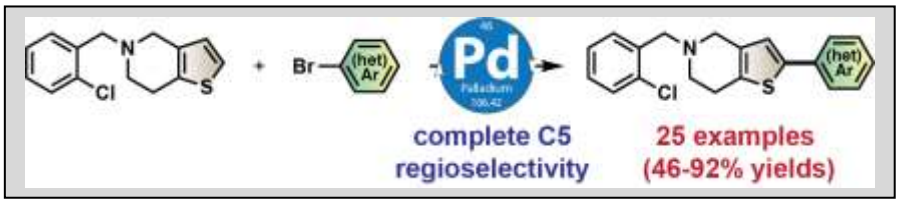

Reaction conditions for the Pd-catalyzed C-H bond functionalization of Ticlopidine allowing to prepare arylated Ticlopidine derivatives in only one step are reported. The arylated compounds were obtained in very high regioselectivities and in good yields using an air-stable Pd-catalyst and aryl bromides as easily available aryl sources. Moreover, no dechlorination or debenzylation of the 2-chlorobenzyl group of Ticlopidine was observed.