Journal of Organometallic Chemistry 897 (2019) 13–22

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Direct C-H bond (Hetero)arylation of thiazole derivatives at 5-position catalyzed by N-heterocyclic carbene palladium complexes at low catalyst loadings under aerobic conditions

Bei-Bei Ma [1], Xiao-Bing Lan [1], Dong-Sheng Shen, Feng-Shou Liu, Chang Xu *

School of Chemistry and Chemical Engineering, Guangdong Pharmaceutical University, Zhongshan, Guangdong, 528458, China

A R T I C L E I N F O

Article history:
Received 24 February 2019
Received in revised form
5 June 2019
Accepted 14 June 2019
Available online 17 June 2019

Keywords:
N-heterocyclic carbene palladium complex
Direct C-H arylation reaction
Aryl bromide
Thiazole derivative

A B S T R A C T

A highly efficient and practical protocol has been developed for the synthesis of 5-(hetero)arylated thiazole derivatives via an N-heterocyclic carbene palladium (Pd-NHC) complex catalyzed direct C-H arylation reaction. Utilization of this methodology, the arylation of substituted thiazoles with (hetero) aryl bromides efficiently proceeded at low catalyst loading (0.1–0.05 mol%) and under aerobic conditions. A variety of (hetero)aryl bromides, even some strongly deactivated or highly congested (hetero)aryl bromides, with a broad range of functional groups were compatible under the optimal reaction conditions. In all cases, the target products were afforded in moderate to quantitative yields.

1. Introduction

The 5-(hetero)aryl substituted thiazoles represent a class of privileged structural units, which are frequently found in organic electronic materials and biologically active compounds as well as pharmaceuticals (Fig. 1) [1–6]. Owing to their widespread applications, the development of practical and versatile synthetic methods has received considerable attention and remains an essential research topic in organic synthesis [7–12].

Since the publication of Ohta's reports [13], the palladium-catalyzed direct C-H bond (hetero)arylation reactions of thiazoles with (hetero)aryl halides has undergone rapid development [14–27]. It has been considered as an environmentally and economically more attractive method compared to the classical palladium-catalyzed cross-coupling reactions with organometallic reagents. In this context, a variety of elegant palladium/ligand catalytic systems have been developed to date (Table 1) [19–22,25–29]. Despite their promising utility in research and industrial applications, in most cases, these catalytic systems still suffered from the extreme susceptibility of the catalytic LPd(0) species toward moisture and oxygen. Therefore, in general, a relatively high concentration of palladium source ligated with ancillary ligands and the strict air- and moisture-free reaction conditions were indispensable [22,30]. Given the above information, the development of more readily available and effective catalytic systems for the direct coupling of thiazole derivatives, especially reducing the amount of the catalyst and easy-of-use manipulation under aerobic conditions, is still challenging.

The N-heterocyclic carbenes (NHCs) recently have become ubiquitous ancillary ligands for metal-catalyzed transformations because of their thermal and oxidative stability, adjustability as electronically and sterically and excellent catalytic activities [31–42]. So far, numerous examples of Pd-NHC complexes catalyzed direct arylations of heteroaromatics have been described by the research groups of Doucet, Shao and ours [43–54]. Notably, it has been disclosed that increasing the steric hindrance of the NHC ligands, including the incorporation of bulky substituents into the nitrogen atoms and the backbones of ligands, is vital to promote catalytic abilities of the Pd-NHC complexes [51,52,55,56]. More importantly, since the elegant publication of Organ in 2006, it has been proved that the PEPPSI (pyridine enhanced precatalyst preparation, stabilization and initiation) type precatalysts, which mix the coordination of NHCs with monodentate pyridine ligand, exhibit higher air-stability and reactivity than that of the NHCs/phosphine ligands in the Pd-catalyzed cross-coupling reactions [57–62]. For example, Lee and co-workers reported the Pd-PEPPSI-

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* Corresponding author.
E-mail address: xcpanda9@163.com (C. Xu).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jorganchem.2019.06.016

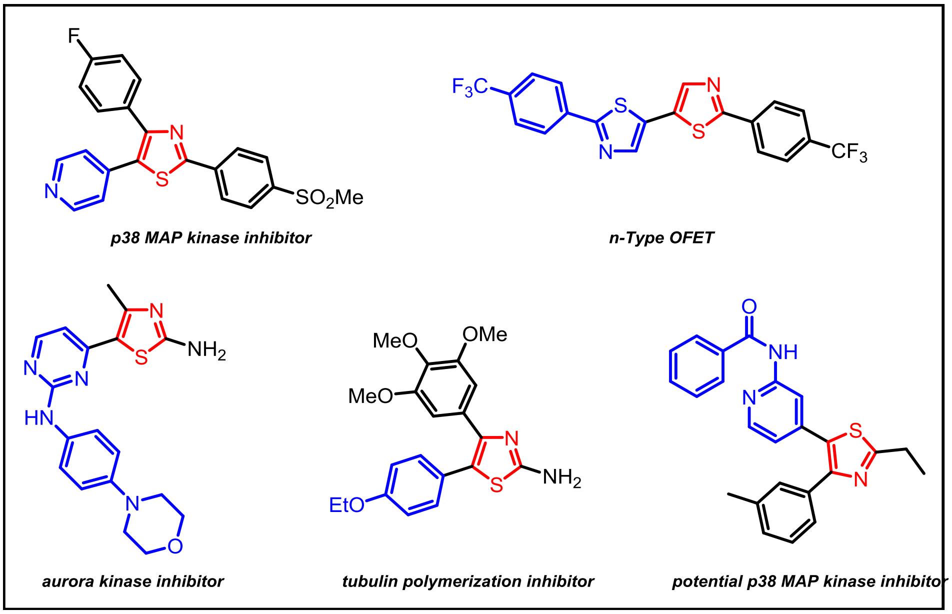
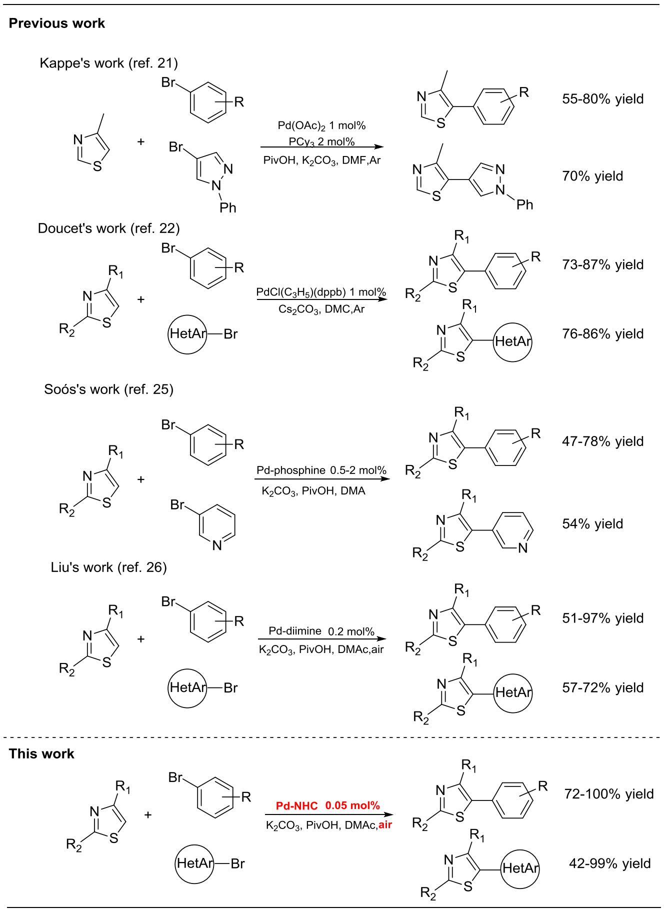


Fig. 1. Selected examples of functional 5-(hetero)aryl thiazoles.

Table 1

Pd-catalyzed direct C-H bond (hetero)arylation reactions of thiazoles.



type NHC complexes as efficient catalysts for the C5 arylation of heteroaromatics, which demonstrated higher catalytic activities than that of Pd ligated with NHCs/phosphine ligands [62]. Recently, we have also developed a series of Pd-PEPPSI-type NHC complexes, which exhibited extremely high catalytic abilities for direct arylation of azoles with aryl bromides in the presence of 0.5–0.05 mol% palladium and under aerobic conditions [56].

Although great advance has been made in Pd-PEPPSI-type NHC complexes catalyzed direct arylation reactions, the structural design of catalysts on N-moieties is still mainly restricted to properly adjust the steric environment at *ortho*-positions to facilitate the reductive elimination process and stabilize the active LPd(0) species [57–62]. Moreover, in light of the experimental evidence of Holland's and ours [52,63], a remote substitution at para-position on N-aryl moieties could further promote the palladium-catalyzed cross-coupling reactions. Thus, it is reasonable to assume that the NHCs bearing with bulky substitution at the *ortho* positions and substituents at the para position on N-aryl moieties should be advantageous, which may also provide us with another insight into the key catalyst design features that are of consequence in the catalytic cycle.

Herein, we wish to present the synthesis of a new type of Pd-PEPPSI-type NHC complexes, describe their structural characterizations and evaluate their potential catalytic performances for direct arylation of a set of thiazoles with a variety of heteroaryl or aryl bromides under aerobic conditions.

2. Result and discussion

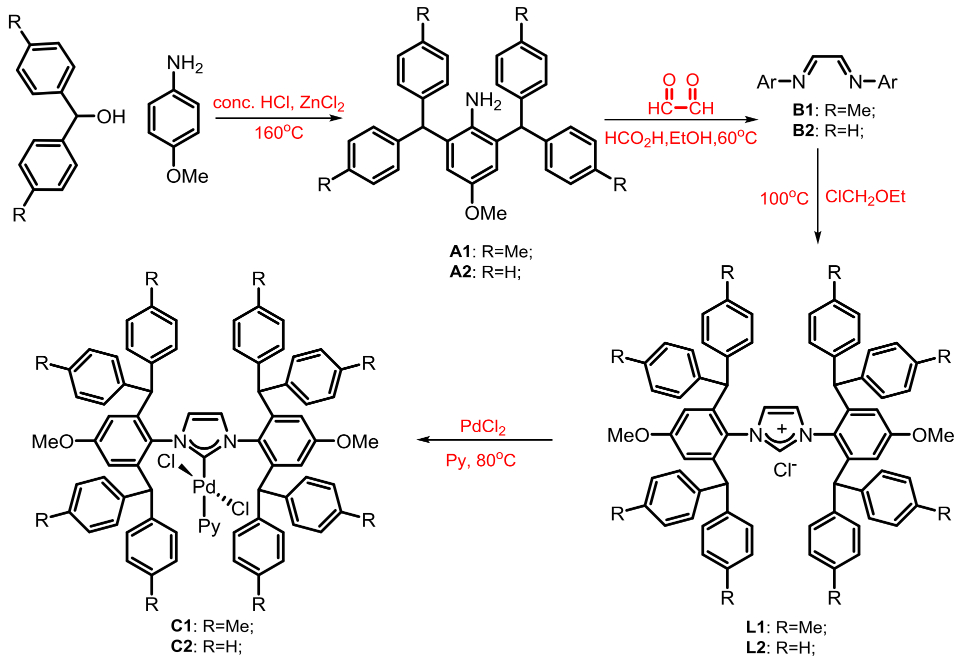
2.1. Synthesis and characterization of palladium complexes C1-2

The N-heterocyclic carbene palladium complexes **C1-2** were synthesized according to procedures similar to those reported previously for other imidazolium carbene Pd-PEPPSI complexes [61]. As can be seen in Scheme 1, *p*-anisidine reacted with diphenylmethanol under solvent-free conditions in the presence of stoichiometric amounts of conc. HCl and $ZnCl_2$ led to the formation of **A1-2**. With the aid of formic acid, **A1-2** underwent a condensation reaction with glyoxal to give α-diimine compounds **B1-2**. Cyclization of **B1-2** with chloromethyl ethyl ether yielded the imidazolinium salts **L1-2** as grey solids in moderate yields. Subsequently, the imidazolinium salts **L1-2** were treated with $PdCl_2$ in the presence of K_2CO_3 in pyridine at 80 °C readily furnished the crude palladium complexes. After purification by chromatograph using silica gel, desired carbene Pd-PEPPSI compounds **C1-2** were obtained in moderate yields as yellowish solids. The **C1-2** complexes, which are highly moisture- and air-stable both in solution and solid state against air, light and moisture, could be stored at room temperature for months without an obvious decline in catalytic efficiency.

The compounds **C1-2** were characterized by ^1H and ^{13}C NMR spectroscopy. The structure of complex **C1** was further confirmed by X-ray single-crystal analysis and illustrated in Fig. 2. The complex **C1** crystallizes in a triclinic system with space group *P*-1 and adopts the expected slightly distorted square-planar geometry around palladium centre. The carbene and the pyridine ligand are in trans-position with respective distances to the Pd centre of 1.973(4) Å and 2.122(4) Å, which are well within the expected range of reported values [57–62]. The N-phenyl rings were found to be approximately perpendicular to the NHC ring with dihedral angles of 70.43° and 68.41°. It is worthy to note that the bulky steric of the 2,6-bis(di-p-tolylmethyl)phenyl is in the position of above and below the palladium coordination plane, which is oriented over the axial sites of the palladium atom. Reasonably, this direction of the axial sites could be effectively shielded and is expected to make a long life of the catalytic species.

2.2. The Pd-catalyzed direct C–H arylation reaction

The direct C-H arylation of heteroarenes with heteroaryl bromides remains challenging due to the low reactivity of substrates and the strong metal coordination ability of heteroatoms, which could cause the poisoning of palladium species. To test the efficiency of these synthesized palladium complexes on the direct C–H arylation reaction, we chose 4-methylthiazole and 3-pyridyl bromide as the model substrates to start our catalytic investigation.



Scheme 1. Synthesis of N-heterocyclic Carbene Palladium Precatalysts.

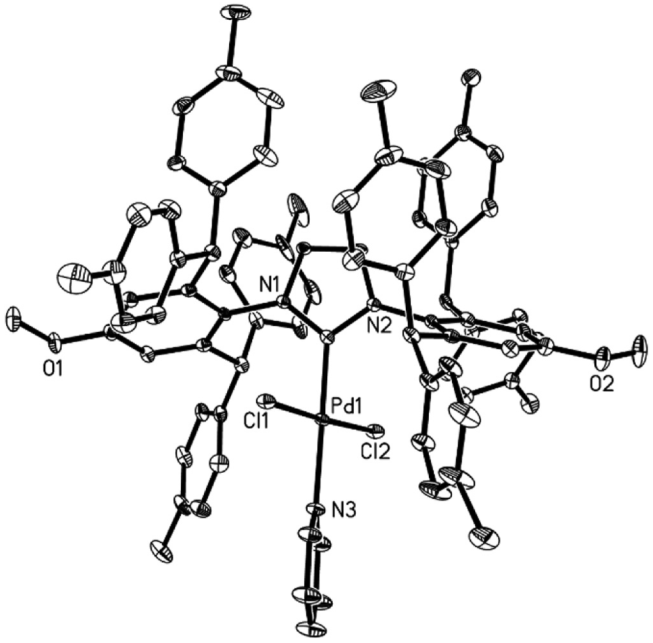
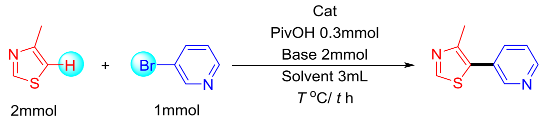


Fig. 2. Molecular structure of **C1** depicted with 30% thermal ellipsoids. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (°): Pd(1)-C(1) 1.9730(38), Pd(1)-N(3) 2.1216(38), Pd(1)-Cl(1) 2.3041(13), Pd(1)-Cl(2) 2.2937(13), N(3)-Pd(1)-C(1) 179.44(17), N(3)-Pd(1)-Cl(1) 91.40(11), N(3)-Pd(1)-Cl(2) 91.52(11), C(1)-Pd(1)-Cl(1) 88.70(12), C(1)-Pd(1)-Cl(2) 88.39(12), Cl(1)-Pd(1)-Cl(2) 177.07(4).

Table 2
Optimization of the reaction conditions[a].



Run	Cat	Base	Solvent	T/°C	t/h	Yield(%)[b]
1	C1 0.5%	K_2CO_3	DMAc	130	4	100
2	C1 0.1%	K_2CO_3	DMAc	130	4	100
3	C1 0.1%	K_2CO_3	DMAc	110	4	72
4	C1 0.05%	K_2CO_3	DMAc	130	4	99
5	C1 0.01%	K_2CO_3	DMAc	130	4	55
6	C2 0.01%	K_2CO_3	DMAc	130	4	48
7	C3 0.01%	K_2CO_3	DMAc	130	4	51
8	C1 0.01%	K_2CO_3	DMAc	130	24	55
9	C1 0.01%	KOAc	DMAc	130	4	33
10	C1 0.01%	K_3PO_4	DMAc	130	4	0
11	C1 0.01%	Cs_2CO_3	DMAc	130	4	0
12	C1 0.01%	K_2CO_3	Dioxane	130	4	0
13	C1 0.01%	K_2CO_3	Toluene	130	4	0
14	C1 0.01%	K_2CO_3	Xylene	130	4	15
15	C1 0.01%	K_2CO_3	NMP	130	4	0
16	C1 0.01%	K_2CO_3	DMSO	130	4	0
17[c]	C1 0.01%	K_2CO_3	DMAc	130	4	0
18[d]	C1 0.01%	K_2CO_3	DMAc	130	4	32
19[e]	C1 0.01%	K_2CO_3	DMAc	130	4	47
20[f]	C1 0.01%	K_2CO_3	DMAc	130	4	55

[a] Reaction conditions: 4-methylthiazole (2 mmol), 3-bromopyridine (1 mmol), palladium source (0.01–0.1 mol %), PivOH (0.3 mmol), K_2CO_3 (2 mmol), DMAc (3 mL), 130 °C, 4 h, in an aerobic atmosphere.

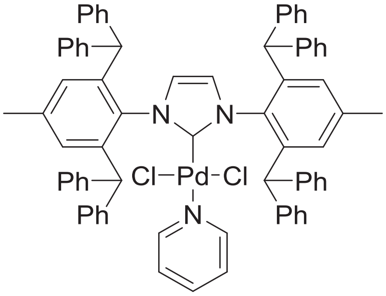
[b] GC yield using (trifluoromethyl)benzene as an internal standard.

[c] No PivOH was added.

[d] 0.1 mmol PivOH was used instead of 0.3 mmol.

[e] 0.2 mmol PivOH was used instead of 0.3 mmol.

[f] 0.4 mmol PivOH was used instead of 0.3 mmol.

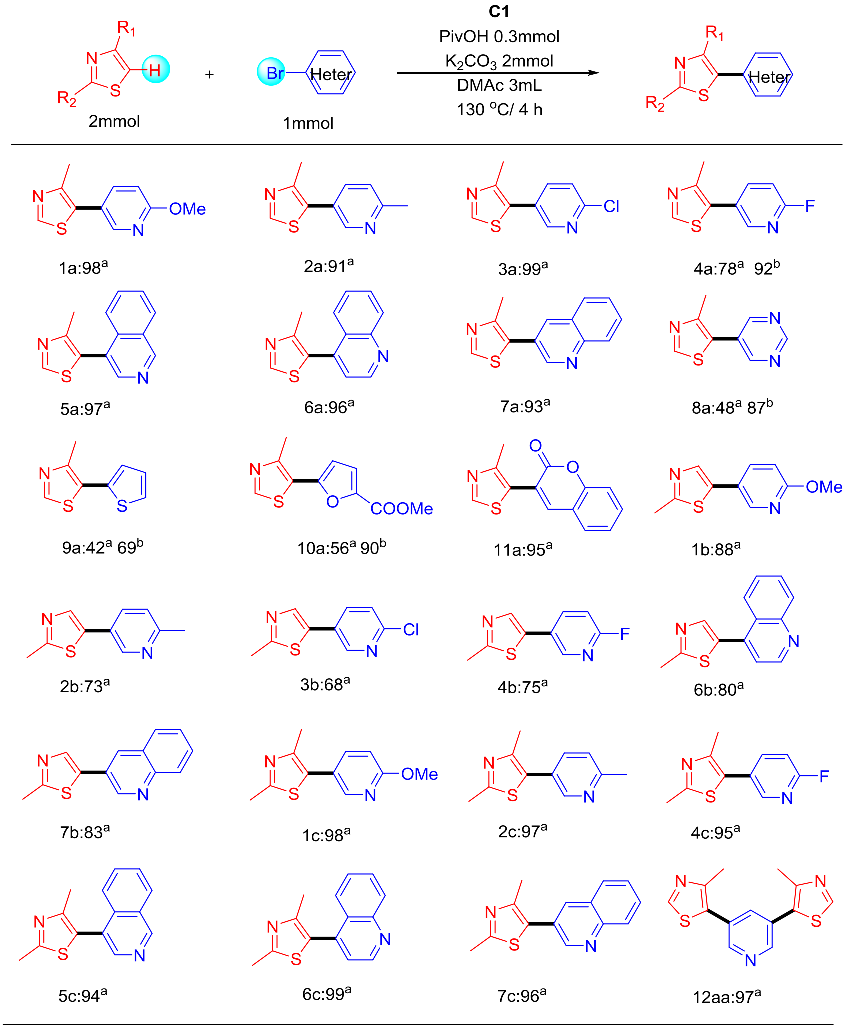


Scheme 2. The structure of the complex **C3**.

The reaction was performed in the open air by using 0.5 mol% of palladium loading, K_2CO_3 as the base, DMAc as the solvent and PivOH as the additive, under the conditions that have been established from our previous studies on palladium-catalyzed C-H arylation (Table 2, entry 1) [61]. We were pleased to obtain the highly regioselective 5-arylated product in quantitative yield. It demonstrates that complex **C1** is extraordinarily effective for this coupling reaction. Because of our continuous interest in developing more efficient Pd-catalyzed systems for direct arylation reactions, the effect of catalyst loading was initially investigated. To our delight, decreasing the catalyst loading from 0.5 to 0.05 mol% did not significantly affect the yields of the desired product (Table 2, entries 1, 2, and 4). However, when the catalyst loading was further declined to 0.01 mol%, much lower activity was observed and the coupled product was afforded in 55% yield (Table 2, entry 5). Additionally, a comparison of the reactivity of **C1** with **C2** and previously reported complex **C3** [64] (Scheme 2) revealed that complexes **C2-C3** were all inferior to **C1** (Table 2, entries 5-7). This result can be attributed to the fact that more steric repulsion of the bulkier substitution on N- aryl moieties causes more axial shielding on the palladium centre, which provides more protection for the metal center to prolong the lifetimes of catalytic species. Thus, **C1** was selected as the standard catalyst for the following screening. With all these preliminary results in hand, the effects of temperature, reaction time, base, solvent and the amount effect of PivOH additive were screened to further optimize the reaction conditions. Different reaction temperatures were examined, and the analysis (Table 2, entries 2, 3) revealed that the use of lower reaction temperature led to a decrease in reactivity. A survey of reaction time was also conducted, and the results showed that there was no significant improvement in the product yield with the prolonged reaction time (Table 2, entries 5, 8). Subsequently, a series of different bases were screened, and it was shown that K_2CO_3 were superior to the others (Table 2, entries 5, 9-11). Among the solvents investigated, DMAc gave the best result, while other solvents such as dioxane, toluene, xylene, NMP and DMSO resulted in lower yields or even completely shut down the reaction (Table 2, entries 5, 12-16). Lastly, the amount effect of PivOH was investigated. In the absence of PivOH, the reaction did not work (Table 2, entry 17). Upon increasing the amount of PivOH, enhanced reaction efficiencies were observed (Table 2, entries 5, 17-19). The yield of product was raised to 55% when employing 0.3 mmol of PivOH (Table 2, entry 5). No more improvement was found when further increasing the amount of PivOH (Table 2, entry 20). Thus, the optimized reaction conditions were established by using 4-methylthiazole (2.0 equiv.), 3-bromopyridine (1.0 equiv.), **C1** (0.05 mol%) as the precatalyst, K_2CO_3 as the base, PivOH (30 mol%) as the acid additive and DMAc as the solvent in an aerobic environment.

With the optimal reaction conditions in hand, we set out to explore the substrate scope of this transformation. To begin with, we evaluated various substituted heteroaryl bromides (Table 3). As

Table 3
Palladium-catalyzed Direct Arylation of thiazole derivatives with heteroaryl bromides.

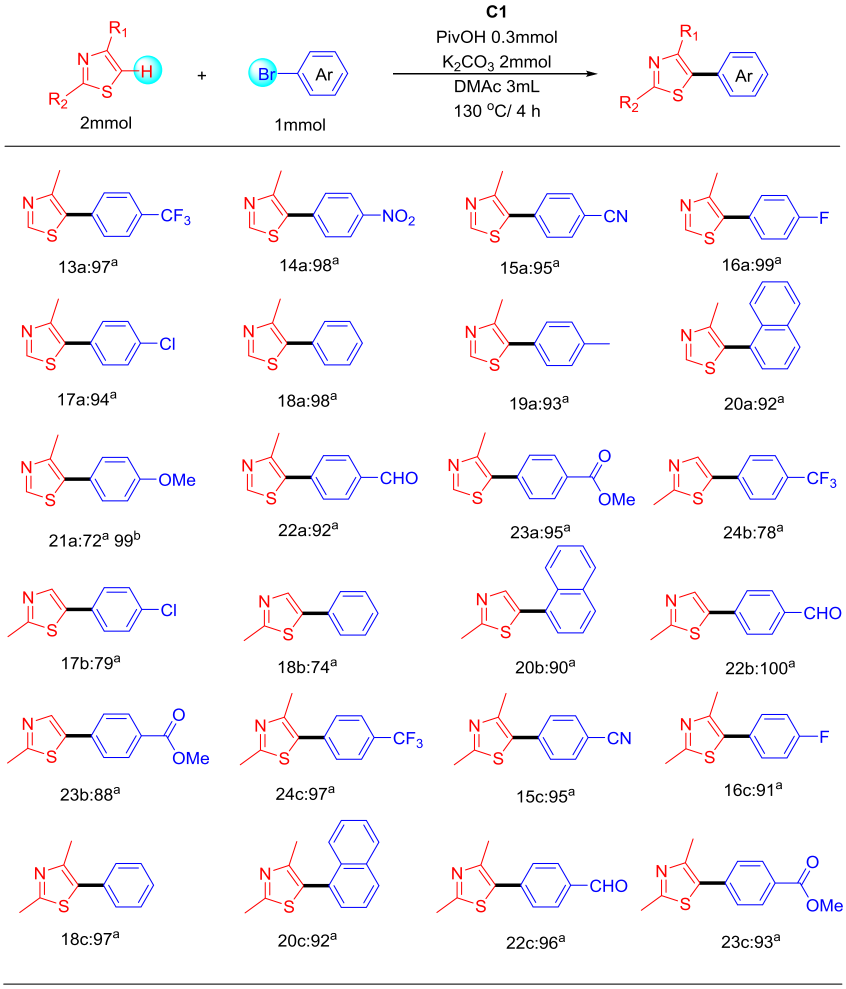


[a]**C1** 0.05 mol%. [b]**C1** 0.1 mol%.

shown in Table 3, this reaction applies to a variety of substituted heteroaryl bromides, affording the corresponding products in moderate to excellent yields. For example, a wide range of π-electron deficient heteroaryl bromides, such as pyridine, quinoline, isoquinoline, pyrimidine, reacted efficiently to afford the corresponding products in excellent yields. On the other hand, it was noted that highly π-electron excessive heteroaryl bromides, such as thiophenes and furans, afforded the coupled products in relative lower yields (42–56%). However, with those kinds of substrates, significant improvement of the yields (69–90%) could be obtained in the presence of slightly higher catalyst loading of 0.1 mol%. In addition, a variety of diverse functional groups on heteroaryl bromides were also examined. It was shown that the electronic properties of the substituents on heteroaryl bromides has limited effect on the reaction efficiency. Both the electron-withdrawing (such as chloro and ester) and the electron-donating substituents (such as methoxy group) on the heteroaryl bromides were all well-tolerated and furnished the corresponding products in excellent yields. Furthermore, 2-methylthiazole and sterically hindered 2-methyl-4-methythiazole were also investigated to determine the influence of a 2-substitution on thiazole on the reaction efficiency. The results demonstrated that thiazoles bearing 2-and/or 4-substituents could feasibly afford the desired product in high yields. It is worthy to point out that the corresponding products, such as 5-(isoquinolin-4-yl)-2,4-dimethylthiazole and 2,4-dimethyl-5-(pyridin-3-yl)thiazole, are biologically interesting heteroaryl thiazoles and could be obtained in almost quantitative yields (94–97%) using the present method. Encouraged by these results, we proceeded to diheteroarylation of 4-methythiazole with 3,5-dibromopyridine. To our delight, the coupling reaction successfully took place and afforded the desired diheteroarylated product in an excellent yield of 97%, which could provide a potential method for the effective direct diheteroarylation reaction to furnish some functional materials.

To further expand the substrate generality of this reaction, we were intrigued to explore the substrate scope with respect to the aryl bromides and the results were summarized in Table 4. In general, all the investigated aryl bromides reacted efficiently with substituted thiazoles to afford the arylated products in moderate to excellent yields. Concerning the electronic properties of the aryl bromides, electron-withdrawing and electron-donating groups were all well tolerated and gave the desired products in high yields. Notably, the presence of the substituents, such as Cl, F and so on, on the arylated thiazole derivatives is very important, which may be

Table 4
Palladium-catalyzed Direct Arylation of thiazole derivatives with aryl bromides.



[a] **C1** 0.05 mol%. [b] **C1** 0.1 mol%.

subjected to further synthetic transformations for the synthesis of diverse natural and biologically active compounds. And it was also found that the sterically-hindered 1-bromonaphthalene could also be employed successfully and similar yields of the desired coupling products were obtained (20a, 92% yield). Moreover, other thiazole substrates, such as 4-methyl-thiazole and sterically hindered 2-methyl-4-methythiazole were also explored with 1-bromonaphthalene. Consistently, the corresponding coupling reactions successfully proceeded again and comparable yields were obtained (20b and 20c, 90 and 92% yield, respectively).

3. Conclusions

In summary, we have developed a well-defined and air-stable Pd-PEPPSI-type NHC complex **C1** and tested its potential catalytic activity in the direct (hetero)arylation of thiazole derivatives at 5-position. The results showed that the complex **C1** is extraordinarily efficient at low catalyst loading and under aerobic conditions. Furthermore, the outstanding performance of **C1** revealed that the combination of bulky substitutions at the *ortho* and *para* position on N-moieties led to significant improvements in the catalytic efficiency. This complex thus has the potential to act as an efficient catalyst in other synthetic scenarios especially in scenarios involving arene C-H functionalization. Further studies focused on its applicability to other reactions are currently underway in our laboratory.

4. Experimental section

4.1. Physical measurements and materials

All thiazole compounds and bromides were purchased from Aldrich Chemical. *p*-methoxyaniline, di-phenylmethanol, chloromethyl ethyl ether, palladium chloride, inorganic bases, and Glyoxal were also purchased from Aldrich Chemical. Pyridine, 3-chloropyridine, and other solvents were purchased from Guangzhou Chemical Reagent Factory and were used as received. The compounds 2,6-bis(di-p-tolylmethyl)-4-methoxyaniline (**A1**) [65], the imidazolium salt **L2** [66] and palladium complex **C3** [64] were synthesized according to literature methods.

The NMR data of compounds were obtained on a Varian Mercury-Plus 400 MHz spectrometer at ambient temperature with the decoupled nucleus, using $CDCl_3$ as solvent and referenced versus TMS as standard. The X-ray diffraction data of single crystals were obtained with the ω-2θ scan mode on a Bruker SMART 1000 CCD diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 173 K for **C1**. The structure was solved using direct methods, and further refinement with full-matrix least-squares on F^2 was obtained with the SHELXTL program package [67,68]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced in calculated positions with the displacement factors of the host carbon atoms. CCDC 1883738 (**C1**) contains the supplementary crystallographic data for this paper.

4.2. Synthesis of the N,N′-bis(2,6-bis(di-p-tolylmethyl)-4-methylphenyl) diazabutadiene (B1)

The titled compound was synthesized according to a modified literature procedure [61]. An aqueous solution of glyoxal (1.82 mg, 13.0 mmol, 40% aq. solution) was added slowly to a pre-made mixture of 2,6-bis(di-p-tolylmethyl)-4-methoxyaniline (**A1**) (5.00g, 10.0 mmol),ethanol (125 mL) and a catalytic amount of formic acid (4 mL). The reaction mixture was stirred at 60 °C for 24h, resulting a suspension of light yellow solids in the solution. The titled compound **B1** solids were collected by filtration and washed with EtOH to remove impurities, then dried under high vacuum. No further purification was required (74% isolated yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23 (*s*, N=C-H, 2H), 6.96 (d, J = 8.0 Hz, Ar-H, 16H), 6.83 (d, J = 8.0 Hz, Ar-H, 16H), 6.39 (s, Ar-H, 4H), 5.15 (s, CH-H, 4H), 3.49 (s, OCH$_3$-H, 6H), 2.23 (s, CH$_3$-H, 24H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.2, 156.1, 142.8, 140.8, 135.7, 134.0, 129.3, 128.9, 113.8, 55.0, 50.4, 21.0.

5. Synthesis of imidazolium Salts(L1)

The titled compound was synthesized according to a modified literature procedure [61]. α-Diimine compounds (**B1**, 1 mmol) and chloromethyl ethyl ether (6 mL) were combined under a nitrogen atmosphere at room temperature, and the resulting mixture was heated at 100 °C overnight. After cooling to room temperature, the reaction mixture was triturated with anhydrous Et$_2$O, resulting a great deal of light yellow precipitate. The precipitate was collected by filtration and washed three times with anhydrous Et$_2$O. The titled product was then obtained as a yellowish white powder in excellent purity, and no further purification was required (60% isolated yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.98 (s, N-CH=N, 1H), 7.05 (s, Ar-H, 16H), 6.92 (d, J = 7.6 Hz, Ar-H, 8H), 6.68 (d, J = 7.7 Hz, Ar-H, 8H), 6.46 (s, Ar-H, 4H), 5.63 (s, C=CH-H, 2H), 5.13 (s, CH-H, 4H), 3.53 (s, OCH$_3$-H, 6H), 2.27 (s, CH$_3$-H, 24H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 160.66 (s), 142.73 (s), 139.41 (s), 138.93 (s), 136.45 (s), 136.28 (s), 129.70 (s), 129.29 (s), 129.20 (s), 128.93 (s), 125.12 (s), 123.88 (s), 115.43 (s), 55.21 (s), 50.74 (s), 21.02 (s).

6. General procedure for the synthesis of Pd-PEPPSI compounds (C1-2)

The titled compounds were synthesized according to a modified literature procedure [61]. A mixture of imidazolium salt (1 mmol), PdCl$_2$ (0.177 g, 1 mmol), and K$_2$CO$_3$ (0.690 g, 10 mmol) in pyridine (4 mL) was stirred at 80 °C for 24 h. After cooling to room temperature, the reaction mixture was added with 20 mL of dichloromethane. The resulting reaction solution was then loaded onto a short silica-gel column (5 cm × 1 cm). After elution with substantial dichloromethane, the filtrate was evaporated to dryness under reduced pressure. The solid residue was stirred with hexane (15 mL), resulting a great deal of precipitate. The precipitate was collected by filtration, and recrystallized from dichloromethane and diethyl ether to give the titled compounds.

The complex **C1** was obtained as a yellowish powder (73% isolated yield). Single crystals of **C1** suitable for X-ray diffraction studies were obtained by layering their dichloromethane solution with hexane at ambient temperature. ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.18–8.92 (m, Ar-H, 2H), 7.78 (t, J = 7.6 Hz, Ar-H, 1H), 7.34 (dd, J = 7.6, 6.5 Hz, Ar-H, 2H), 7.30 (d, J = 8.1 Hz, Ar-H, 8H), 6.98 (d, J = 7.9 Hz, Ar-H, 8H), 6.82 (d, J = 7.9 Hz, Ar-H, 8H), 6.65 (d, J = 8.0 Hz, Ar-H, 8H), 6.50 (s, Ar-H, 4H), 6.27 (s, Ar-H, CH-H4H), 5.03 (s, CH-H, 2H), 3.53 (s, OCH$_3$-H, 6H), 2.26 (d, J = 11.8 Hz, CH$_3$-H, 24H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 158.5, 151.9, 143.6, 141.6, 141.2, 135.2, 130.9, 130.3, 129.1, 128.8, 128.5, 124.2, 115.2, 54.9, 50.2, 21.0.

The complex **C2** was obtained as a yellowish powder (80% isolated yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.11–9.06 (m, Ar-H,2H), 7.79 (td, J = 7.6, 1.3 Hz, Ar-H,1H), 7.45 (d, J = 7.5 Hz, Ar-H,8H), 7.39–7.33 (m, Ar-H, 2H), 7.24–7.13 (m, Ar-H, 12H), 7.09–6.98 (m, Ar-H, 12H), 6.77 (d, J = 7.5 Hz, Ar-H, 8H), 6.49 (s, Ar-H, 4H), 6.36 (s, CH-H, 4H), 4.82 (s, C=C-H,2H), 3.52 (s, OMe-H,6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 158.7, 151.8, 151.6, 144.3, 143.8, 143.6, 137.9, 130.9, 130.5, 129.3, 128.1, 127.8, 126.2, 126.1, 124.3, 124.0, 115.4, 54.8, 51.1.

6.1. General procedure for direct arylation promoted by palladium complexes

Typically, (hetero)aryl bromide (1.0 mmol), thiazole derivatives (2.0 mmol), Pd-PEPPSI complexes (0.01–0.5 mol%), base (2 mmol), acid additive (0.3 mmol), and 3 mL of DMAc solvent were added into a parallel reactor. After heating at 130 °C for 4 h, the resulting mixture was cooled to room temperature. Subsequently, 25 mL of water and 20 mL of dichloromethane were added into the reactor, and the mixture was stirred for another several minutes, followed by extraction three times with dichloromethane (3 × 5 mL). The organic layer was then combined, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give the crude products. The crude products were then purified by silica-gel column chromatography using petroleum ether–dichloromethane (15/1) as the eluent. The obtained pure products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, and the spectra can be found in the Supporting Information. And the isolated yields of products were obtained based on the amounts of (hetero)aryl bromides.

6.2. General information for NMR data

The NMR data of compounds were obtained on a Varian Mercury-Plus 400 MHz spectrometer at ambient temperature, using CDCl$_3$ as solvent and referenced versus TMS as standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz.

*6.2.1. 5-(6-Methoxypyridin-3-yl)-4-methylthiazole (**1a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.66 (s, Ar-H, 1H), 8.20 (dd, J = 2.5, 0.6 Hz, Ar-H, 1H), 7.58 (dd, J = 8.6, 2.5 Hz, Ar-H, 1H), 6.77 (dd, J = 8.6, 0.7 Hz, Ar-H, 1H), 3.93 (s, Ar-OCH$_3$, 3H), 2.46 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.6, 150.4, 148.9, 146.8, 139.3, 128.2, 121.0, 110.8, 77.3, 77.0, 76.7, 53.5, 15.7.

*6.2.2. 4-Methyl-5-(6-methylpyridin-3-yl)thiazole (**2a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.69 (s, Ar-H, 1H), 8.56 (d, J = 1.3 Hz, Ar-H, 1H), 7.61 (dd, J = 8.0, 2.0 Hz, Ar-H, 1H), 7.20 (d, J = 8.0 Hz, Ar-H, 1H), 2.57 (s, Ar-CH$_3$, 3H), 2.50 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 157.9, 150.8, 149.4, 148.9, 136.7, 128.2, 125.1, 123.0, 24.1, 15.9.

*6.2.3. 5-(6-Chloropyridin-3-yl)-4-methylthiazole (**3a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.75 (s, Ar-H,1H), 8.47 (s, Ar-H, 1H), 7.70 (dd, J = 8.2, 2.1 Hz, Ar-H, 1H), 7.40 (d, J = 8.2 Hz, Ar-H, 1H), 2.52 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 151.5, 150.8, 150.2, 149.4, 139.0, 127.2, 126.7, 124.2, 16.0.

*6.2.4. 5-(6-Fluoropyridin-3-yl)-4-methylthiazole (**4a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.74 (s, Ar-H, 1H), 8.29 (dd, J = 1.7, 0.8 Hz, Ar-H, 1H), 7.84 (ddd, $J = 8.4$, 7.5, 2.6 Hz, Ar-H, 1H), 7.01 (ddd, $J = 8.5$, 3.1, 0.6 Hz, Ar-H, 1H), 2.51 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.2, 161.8, 151.3, 145.0, 147.8, 147.6, 141.8, 141.7, 126.7, 126.2, 126.1, 109.8, 109.4, 15.8.

*6.2.5. 5-(Isoquinolin-4-yl)-4-methylthiazole (**5a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.22 (s, Ar-H, 1H), 8.82 (s, Ar-H, 1H), 8.45 (s, Ar-H, 1H), 7.97 (d, $J = 7.9$ Hz, Ar-H, 1H), 7.67–7.50 (m, Ar-H, 3H), 2.24 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.0, 152.1, 151.6, 144.6, 134.7, 131.0, 128.0, 127.8, 127.4, 125.1, 124.1, 122.7, 15.6.

*6.2.6. 4-Methyl-5-(quinolin-4-yl)thiazole (**6a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.91 (d, $J = 4.4$ Hz, Ar-H, 1H), 8.85 (s, Ar-H, 1H), 8.15 (d, $J = 8.4$ Hz, Ar-H, 1H), 7.72–7.66 (m, Ar-H, 2H), 7.50 (ddd, $J = 8.3$, 6.8, 1.2 Hz, Ar-H, 1H), 7.33 (d, $J = 4.4$ Hz, Ar-H, 1H), 2.27 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 152.3, 151.4, 149.5, 148.4, 138.1, 129.9, 129.7, 127.1, 126.0, 125.2, 123.2, 15.8.

*6.2.7. 4-Methyl-5-(quinolin-3-yl)thiazole (**7a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.98 (d, $J = 2.3$ Hz, Ar-H, 1H), 8.78 (s, Ar-H, 1H), 8.18 (d, $J = 2.1$ Hz, Ar-H, 1H), 8.12 (d, $J = 8.5$ Hz, Ar-H, 1H), 7.86–7.81 (m, Ar-H, 1H), 7.74 (ddd, $J = 8.4$, 6.9, 1.4 Hz, Ar-H, 1H), 7.58 (ddd, $J = 8.1$, 7.0, 1.1 Hz, Ar-H, 1H), 2.59 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 151.3, 150.5, 150.0, 147.2, 135.6, 130.0, 129.3, 128.2, 127.8, 127.4, 125.3, 16.1.

*6.2.8. 4-Methyl-5-(pyrimidin-5-yl)thiazole (**8a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.21 (s, Ar-H, 1H), 8.85 (s, Ar-H, 3H), 2.58 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.7, 156.3, 152.2, 151.0, 126.9, 124.2, 16.0.

*6.2.9. 4-Methyl-5-(thiophen-2-yl)thiazole (**9a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.61 (s, Ar-H, 1H), 7.35 (dd, $J = 5.1$, 1.2 Hz, Ar-H, 1H), 7.14 (dd, $J = 3.6$, 1.2 Hz, Ar-H, 1H), 7.08 (dd, $J = 5.1$, 3.6 Hz, Ar-H, 1H), 2.61 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 149.9, 149.0, 133.2, 127.6, 127.1, 126.2, 125.5, 16.5.

*6.2.10. 4-Methyl 5-(4-methylthiazol-5-yl)furan-2-carboxylate (**10a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (s, Ar-H, 1H), 7.21 (d, $J = 3.4$ Hz, Ar-H, 1H), 6.56 (d, $J = 3.4$ Hz, Ar-H, 1H), 3.91 (s, Ar-CH$_3$, 3H), 2.74 (s, Ar-CH3, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 158.9, 151.4, 151.2, 150.6, 143.8, 1213, 119.8, 109.5, 52.0, 17.00.

*6.2.11. 3-(4-Methylthiazol-5-yl)-2H-chromen-2-one (**11a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.81 (s, Ar-H, 1H), 7.85 (s, Ar-H, 1H), 7.57 (t, $J = 4.5$ Hz, Ar-H, 2H), 7.41–7.33 (m, Ar-H, 2H), 2.61 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 160.1, 153.2, 152.8, 152.1, 141.2, 132.1, 128.0, 124.9, 124.0, 120.4, 118.9, 116.7, 17.2.

*6.2.12. 4-Methyl-5-(pyridin-3-yl)thiazole (**12a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.74 (s, Ar-H, 1H), 8.70 (s, Ar-H, 1H), 8.59 (d, $J = 4.1$ Hz, Ar-H, 1H), 7.78–7.72 (m, Ar-H, 1H), 7.37 (dd, $J = 7.8$, 4.9 Hz, Ar-H, 1H), 2.53 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 151.2, 149.7, 149.6, 148.8, 136.3, 128.2, 128.0, 123.4, 15.9.

*6.2.13. 5-(6-Methoxypyridin-3-yl)-2-methylthiazole (**1b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.30 (d, $J = 2.1$ Hz, Ar-H, 1H), 7.68 (dd, $J = 8.8$, 2.4 Hz, Ar-H, 2H), 6.76 (dd, $J = 8.6$, 0.5 Hz, Ar-H, 1H), 3.95 (s, Ar-OCH$_3$, 3H), 2.72 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 165.0, 163.7, 144.4, 137.3, 136.6, 135. 121.0, 111.0, 53.5, 19.2.

*6.2.14. 2-Methyl-5-(6-methylpyridin-3-yl)thiazole (**2b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.66 (s, Ar-H, 1H), 7.82–7.65 (m, Ar-H, 2H), 7.18 (d, $J = 7.7$ Hz, Ar-H, 1H), 2.75 (d, $J = 2.7$ Hz, Ar-CH$_3$ 3H), 2.58 (s, Ar-CH$_3$ 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 165.8, 158.0, 146.7, 138.2, 135.2, 133.9, 124.9, 123.2, 24.2, 19.4.

*6.2.15. 5-(6-Chloropyridin-3-yl)-2-methylthiazole (**3b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.55–8.53 (m, Ar-H, 1H), 7.83 (s, Ar-H, 1H), 7.76 (dd, $J = 8.3$, 2.6 Hz, Ar-H, 1H), 7.36 (dd, $J = 8.3$, 0.6 Hz, Ar-H, 1H), 2.75 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 166.9, 150.6, 147.0, 139.1, 136.2, 133.6, 126.8, 124.5, 19.5.

*6.2.16. 5-(6-Fluoropyridin-3-yl)-2-methylthiazole (**4b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.32 (dd, $J = 1.7$, 0.8 Hz, Ar-H, 1H), 7.86 (ddd, $J = 8.5$, 7.4, 2.6 Hz, Ar-H, 1H), 7.74 (s, Ar-H, 1H), 6.94 (ddd, $J = 8.5$, 3.1, 0.6 Hz, Ar-H, 1H), 2.70 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.4, 164.1, 161.8, 145.1, 145.0, 139.0, 138.9, 138.7, 138.7, 133.5, 125.9, 125.8, 110.0, 109.6, 19.3.

*6.2.17. 2-Methyl-5-(quinolin-4-yl)thiazole (**6b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.89 (d, $J = 4.4$ Hz, Ar-H, 1H), 8.17 (dd, $J = 8.4$, 0.8 Hz, Ar-H, 2H), 7.85 (s, Ar-H, 1H), 7.74 (ddd, $J = 8.5$, 6.9, 1.3 Hz, Ar-H, 1H), 7.56 (ddd, $J = 8.2$, 6.9, 1.3 Hz, Ar-H, 1H), 7.38 (d, $J = 4.4$ Hz, Ar-H, 1H), 2.81 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 167.5, 149.6, 148.5, 142.0, 137.4, 132.9, 129.9, 129.6, 127.1, 126.1, 124.8, 121.8, 19.1.

*6.2.18. 2-Methyl-5-(quinolin-3-yl)thiazole (**7b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.09 (d, $J = 2.3$ Hz, Ar-H, 1H), 8.18 (d, $J = 2.2$ Hz, Ar-H, 1H), 8.11–8.08 (m, Ar-H, 1H), 7.97 (s, Ar-H, 1H), 7.83–7.80 (m, Ar-H, 1H), 7.70 (ddd, $J = 8.4$, 6.9, 1.5 Hz, Ar-H, 1H), 7.56 (ddd, $J = 8.1$, 6.9, 1.2 Hz, Ar-H, 1H), 2.77 (s, Ar-CH$_3$, 3H).13C NMR (101 MHz, CDCl$_3$) δ 166.4, 148.6, 147.4, 138.9, 135.4, 132.4, 129.7,127.4, 129.3, 127.8, 127.4, 124.9, 19.5.

*6.2.19. 5-(6-Methoxypyridin-3-yl)-2,4-dimethylthiazole (**1c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.18 (s, Ar-H, 1H), 7.56 (d, $J = 8.5$ Hz, Ar-H, 1H), 6.76 (d, $J = 8.5$ Hz, Ar-H, 1H), 3.94 (s, Ar-OCH$_3$, 3H), 2.66 (s, Ar-CH$_3$, 3H), 2.39 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 163.4, 147.5, 146.7, 139.2, 127.6, 121.4, 110.8, 53.5, 19.1, 15.7.

*6.2.20. 2,4-Dimethyl-5-(6-methylpyridin-3-yl)thiazole (**2c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.51 (d, $J = 2.0$ Hz, Ar-H, 1H), 7.56 (dd, $J = 8.0$, 2.4 Hz, Ar-H, 1H), 7.17 (d, $J = 8.0$ Hz, Ar-H, 1H), 2.66 (s, 3H), 2.56 (s, Ar-CH$_3$, 3H), 2.41 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.9, 157.5, 148.8, 145.0, 136.5, 127.5, 125.5, 122.9, 24.1, 19.1, 15.8.

*6.2.21. 5-(6-Fluoropyridin-3-yl)-2,4-dimethylthiazole (**4c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.20 (d, $J = 2.4$ Hz, Ar-H, 1H), 7.76 (ddd, $J = 8.4$, 7.6, 2.6 Hz, Ar-H, 1H), 6.99–6.90 (m, Ar-H, 1H), 2.65 (s, Ar-CH$_3$, 3H), 2.37 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.3, 163.9, 161.5, 148.4, 147.4, 147.3, 141.5, 141.4, 126.4, 126.4, 126.0, 125.9, 109.6, 109.2, 19.0, 15.7.

*6.2.22. 5-(Isoquinolin-4-yl)-2,4-dimethylthiazole (**5c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.27 (s, Ar-H, 1H), 8.49 (s, Ar-H, 1H), 8.04 (d, $J = 8.1$ Hz, Ar-H, 1H), 7.83–7.57 (m, Ar-H, 3H), 2.76 (s, Ar-CH$_3$, 3H), 2.22 (s, Ar-CH3, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 165.4, 153.0, 150.4, 144.7, 135.0, 131.1, 128.3, 128.0, 127.6, 124.6, 124.5, 123.3, 19.2, 15.7.

*6.2.23. 2,4-Dimethyl-5-(quinolin-4-yl)thiazole (**6c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.90 (d, $J = 4.4$ Hz, Ar-H, 1H), 8.16 (d, $J = 8.4$ Hz, Ar-H, 1H), 7.80 (dd, $J = 8.4$, 0.8 Hz, Ar-H, 1H), 7.73 (ddd, $J = 8.4$, 6.9, 1.4 Hz, Ar-H, 1H), 7.54 (ddd, $J = 8.3$, 6.9, 1.2 Hz, Ar-H, 1H), 7.34 (d, $J = 4.4$ Hz, Ar-H, 1H), 2.81 (s, Ar-CH3,3H), 2.22 (s, Ar-CH$_3$,3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.5, 149.6, 148.5, 142.0, 137.4, 132.9, 129.9, 129.5, 127.1, 126.1, 124.8, 121.8, 19.1, 15.9.

*6.2.24. 2,4-Dimethyl-5-(quinolin-3-yl)thiazole (**7c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.91 (d, J = 2.3 Hz, Ar-H, 1H), 8.09–8.04 (m, Ar-H, 2H), 7.77 (dd, J = 8.2, 1.1 Hz, Ar-H, 1H), 7.67 (ddd, J = 8.3, 7.0, 1.4 Hz, Ar-H, 1H), 7.54–7.46 (m, Ar-H, 1H), 2.67 (s, Ar-CH$_3$, 3H), 2.47 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 164.4, 150.4, 148.5, 146.8, 135.0, 129.7, 129.1, 127.6, 127.5, 127.4, 127.2, 125.6, 19.1, 15.9.

*6.2.25. 3,5-bis(4-methylthiazol-5-yl)pyridine (**12aa**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.79 (s, Ar-H, 2H), 8.70 (d, J = 2.1 Hz, Ar-H, 2H), 7.80 (t, J = 2.2 Hz, Ar-H, 1H), 2.59 (s, Ar-CH$_3$, 6H).^{13}C NMR (101 MHz, CDCl$_3$) δ 151.6, 150.3, 148.8, 136.5, 128.3, 127.4, 16.1.

*6.2.26. 4-Methyl-5-(4-(trifluoromethyl)phenyl)thiazole (**13a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.70 (s, Ar-H, 1H), 7.65 (d, J = 7.4 Hz, Ar-H, 2H), 7.52 (d, J = 7.6 Hz, Ar-H, 2H), 2.52 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 151.0, 149.4, 135.6, 130.3, 129.4, 125.6, 125.6, 125.5, 125.5, 125.2, 122.5, 119.8, 16.0.

*6.2.27. 4-Methyl-5-(4-nitrophenyl)thiazole (**14a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.79–8.74 (m, Ar-H, 1H), 8.27 (t, J = 10.3 Hz, Ar-H, 2H), 7.61 (dd, J = 10.1, 5.8 Hz, Ar-H, 2H), 2.59 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 151.8, 150.4, 147.0, 138.8, 129.8, 124.0, 113.9, 16.4.

*6.2.28. 4-(4-Methylthiazol-5-yl)benzonitrile (**15a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.75 (s, Ar-H, 1H), 7.73 (d, J = 1.9 Hz, Ar-H, 1H), 7.71 (d, J = 2.0 Hz, Ar-H, 1H), 7.57 (d, J = 2.0 Hz, Ar-H, 1H), 7.55 (d, J = 1.9 Hz, Ar-H, 1H), 2.56 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 151.6, 150.0, 136.8, 132.5, 130.1, 129.7, 118.4, 111.5, 16.3.

*6.2.29. 5-(4-fluorophenyl)-4-methylthiazole (**16a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.67 (s, Ar-H, 1H), 7.42–7.35 (m, Ar-H, 2H), 7.11 (t, J = 8.1 Hz, Ar-H, 2H), 2.50 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 163.6, 161.1, 150.3, 148.54, 131.0, 131.0, 115.8, 115.6, 15.9.

*6.2.30. 5-(4-chlorophenyl)-4-methylthiazole (**17a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.68 (s, Ar-H, 1H), 7.41–7.33 (m, Ar-H, 4H), 2.51 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 150.5, 148.8, 133.9, 130.6, 130.5, 130.4, 128.9, 16.0.

*6.2.31. 4-Methyl-5-phenylthiazole (**18a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.68 (s, Ar-H, 1H), 7.46–7.42 (m, Ar-H, 4H), 7.38–7.34 (m, Ar-H, 1H), 2.54 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 150.3, 148.5, 131.9, 131.9, 129.3, 128.7, 127.9, 16.1.

*6.2.32. 4-Methyl-5-(p-tolyl)thiazole (**19a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.66 (s, Ar-H, 1H), 7.34 (d, J = 8.1 Hz, Ar-H, 2H), 7.23 (dd, J = 8.4, 0.6 Hz, Ar-H, 2H), 2.53 (s, Ar-CH$_3$, 3H), 2.39 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 150.0, 148.2, 137.8, 132.0, 129.4, 129.2, 128.9, 21.2, 16.0.

*6.2.33. 4-Methyl-5-(naphthalen-1-yl)thiazole (**20a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.83 (s, Ar-H, 1H), 7.90 (d, J = 7.8 Hz, Ar-H, 2H), 7.70 (d, J = 8.1 Hz, Ar-H, 1H), 7.52–7.44 (m, Ar-H, 4H), 2.30 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 151.4, 150.6, 133.5, 132.3, 129.2, 129.0, 1289, 128.6, 128.3, 126.54, 126.0, 125.4, 125.0, 15.6.

*6.2.34. 5-(4-methoxyphenyl)-4-methylthiazole (**21a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.60 (s, Ar-H, 1H), 7.34–7.30 (m, Ar-H, 2H), 6.93–6.89 (m, Ar-H, 2H), 3.79 (s, Ar-OCH$_3$, 3H), 2.48 (s, Ar-CH$_3$, 3H). ^{13C} NMR (101 MHz, CDCl$_3$) δ 159.2, 149.5, 147.7, 131.5, 130.3, 123.9, 114,0, 55.1, 15.8.

*6.2.35. 4-(4-Methylthiazol-5-yl)benzaldehyde (**22a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 10.03 (s,CHO-H 1H), 8.74 (s, Ar-H, 1H), 7.93 (d, J = 8.1 Hz, Ar-H, 2H), 7.61 (d, J = 8.1 Hz, Ar-H, 2H), 2.58 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 191.4, 151.4, 149.8, 138.2, 135.3, 130.7, 130.0, 129.6, 16.4.

*6.2.36. 4-Methyl -(4-methylthiazol-5-yl)benzoate (**23a**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.71 (s, Ar-H, 1H), 8.07 (d, J = 8.5 Hz, Ar-H, 2H), 7.50 (d, J = 8.5 Hz, Ar-H, 2H), 3.92 (s, Ar-COOCH$_3$, 3H), 2.55 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.5, 151.0, 149.4, 136.6, 130.9, 129.9, 129.3, 129.0, 52.2, 16.3.

*6.2.37. 2-Methyl-5-(4-(trifluoromethyl)phenyl)thiazole (**24b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (s, Ar-H, 1H), 7.61 (d, J = 2.0 Hz, Ar-H, 4H), 2.74 (s, Ar-CH3, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.6, 138.9, 137.2, 135.1, 130.3, 129.9, 129.6, 129.3, 128.0, 126.6, 126.0, 126.0, 126.0, 125.9, 125.3, 122.6, 119.9, 19.4.

*6.2.38. 5-(4-chlorophenyl)-2-methylthiazole (**17b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, J = 1.0 Hz, Ar-H, 1H), 7.45–7.40 (m, Ar-H, 2H), 7.34 (dd, J = 7.9, 1.3 Hz, Ar-H, 2H), 2.71 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 165.6, 137.9, 137.6, 133.8, 130.1, 129.2, 127.7, 19.3.

*6.2.39. 2-Methyl-5-phenylthiazole (**18b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 (s, Ar-H, 1H), 7.44 (t, J = 1.7 Hz, Ar-H, 1H), 7.42–7.41 (m, Ar-H, 1H), 7.31–7.27 (m, Ar-H, 2H), 7.24–7.20 (m, Ar-H, 1H), 2.63 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.2, 138.8, 137.6, 131.5, 128.9, 127.9, 126.5, 19.3.

*6.2.40. 2-Methyl-5-(naphthalen-1-yl)thiazole (**20b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16–8.12 (m, Ar-H, 1H), 7.91–7.85 (m, Ar-H, 2H), 7.74 (s, Ar-H, 1H), 7.55–7.45 (m, Ar-H, 4H), 2.80 (s, Ar-CH3, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 166.3, 141.1, 135.7, 133.7, 131.9, 129.0, 128.8, 128.5, 128.4, 126.7, 126.1, 125.2, 125.2, 19.2.

*6.2.41. 4-(2-Methylthiazol-5-yl)benzaldehyde (**22b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 10.00 (s, CHO-H,1H), 7.93 (s, Ar-H, 1H), 7.90–7.87 (m, Ar-H, 2H), 7.68–7.65 (m, Ar-H, 2H), 2.75 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 191.3, 167.1, 139.5, 137.5, 137.4, 135.5, 130.5, 126.8, 19.5.

*6.2.42. Methyl 4-(2-methylthiazol-5-yl)benzoate (**23b**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (d, J = 8.6 Hz, Ar-H, 2H), 7.87 (s, Ar-H, 1H), 7.55 (d, J = 8.6 Hz, Ar-H, 2H), 3.91 (s, Ar-OCH$_3$, 3H), 2.72 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.5, 166.4, 138.9, 137.7, 135.9, 130.3, 129.3, 126.2, 52.1, 19.4.

*6.2.43. 2,4-Dimethyl-5-(4-(trifluoromethyl)phenyl)thiazole (**24c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, J = 8.2 Hz, Ar-H, 2H), 7.47 (d, J = 8.1 Hz, Ar-H, 2H), 2.65 (s, Ar-CH$_3$, 3H), 2.43 (s, Ar-CH$_3$, 3H).^{13}C NMR (101 MHz, CDCl$_3$) δ 164.1, 148.1, 136.0, 129.7, 129.1, 125.5, 125. 4, 125.4, 122.5, 119.9, 18.9, 16.0.

*6.2.44. 4-(2,4-Dimethylthiazol-5-yl)benzonitrile (**15c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (d, J = 8.5 Hz, Ar-H, 2H), 7.49 (d, J = 8.5 Hz, Ar-H, 2H), 2.67 (s, Ar-CH$_3$, 3H), 2.46 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.7, 148.7, 137.1, 132.3, 129.4, 129.3, 118.5, 110.9, 19.1, 16.3.

*6.2.45. 5-(4-fluorophenyl)-2,4-dimethylthiazole (**16c**)*

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 (dd, J = 8.6, 5.4 Hz, Ar-H, 2H), 7.04 (t, J = 8.7 Hz, Ar-H, 2H), 2.63 (s, Ar-CH$_3$, 3H), 2.38 (s, Ar-CH$_3$, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.20 (d, $J = 16.2$ Hz), 160.8, 147.0, 130.7, 130.1, 128.2, 115.6 115.4, 18.9, 15.7.

6.2.46. *2,4-Dimethyl-5-phenylthiazole (**18c**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.34 (m, Ar-H, 4H), 7.32–7.27 (m, Ar-H, 1H), 2.65 (s, Ar-CH_3, 3H), 2.44 (s, Ar-CH_3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 146.9, 132.2, 131.2, 129.0, 128.5, 127.4, 77.3, 77.0, 76.7, 18.9, 15.9.

6.2.47. *2,4-Dimethyl-5-(naphthalen-1-yl)thiazole (**20c**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.87 (m, Ar-H, 2H), 7.79–7.75 (m, Ar-H, 1H), 7.53–7.45 (m, Ar-H, 4H), 2.76 (s, Ar-CH_3, 3H), 2.21 (s, Ar-CH_3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 149.3, 133.6, 132.4, 129.2, 129.2, 128.9, 128.3, 128.3, 126.5, 126.0, 125.6, 125.1, 19.1, 15.6.

6.2.48. *4-(2,4-Dimethylthiazol-5-yl)benzaldehyde (**22c**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, Ar-H, 1H), 7.90 (d, $J = 8.2$ Hz, Ar-H, 2H), 7.56 (d, $J = 8.2$ Hz, Ar-H, 2H), 2.69 (s, Ar-CH_3, 3H), 2.49 (s, Ar-CH_3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 164.6, 148.5, 138.6, 135.0, 130.0, 129.3, 19.1, 16.4.

6.2.49. *Methyl 4-(2,4-dimethylthiazol-5-yl)benzoate (**23c**)*

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, $J = 8.0$ Hz, Ar-H, 2H), 7.45 (d, $J = 8.0$ Hz, Ar-H, 2H), 3.91 (s, Ar-OCH_3, 3H), 2.67 (s, Ar-CH_3, 3H), 2.47 (s, Ar-CH_3, 3H). ^{13C} NMR (101 MHz, $CDCl_3$) δ 166.5, 164.1, 148.1, 137.0, 130.3, 129.8, 128.9, 128.7, 52.1, 19.1, 16.3.

Declarations of interest

None.

Acknowledgements

The authors gratefully thank the Natural Science Foundation of Guangdong Province (No. 2018A030313296), Key Laboratory of Polymeric Composite & Functional Materials of Ministry of Education (No. PCFM-2017-03) and Special funds of Key disciplines construction from Guangdong and Zhongshan cooperating for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2019.06.016.

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